Asymmetric Morita-Baylis-Hillman Reaction: Catalyst Development and Mechanistic Insights Based on Mass Spectrometric Back Reaction Screening

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Dekan

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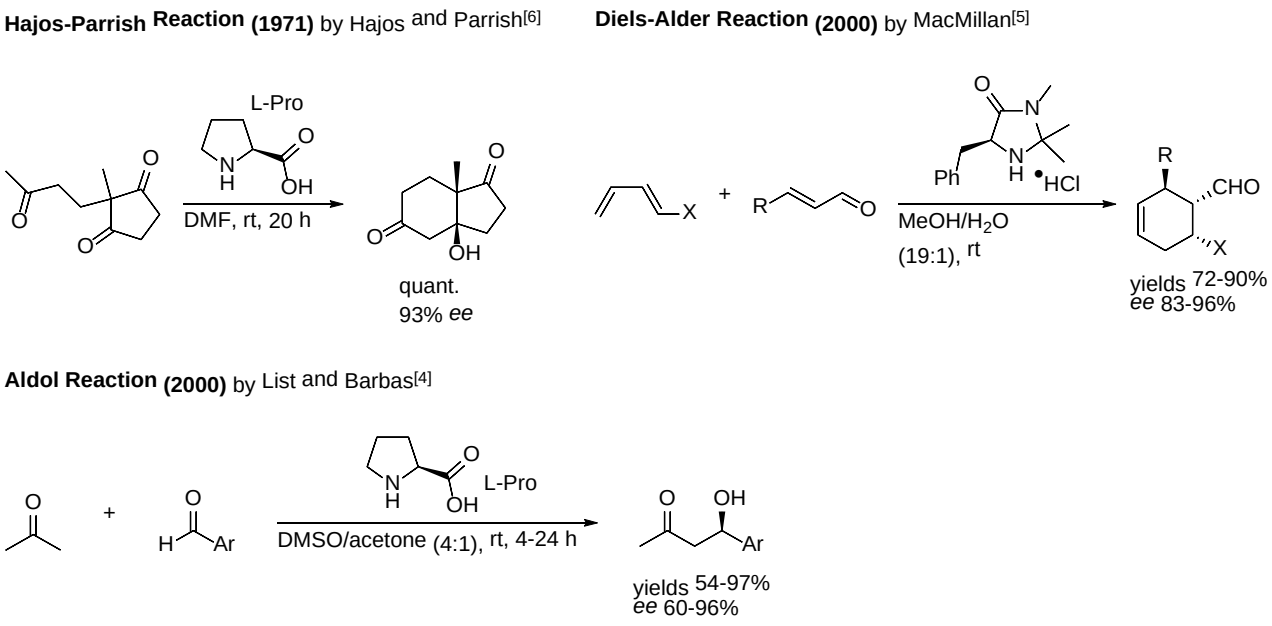
Chapter 1

Introduction

1.1 Organocatalysis

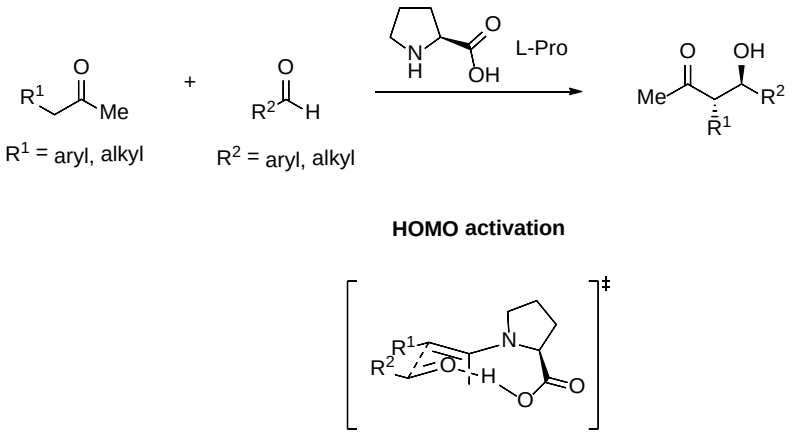
Asymmetric catalysis has seen enormous growth over the last two decades and has found many applications in the synthesis of pharmaceuticals, polymers, fine chemicals and pesticides. Indeed, an impressive selection of enantioselective catalytic reactions has become readily available which covers a wide spectrum of synthetically useful transformations. In general, a catalyst acts by lowering the activation energy barrier of a chemical process, which results in the initiation or acceleration of a chemical reaction. In asymmetric synthesis chiral catalysts are used to induce some level of enantioselectivity. In the beginning metal-based catalysts were typically applied for effecting asymmetric transformations.[1] Years later, when the field of organocatalysis emerged, small, organic molecules lacking a metal-center were exploited as chiral catalysts.[2] Although the concept of organocatalysis has been known for more than 150 years after the discovery of the synthesis of oxamide from cyanogen and water by Liebig[3], the major breakthrough did not occur until 2000 (see Scheme 1 for seminal examples).[4–6] Since that time, more than 7500 scientific reports which describe the use of organocatalysts in 130 different reaction types have been published, indicating the importance of this research area.



Scheme 1: Seminal examples by Hajos and Parrish,[6] MacMillan[5] and List and Barbas.[4]

The reason why many chemists are interested in this research field is because of the advantages that organocatalysts offer over classical transition metal types such as better stability against oxygen or moisture. Moreover, enantiopure organocatalysts are often cheap and easily available in large quantities due to their derivation from chiral naturally occurring precursors. Furthermore, small molecules are typically less toxic than metal catalysts and therefore have a positive impact on environmental compatibility. Lastly, metallic impurities in pharmaceuticals intermediates can be eliminated when organocatalysts are employed.[7,8]

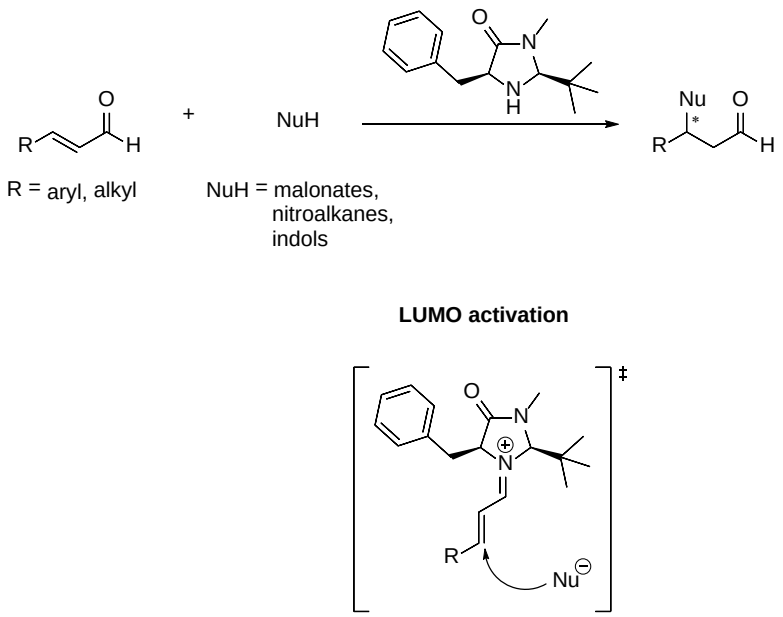
In organocatalysis, different activation modes by the catalyst are known. One possible mode is enamine catalysis. An enolizable carbonyl group is converted to a nucleophilic enamine intermediate by condensation with a secondary amine catalyst.[9] This allows the organocatalytic enantioselective functionalization of carbonyl compounds at the α-position by reaction with an electrophile. In the last decades, many different chiral secondary amines have been developed for the reaction of aldehydes and ketones with various electrophiles. For example, the aldol reaction is a powerful method for the formation of chiral β-hydroxy-carbonyl compounds starting from simple ketones and aldehydes (Scheme 2). In the proline-catalyzed aldol addition, the stereoselectivity is controlled *via* a six-membered transition state in which the aromatic aldehyde is preferably attacked by the enamine intermediate from the *re*-face.[10,11]



Scheme 2: HOMO activation mode in the aldol reaction.

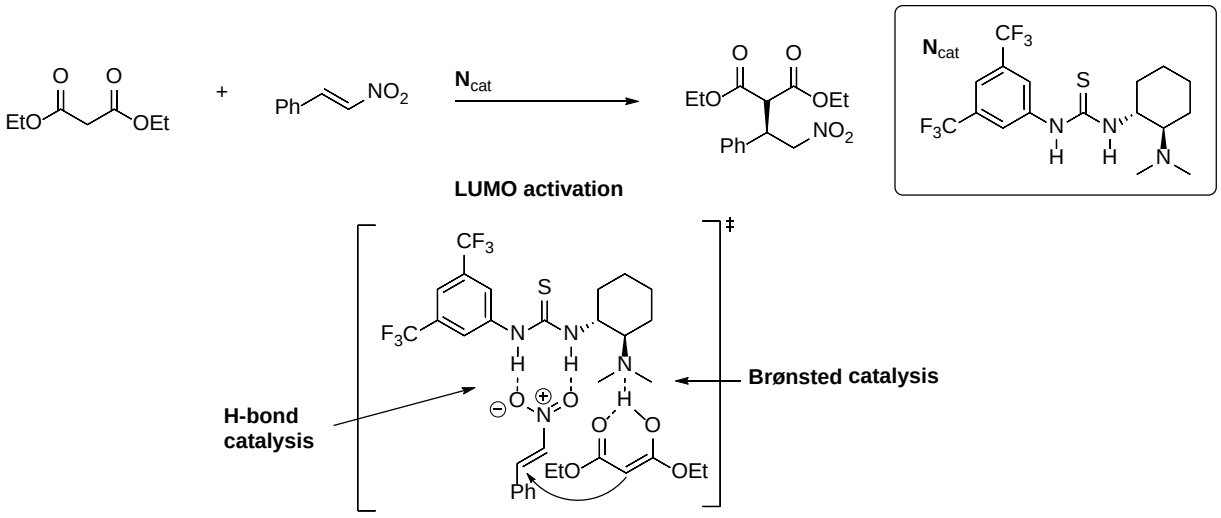
A different activation mode is used in iminium catalysis, which is comparable to Lewis acid or Brønsted catalysis. Herein, the energy of the lowest unoccupied molecular orbital (LUMO) of the electrophile is lowered by iminium ion formation. For example, when an α,β-unsaturated carbonyl compound is treated with a secondary amine catalyst the resulting iminium ion intermediate is formed. In this intermediate, both C2 and C4 positions are activated, however the higher orbital

coefficient in C4 facilitates the occurrence of conjugated additions or pericyclic reactions into this iminium intermediate (Scheme 3). Since 2000, several secondary chiral imidazole-based organocatalysts by MacMillan or proline-derived catalysts by Jørgensen and Hayashi have been developed and established for several reaction types. These include asymmetric epoxidations, cyclopropanation and conjugate reductions.[8,12]



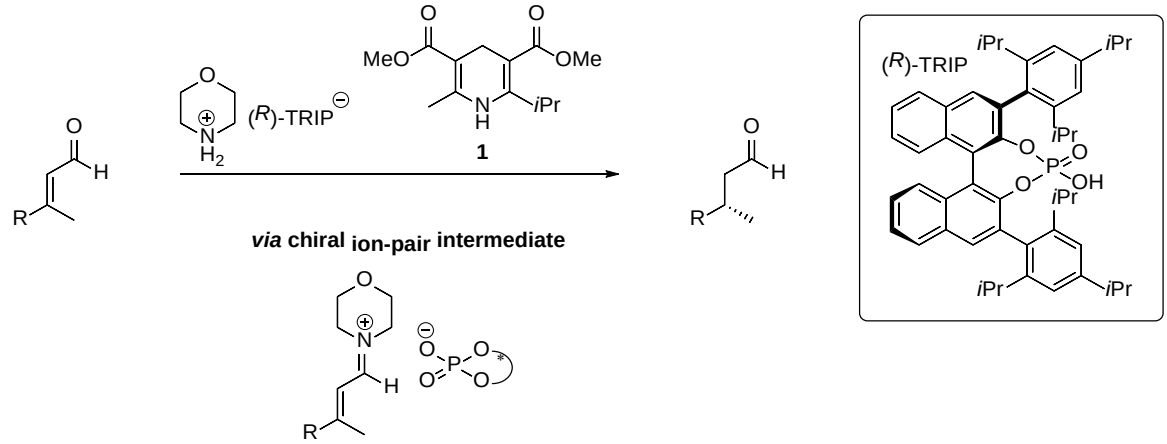
Scheme 3: LUMO activation mode in iminium catalysis.

In nature, many enzymes use hydrogen-bonding interactions between the amino acids residues of the protein and the substrate for biocatalytic transformations.[13] Inspired by these observations, small molecules containing hydrogen bond donators such as urea, thiourea and squaramides were developed as catalyst for asymmetric organocatalysis. These H-bond donors can interact with the substrate *via* non-covalent dualistic H-bond interactions and increase its reactivity by lowering the LUMO energy. Moreover, H-bond interactions may help in the orientation of the substrate or can stabilize the transition state to have an impact on the stereoselectivity of the reaction. Since this concept has proved to be useful for many organocatalytic transformations,[14] bifunctional organocatalysts are often developed. For example, the Michael addition of malonates to nitroolefins is catalyzed by a thiourea containing tertiary amine catalyst (Scheme 4).[15] The nitroolefin is activated by H-bonding and the tertiary-amine group is acting as a Brønsted base.



Scheme 4: Bifunctional catalyst for the Michael addition of malonates to nitroolefins.

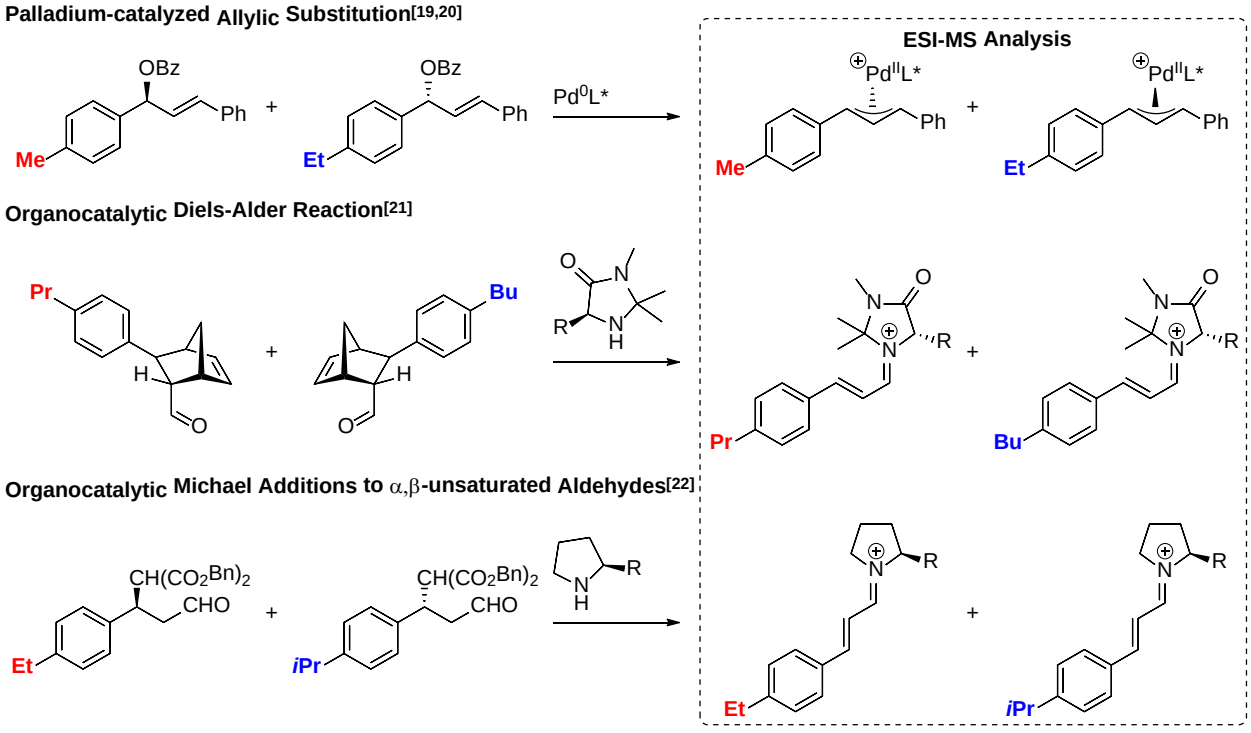
When enantioselectivity is induced by a chiral ion-pair intermediate, this process is defined as asymmetric counterion-directed catalysis (ACDC). In this ion pair intermediate, the cationic species is non-covalently bound to a chiral anion. In the approach of Jacobsen, thiourea groups are used for anion-binding and this concept was successfully applied for a wide variety of chemical transformations.[14] In 2006, Benjamin List introduced the usage of chiral phosphoric acids in ACDC.[16] One example is the asymmetric transfer hydrogenation of unsaturated aldehydes. In this protocol, the aldehyde is transferred into a reactive iminium ion intermediate which can then form a chiral ion pair with the (*R*)-TRIP anion. In this chiral environment, the hydride transfer from NADH derivative **1** to unsaturated iminium ion intermediate can occur enantioselectively to form the corresponding chiral saturated aldehydes (Scheme 5).[16]



Scheme 5: Asymmetric counterion-directed catalysis.

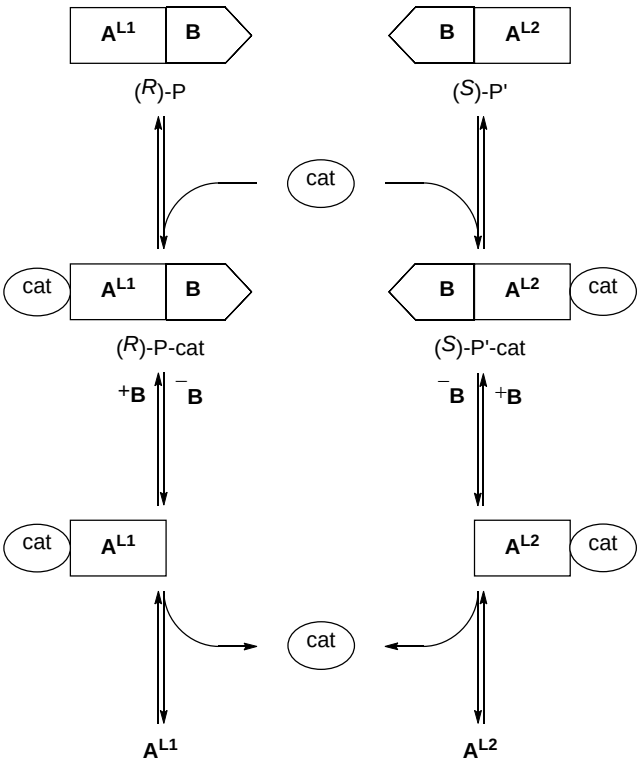
1.2 Back Reaction Screening of Quasi-Enantiomeric Products

The ESI-MS screening, which was originally developed in our laboratory for the evaluation of chiral catalysts and catalyst mixtures, is based on monitoring the back reaction of mass-labelled quasi-enantiomeric products by electrospray ionization mass spectrometry (ESI-MS). In this way, the intrinsic enantioselectivity of a chiral catalyst can be determined directly by quantification of catalytically relevant intermediates. In contrast to conventional screening methods based on product analysis, the results are not affected by catalytically active impurities or a non-catalytic background reaction. Moreover, mixtures of chiral catalysts with different molecular masses can be screened simultaneously, which is not possible by product analysis. By multi-catalyst screening of combinatorial catalyst libraries, catalyst discovery and optimization can be considerably accelerated. This screening protocol is fast and operationally simple, as it does not require any work-up or purification steps.[17,18] Although application of this method is limited to reactions that show some degree of reversibility and proceed *via* catalytic intermediates that are detectable by ESI-MS, screening protocols have been developed for many synthetically useful reactions in recent years. Examples are Pd-catalyzed allylic substitutions,[19,20] Cu- and organocatalyzed Diels-Alder reactions,[21] organocatalytic aldol and Michael reactions[22] (Scheme 6).



Scheme 6: Overview of previous screening protocols by the Pfaltz group.

The basic concept of our back reaction screening method is displayed in Scheme 7. Starting from a 1:1 mixture of mass-labelled quasi-enantiomeric reaction products (*R*)-**P** and (*S*)-**P'** a back reaction leading to components $\mathbf{A}^{L1}$, $\mathbf{A}^{L2}$ and **B** is induced by addition of a chiral catalyst. Shortly after, a sample is taken and analyzed by ESI-MS. From the signals of the mass-labelled fragment-catalyst adducts $\mathbf{A}^{L1}$-cat and $\mathbf{A}^{L2}$-cat their ratio can be determined, which is equivalent to the ratio of the rates of conversion of (*R*)-**P** and (*S*)-**P'** to $\mathbf{A}^{L1}$ and $\mathbf{A}^{L2}$. Although the concentration of catalytic intermediates is generally very low, charged signals can be reliably detected and the relative intensities quantified with sufficient accuracy, due to the high sensitivity of ESI-MS. Because the steps interconnecting the reactants $\mathbf{A}^{L1}$ and $\mathbf{A}^{L2}$ with products (*R*)-**P** and (*S*)-**P'** are reversible, sampling has to be done in the initial phase of the reaction (typically after ≤1 turnover), in order to avoid problems caused by racemization of (*R*)-**P** and (*S*)-**P**.



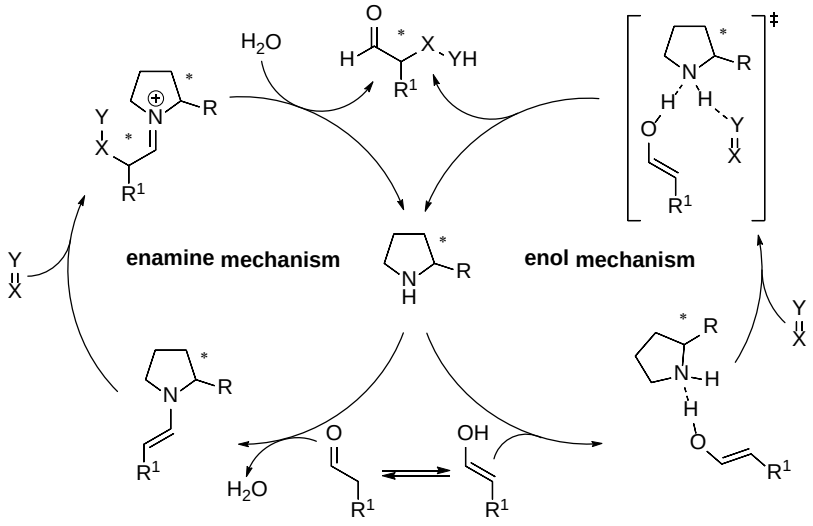
Scheme 7: Basic principle of back reaction screening.

If the step, in which the substrate-catalyst complex **A**-cat reacts with **B**, is rate-determining in the forward reaction, the enantioselectivity of the overall reaction will be determined by the energy difference of the transition states of this step leading to (*R*)- and (*S*)-**P**-cat. In this case, the same transition states also control the enantioselectivity of the back reaction, according to the principle

of microscopic reversibility. Under this kinetic regime, formation of the catalyst-product adducts (*R*)-**P**-cat and (*S*)-**P'**-cat from (*R*)-**P** and (*S*)-**P'** in the back reaction is fast and reversible, followed by a slow rate-determining bond cleavage leading to $\mathbf{A}^{L1}$-cat and $\mathbf{A}^{L2}$-cat (Curtin-Hammet conditions). Consequently, the ratio $\mathbf{A}^{L1}$-cat/$\mathbf{A}^{L2}$-cat determined by back reaction screening should be identical to the enantiomeric ratio (*R*)-**P**/(*S*)-**P** observed for the preparative reaction in the forward direction.

A close match between the enantiomeric ratio produced in the forward reaction and the ratio $\mathbf{A}^{L1}$-cat/$\mathbf{A}^{L2}$-cat measured for the back reaction also provides strong evidence that the substrate-catalyst complex **A**-cat is involved in the rate- and enantioselectivity-determining step. If the selectivities of the forward and back reaction differ, this would imply that a different step in the catalytic cycle is responsible for the observed enantioselectivity. In this way, mechanistic insights into the enantioselective step of a catalytic process can be obtained, which are not directly available by other methods.

As an example, this methodology was used for mechanistic investigations of the conjugate addition of aldehydes to nitroolefins.[23] The most widely accepted mechanism for reactions of this type involves an enamine as the central intermediate which undergoes α-functionalization with the electrophile (Scheme 8, left cycle). As an alternative, a catalytic cycle has been proposed that proceeds *via* an enol that interacts with the catalyst through hydrogen bonding (Scheme 8, right cycle). The back reaction screening approach helped to resolve this controversy based on the detection of the ratio of quasi-enantiomeric enamine intermediates and by comparison of the obtained ratios of the with the enantiomeric ratios obtained in the forward reaction.



Scheme 8: Enamine versus enol mechanism.

1.3 Thesis Outline

The aim of the research project described in chapter 2 of this thesis was to develop an efficient bifunctional phosphine catalyst that outperforms literature-known catalysts in the Morita-Baylis-Hillman reaction of methyl acrylate with aldehydes. For the evaluation of the chiral organocatalysts a mass spectrometric back reaction screening protocol of quasi-enantiomeric substrates was applied. Based on this technique, a multi-catalyst screening was developed which allowed the simultaneous determination of the intrinsic enantioselectivities of phosphines in a crude catalyst mixture. Finally, based on the data from the back reaction screening in hand together with kinetic measurements, the rate- and enantioselectivity-determining step in the catalytic cycle were identified.

In chapter 3, the synthesis of new morpholine- and piperidine-based triazolium salts and their use as NHC catalysts for the asymmetric cross-benzoin reaction is discussed. In particular, the cross-benzoin reaction between benzaldehyde and hydrocinnamaldehyde was studied. The aim of this project was to design a catalyst that could produce the desired cross-benzoin product with high enantiomeric excess and chemoselectivity.

Chapter 4 deals with the development of chiral NHC-phosphine ligands for the asymmetric iridium-catalyzed hydrogenation of different model substrates. This project was inspired by the previous work of Nanchen, a former member of the Pfaltz group. He synthesized a small library of different NHC-phosphine ligands for the hydrogenation of various substrates, however only moderate results in terms of reactivity and enantioselectivity were achieved. The aim of this project was to investigate NHC-based catalysts with conformationally more rigid structures.

Chapter 2

Asymmetric Morita-Baylis-Hillman Reaction

2.1 Introduction

2.1.1 Multifunctional Chiral Phosphine Organocatalysts

Despite the discoveries of Price[24], Rauhut and Currier[25] and Morita[26] in the 1960s using nucleophilic phosphines as catalysts for Michael-type addition reactions, no further applications were published until the mid-1990s, when the great potential of phosphines was rediscovered by Lu[27] for [3 + 2] annulation reactions. Since then, the research field of phosphine-catalyzed reactions has massively grown and for many asymmetric reactions chiral phosphine-based catalysts were developed.[28] Compared to amine-based organocatalysts, the phosphorus center has several advantages for asymmetric catalysis. Phosphines are less basic and more nucleophilic compared to amines with similar substitution patterns at the heteroatom center.[29,30] The most commonly used lead structure of chiral phosphines for asymmetric catalysis is presented in Figure 1. Many bifunctional phosphines are derived from commercially available amino acids, which facilitate the synthesis of enantiopure organocatalysts. The modular nature of the lead structure is ideal for systematic structural optimization. This multifunctional system has a nucleophilic phosphorus center which can react with various electrophiles to form nucleophilic zwitterionic intermediates. Moreover, a hydrogen-bonding unit (typically a thiourea moiety) is attached to the chiral backbone and can interact with the substrate or the zwitterionic intermediate *via* hydrogen-bonding interactions and these non-covalent interactions can increase the reactivity or selectivity of the reaction. By changing the residue of the chiral backbone the effect of steric hindrance can be investigated.[28]

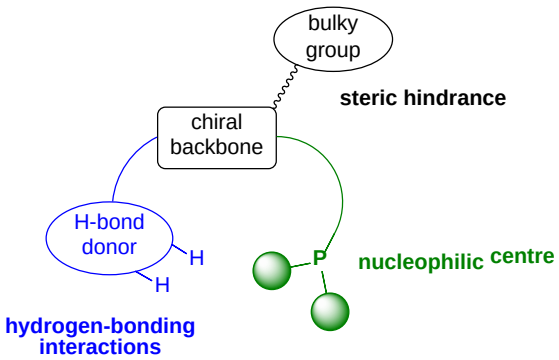
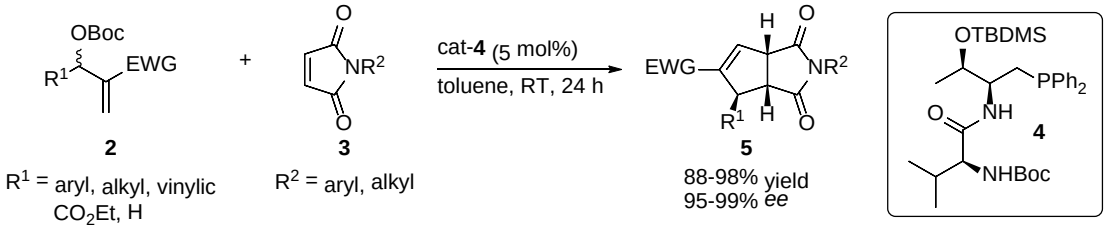


Figure 1: General structure of a multifunctional chiral phosphine catalyst.

A potential application area of bifunctional phosphines is the enantioselective annulation reaction of allenes and Michael acceptors to form chiral cyclic molecules.[31] Another example is the formation of chiral bicyclic imides **5** *via* [3 + 2] annulation of MBH carbonates **2** and maleimides **3** catalyzed by functionalized phosphine **4** (Scheme 9).[32]



Scheme 9: [3 + 2] annulation of MBH carbonates.

In the first step of the proposed mechanism of the [3 + 2] annulation of MBH carbonates (Figure 2), the MBH adduct undergoes a nucleophilic attack by the phosphine catalyst to form a cationic intermediate after decarboxylation. At this point proton α to the phosphorus center is deprotonated to form a ylide adduct which attacks the γ-position of maleimide. In the last steps, cyclization of the enolate intermediate followed by β-elimination of the catalyst generates the final product.

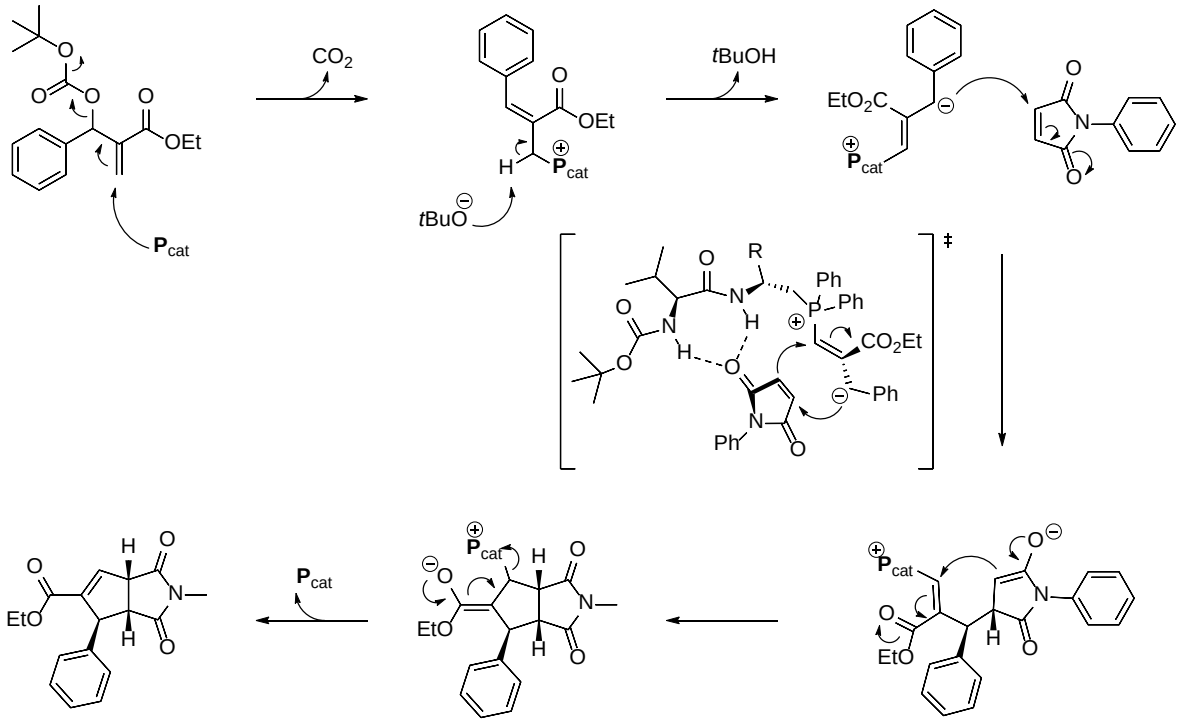
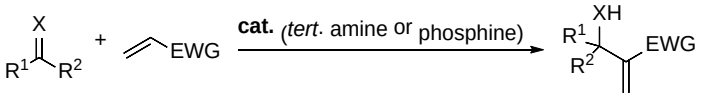


Figure 2: Proposed mechanism of the [3 + 2] annulation of MBH carbonates by Lu.[32]

2.1.2 Morita-Baylis-Hillman Reaction

The Morita-Baylis-Hillman (MBH) reaction is a powerful method for the atom-economical formation of a carbon-carbon bond between the α position of a Michael acceptor and an electrophile (Scheme 10). In 1968, the first phosphine-catalyzed addition of acrylates to aldehydes yielding functionalized allylic alcohols was published by Morita.[26] In their approach, they used tricyclohexylphosphine as a catalyst for the formation of MBH-adducts between methyl acrylate or acrylonitrile and different aldehydes. Four years later the tertiary amine-catalyzed version of this transformation was described in a patent by Baylis and Hillman.[33]



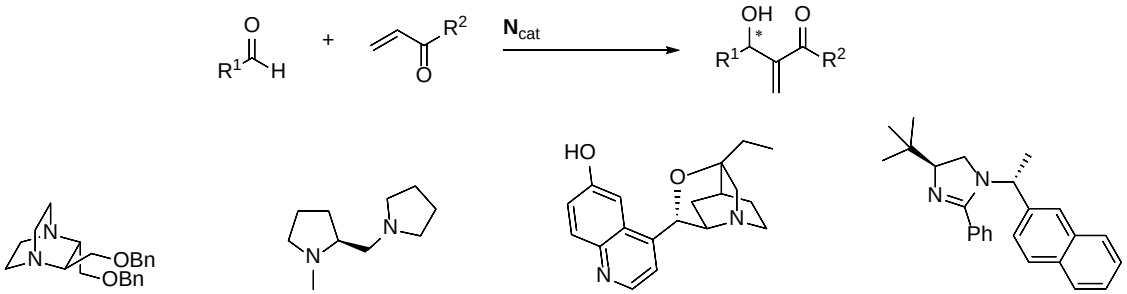
R^1 = aryl, alkyl, hetereoaryl
R^2 = H, CO_2R, alkyl
X = O, NCO_2R^3, NSO_2Ar
EWG = COR^3, CHO, CN, CO_2R^3, $PO(OEt)_2$, SO_2Ph

Scheme 10: General scheme for the Morita-Baylis-Hillman reaction.

In the last two decades, many variations of the MBH reaction were developed such as the *aza*-MBH reaction,[34,35] using imines as electrophiles or the intramolecular MBH reaction.[36,37] This reaction has several advantages compared to metal-catalyzed transformations. The use of a nucleophilic organocatalyst instead of metal-based catalyst is advantageous for the synthesis of pharmaceutical compounds in industry by avoiding metal impurities in products. Furthermore, this organocatalytic transformation is performed under mild reaction conditions at room temperature and does not need any special experimental setup.[38] Moreover a huge variety of different starting materials are commercially available, allowing for broad substrate scope. Finally, resulting MBH products are densely functionalized building blocks, which can be easily modified in various ways to form complex molecules starting from simple educts.[37,39–41]

2.1.3 Asymmetric Morita-Baylis-Hillman Reaction

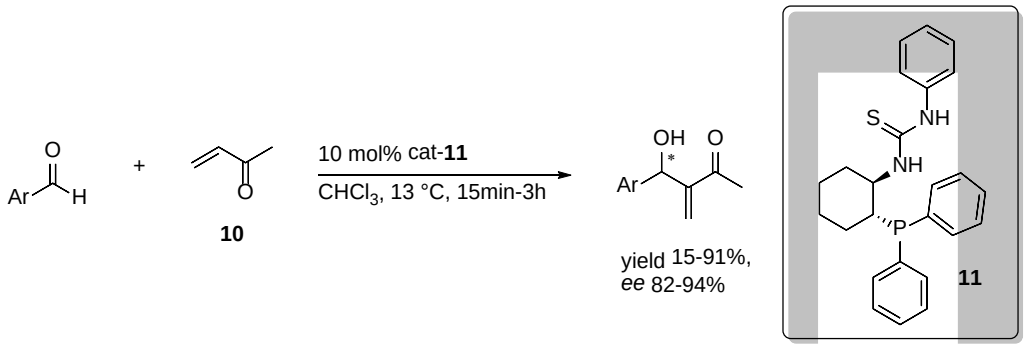
In the last two decades many chiral tertiary-amine-based catalysts have been reported for the MBH reaction, however their scope is generally limited (representative examples in Scheme 11). In 1995, Hirama and coworkers introduced a chiral 2,3-disubstituted 1,4-diazabicyclo[2.2.2]octane catalyst **6** for the asymmetric Baylis-Hillman (BH) reaction between aromatic aldehydes and methyl vinyl ketones or methyl acrylates to form the resulting MBH adducts with low to moderate yield and very low enantioselectivity. Moreover, the desired product was only observed under high-pressure.[42] Nine years later, Hayashi developed the chiral diamine catalyst **7** which forms the corresponding BH products with moderate to excellent yield and moderate to good enantioselectivity.[43] The catalytic potential of β-isocupreidine **8** as BH catalyst was investigated by Hatakeyama in 2006. Good yield and excellent selectivities were achieved when hexafluoroisopropyl acrylate was used as a Michael acceptor. Unfortunately, for all other acrylates only poor yield and enantioselectivities were detected.[44] In 2011, the Tan group from Singapore published a new approach using chiral imidazolines as organocatalysts. In this work catalyst **9** was used for the BH reaction between different aromatic aldehydes and vinyl ketones or acrylates. Using a high catalyst loading and after long reaction times, the resulting BH adducts were formed with moderate to good yield and moderate selectivity.[45]



6[42]	**7**[43]	**8**[44]	**9**[45]
with 15 mol% cat-**6**, THF, 30 °C, 10 kBar, 17-23 h	with 30 mol% cat-**7**, EtOH, 0 °C, 2-6 d	with 10 mol% cat-**8**, DMF, −55 °C, 1-120 h	with 50 mol% cat-**9**, toluene, RT, 3-11 d
R^1 = aryl, R^2 = Me or OMe	R^1 = aryl, R^2 = Me	R^1 = aryl or alkyl, R^2 = $OCH(CF_3)_2$	R^1 = aryl, R^2 = alkyl or OMe
yield 14-68%, *ee* 12-15%	yield 40-96%, *ee* 44-75%	yield 23-82%, *ee* 1-99%	yield 59-84%, *ee* 47-69%

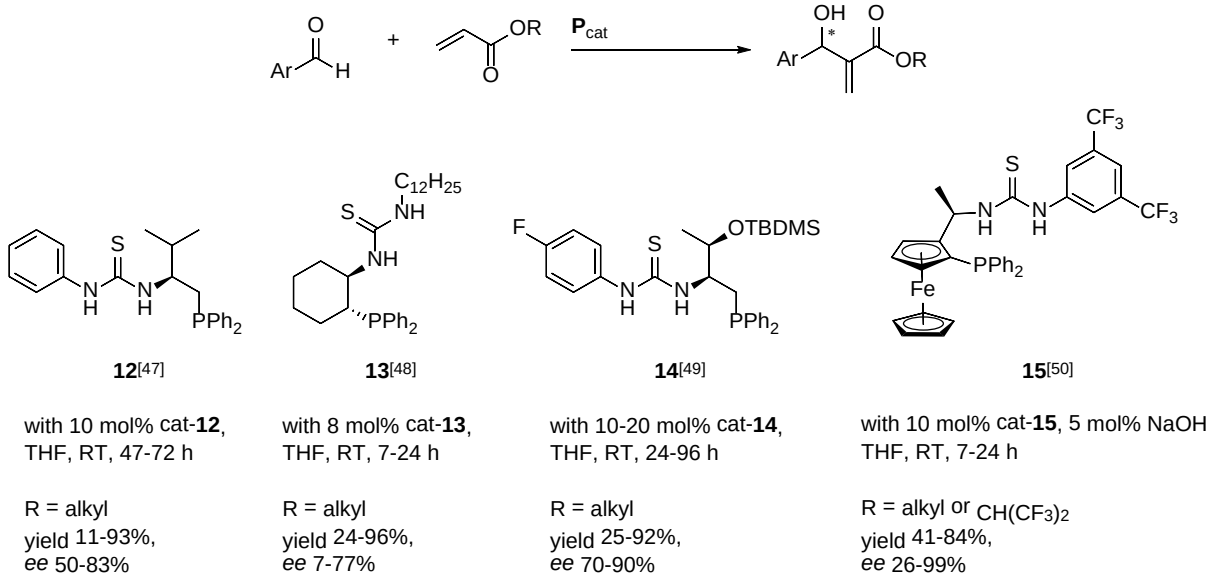
Scheme 11: Overview of literature-known chiral tertiary-amine-based organocatalyst.

In 2008, Wu and coworkers published the first asymmetric MBH reaction between aryl aldehydes and methyl vinyl ketone **10** using a chiral phosphine-based catalyst **11** (Scheme 12). Compared to the previous work using amine-based organocatalysts they were able to isolate the resulting products with higher yield (up to 91%) and excellent enantioselectivity (up to 94%) after a shorter reaction time (three hours).[46]



Scheme 12: Asymmetric MBH reaction of aryl aldehydes and vinyl ketone catalyzed by bifunctional phosphine **11**.

Inspired by these results many groups began to develop new chiral phosphine-based organocatalysts for the more challenging MBH reaction between simple acrylic esters and various aldehydes (representative examples in Scheme 13). The valine-derived catalyst **12** was able to perform the MBH reaction between acrylates and electron-deficient aromatic aldehydes in good yield and selectivities.[47] With the cyclic catalyst **13** slightly better yield and similar enantioselectivities were observed for the MBH reaction.[48] In 2011, Lu introduced a threonine-derived bifunctional organocatalyst **14** for the asymmetric MBH reaction between a wide range of aryl aldehydes and methyl acrylate to form the resulting adducts with moderate to high yield and good to very good enantioselectivity.[49] Excellent yield and enantioselectivities were observed when a ferrocene-derived catalyst **15** was tested for the MBH reaction but unfortunately only when hexafluoroisopropyl acrylate was used was Michael acceptor.[50] For all literature-known catalytic systems benzaldehyde, halogenated aromatic aldehydes or aliphatic aldehydes are very challenging substrates.



12[47] **13**[48] **14**[49] **15**[50]

with 10 mol% cat-**12**, THF, RT, 47-72 h	with 8 mol% cat-**13**, THF, RT, 7-24 h	with 10-20 mol% cat-**14**, THF, RT, 24-96 h	with 10 mol% cat-**15**, 5 mol% NaOH THF, RT, 7-24 h
R = alkyl yield 11-93%, *ee* 50-83%	R = alkyl yield 24-96%, *ee* 7-77%	R = alkyl yield 25-92%, *ee* 70-90%	R = alkyl or $CH(CF_3)_2$ yield 41-84%, *ee* 26-99%

Scheme 13: Overview of literature-known chiral phosphine-based organocatalysts.

However, although many chiral catalysts have been reported, their scope is generally limited. Especially for MBH reactions of simple acrylic esters with aldehydes, more efficient catalysts with broader application range are needed.

2.1.4 Mechanistic Investigations

In 1983, the first mechanistic proposal was reported by Hoffmann and coworkers,[51] which a few years later was supported by kinetic investigations of Hill and Isaacs (Figure 1).[52] In the catalytic cycle, the Michael acceptor undergoes first a reversible nucleophilic attack by the amine-catalyst and the resulting zwitterionic intermediate **A** is formed. Subsequently, the carbon-carbon bond between the α position of the DABCO-acrylonitrile adduct and the aldehyde is formed by an aldol type reaction. After an intramolecular 1,3 proton shift followed by catalyst elimination, the BH product is generated. In this complex catalytic cycle either the aldol step or the proton transfer can be the rate-determining step (RDS). As a model system Hill and Isaacs investigated the kinetics of the DABCO catalyzed BH reaction between acetaldehyde and acrylonitrile and the results showed third-order kinetics (rate = *k*[MeCHO][acrylonitrile][DABCO]). Based on the comparison of the experimental results between acrylonitrile and the α-deuterated acrylonitrile a low kinetic isotopic effect (KIE) was detected and therefore they suggested that the aldol step is the RDS.[52]

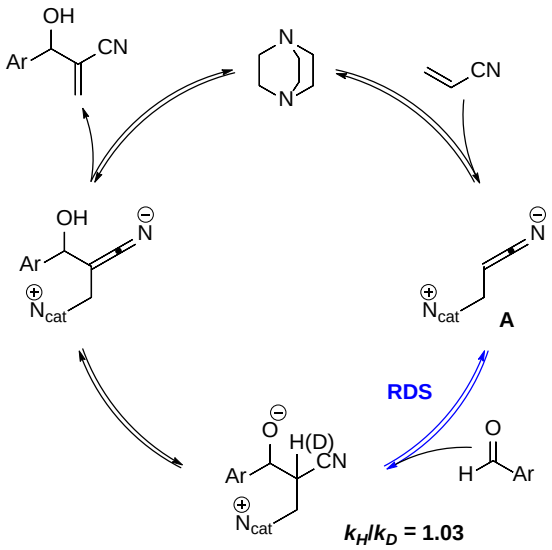


Figure 3: Mechanism proposed by Hofmann.[51]

Because of the complexity of the catalytic cycle various research groups became interested in clarifying the BH mechanism. Recent mechanistic studies by Singleton have demonstrated that at current computational methods are unable to cope with the complex multi-step catalytic cycle of MBH reactions and, therefore, fail to produce reliable results.[53]

In 2005, Aggarwal and Lloyd-Jones reevaluated the mechanism using kinetic studies. In their approach, competitions experiments between α-deuterated ethyl acrylate and ethyl acrylate were performed to determine KIEs. Based on these results they proposed that in the beginning of the reaction (< 20% conversion) the proton transfer is the rate-limiting step. Afterwards the aldol step becomes rate-limiting because the proton transfer step is accelerated by autocatalysis of the product (Figure 4). For the proton shift, a six-membered transition state was predicted in which the alkoxide is protonated by the alcohol intermediate and at the same time the α-methine is deprotonated. An intramolecular proton transfer is disfavored because the proton shift would proceed *via* a strained four membered transitions state.[54–56]

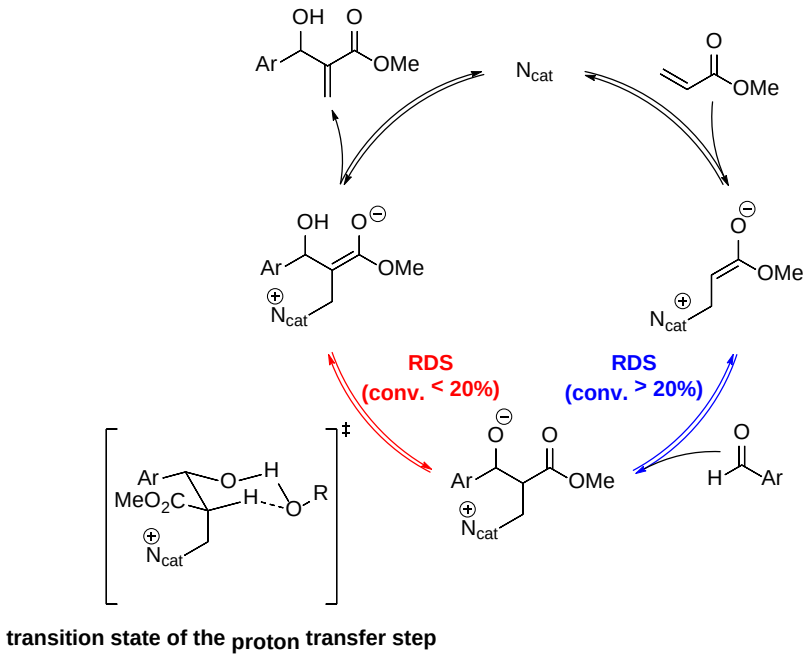


Figure 4: Mechanism proposed by Aggarwal.[54-56]

A different mechanism was postulated by McQuade and coworkers (Figure 5). Under the investigated reaction conditions, they observed that the reaction is second order in aldehyde. Due to this result two aldehyde molecules must be present in the rate-limiting step and therefore the aldol step cannot be the RDS. In the proposed catalytic cycle, the alkoxide intermediate is reacting with a second equivalent of aldehyde to form a hemiacetal intermediate followed by a rate-limiting proton shift. This proton transfer is mediated by the alkoxide group *via* a six-membered transition state. In a further experiment using methyl α-^{2}H acrylate, a primary KIE (KIE = 5.2 in DMSO) was observed. Thins findings supports their proposed mechanism, with the C-H cleavage being involved in the RDS.[57]

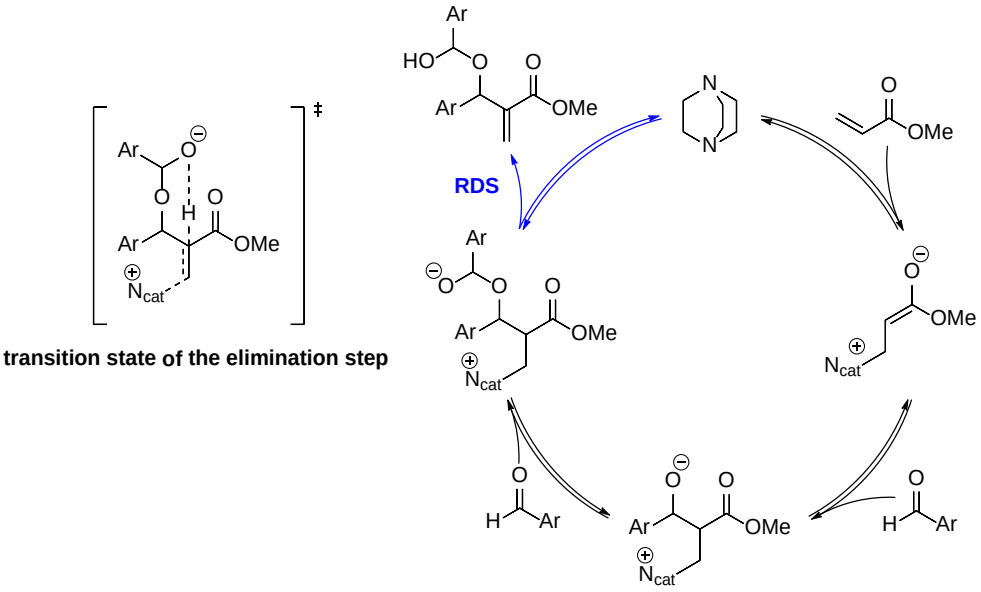


Figure 5: Mechanism proposed by McQuade.[57]

For phosphine-based catalysts only one computational study was reported, which predicted the proton transfer step to be rate-determining. The total free energy profile of the trimethylphosphine catalyzed MBH reaction between ethanal and acrylonitrile in CH_2Cl_2 was calculated using DFT methods (Figure 6).[58]

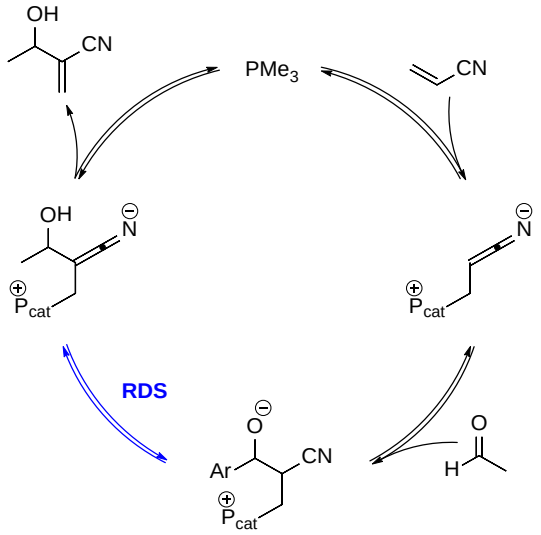


Figure 6: Proposed catalytic cycle of the MBH calculated by DFT calculations.[58]

2.2 Catalyst Synthesis

Based on the results obtained during my master thesis and various studies reported in the literature (see chapter 2.1.2), we became interested in the use of bifunctional phosphines as suitable catalysts for the asymmetric MBH reaction. Starting point was the lead structure shown in Figure 7 that was patterned after the catalysts developed by Wu[47] and Lu[49]. Due to the modular nature it seemed to be ideal to further catalyst optimization studies. The core structure can be varied at several positions to investigate the effect for each unit in terms of reactivity or enantioselectivity. For example, starting from different enantiopure amino acids, the influence of the chiral backbone can be investigated. Moreover, the effect of the phosphine residue can be studied by using various phosphine precursors in the catalyst synthesis. Also the hydrogen-bonding subunit can be diversified to see how different functional groups such as thioureas or squaramides influence the stereoselectivity of the MBH reaction. Furthermore, the pK_a value of the two acidic N-H bonds of the bifunctional subunit can be tuned and therefore the hydrogen-bond interaction with the substrate can be optimized simply by changing the residue at the *N*-position of the H-bonding moiety.

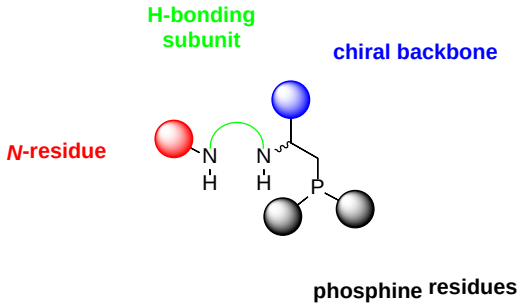
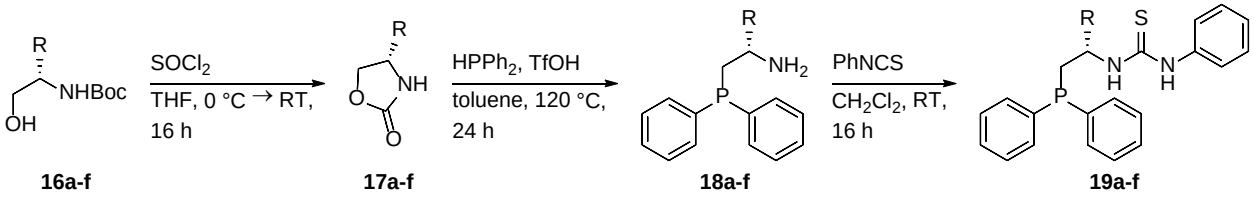


Figure 7: Catalyst lead structure for the asymmetric MBH reaction.

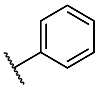
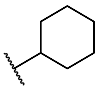
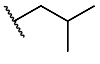
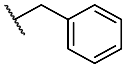
2.2.1 Synthesis of 1st Generation Catalysts

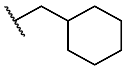
The first generation catalyst contains a thiourea group as an additional functional group. All amino phosphine precursors were derived from commercially available *N*-Boc-protected amino alcohols. For the investigation of the effect of the chiral backbone, different phenyl thiourea-based catalysts **19a-f** were synthesized according to a slightly modified literature-known three-step procedure developed by Wu (Table 1).[60] In the first step, thionyl chloride was allowed to react with the hydroxy group of substrates **16a-f** to yield the alkyl chloride intermediate, which was subsequently cyclized by intramolecular nucleophilic attack of the amine group. The Boc group was deprotected to give the corresponding 2-oxazolidinones **17a-f** in good to excellent yield. In the next step, the cyclic structure of the oxazolidione intermediate **17** was opened under acidic conditions by nucleophilic attack of diphenylphosphide. This gave amino phosphines **18a-f** in moderate to good yield. In the last step of the synthetic sequence, the amine group in **18a-f** was coupled with phenyl isothiocyanate to afford the *N*-phenyl thiourea-based organocatalysts **19a-f** in high yield.

Table 1: Synthesis of *N*-phenyl thiourea-based organocatalysts **19a-f** derived from various Boc-amino alcohols **16a-f**.



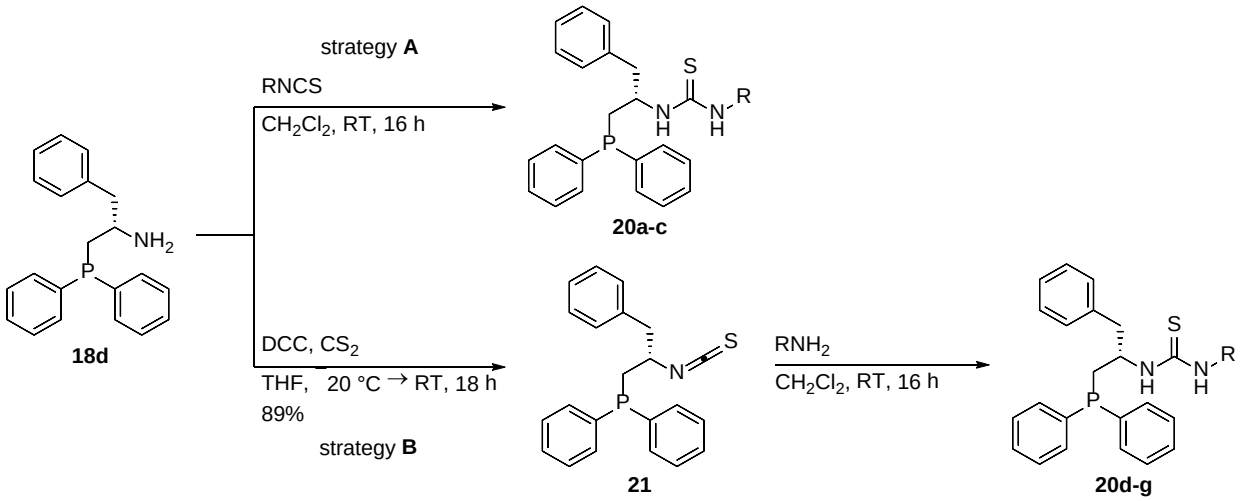
16a-f **17a-f** **18a-f** **19a-f**

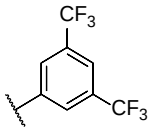
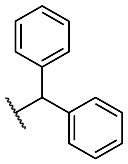
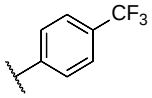
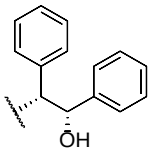
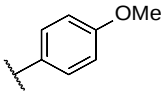
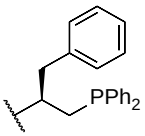
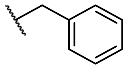
entry	R	oxazolidinone 17 (yield in %)	amino phosphine 18 (yield in %)	catalyst 19 (yield in %)
1		**17a** (94)	**18a** (69)	**19a** (90)
2		**17b** (85)	**18b** (54)	**19b** (99)
3		**17c** (90)	**18c** (50)	**19c** (92)
4		**17d** (95)	**18d** (89)	**19d** (96)

5		**17e** (85)	**18e** (62)	**19e** (71)
6		**17f** (90)	**18f** (70)	**19f** (70)

To study the effect of the *N*-residue of the thiourea-group, different derivatives of the phenylalanine-derived amino phosphine **18d** were synthesized. For the synthesis of the resulting bifunctional phosphines two different strategies were pursued. In strategy **A**, the amine group in **18d** was coupled with commercially available *N*-aryl isothiourea precursors. This procedure was applied to the synthesis of catalyst **20a-c** and the resulting products were isolated in high yield (Table 2, entries 1-3). The thiourea products derived from non-commercially available isothiourea precursors were synthesized based on a different approach (strategy **B**). In this synthetic route, originally developed by Shi,[61] the amine group in **18d** was converted to an isothiocyanate group. Subsequent attack of carbon disulfide by the amine group gives a dithiocarbamic acid intermediate which undergoes decomposition to the isothiocyanato **21** mediated by *N*,*N*'-dicyclohexyl-carbodiimide (DCC). Afterwards, the intermediate **21** was treated with various amines to provide the resulting organocatalysts **20d-g** in excellent yield (entries 4-7). This advantageous strategy allows the construction of diverse catalysts through the late stage reaction with structurally diverse and readily available primary amines.

Table 2: Synthesis of thiourea-based organocatalysts **20a-g** derived from amino phosphine **18d**.

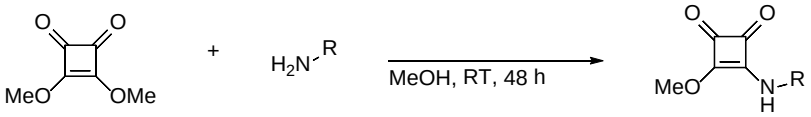


entry	strategy	R	catalyst 20 (yield in %)	entry	strategy	R	catalyst 20 (yield in %)
1	**A**		**20a** (85)	4	**B**		**20d** (92)
2	**A**		**20b** (92)	5	**B**		**20e** (96)
3	**A**		**20c** (83)	6	**B**		**20f** (94)
				7	**B**		**20g** (99)

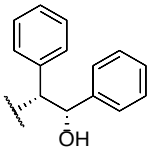
2.2.2 Synthesis of 2nd Generation Catalysts

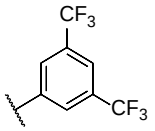
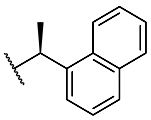
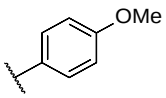
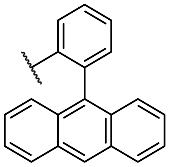
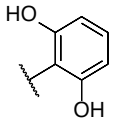
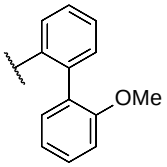
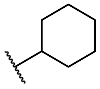
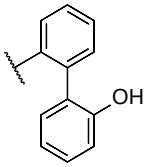
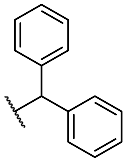
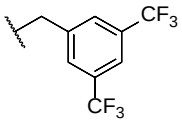
The key element in the lead structure of the second generation catalyst is a squaramide group. Compared to thioureas, squaramides are more acidic and form stronger hydrogen-bonding interactions.[62] Moreover, the corresponding catalysts are easily prepared starting from inexpensive dimethyl squarate **22**. Different monosubstituted squaramide precursors **24a-m** were formed by treating dimethyl squarate **22** with one equivalent of the corresponding primary amine **23a-m**. After filtration, the resulting precipitated squaramide intermediates **24a-m** were isolated in good yield, except when electron-deficient aniline **23b** was employed (Table 3, entry 1 vs entry 2). The low yield obtained for the 3,5-bis(trifluoromethyl)aniline-derived adduct **24b** can be explained by the lower nucleophilicity of the amine group which disfavors the nucleophilic substitution of the methoxy group of the squarate **22** (entry 2). In the case of the cyclohexyl amine, the high nucleophilicity tended to promote competitive disubstitution of compound **22** and the desired monosubstituted product **24e** (entry 5) was isolated in low yield. However, for squaramides-derived from benzhydrylamine **23f** (entry 6), 3,5-bis(trifluoromethyl)benzylamine **23g** (entry 7), (1*S*,2*R*)-2-amino-1,2-diphenylethanol **23h** (entry 8) or (*R*)-(+)-alpha-(1-napthyl)ethylamine **23i** (entry 9) good yield were achieved. The amine precursors **23j, 23k** and **23l** were synthesized according to a modified procedure by Huang.[63] In this two-step process, a nitro diaryl intermediate was formed by a Suzuki coupling of the corresponding aryl bromide with the boronic acid. Reduction of the nitro group by Pd/C in hydrazine afforded the crude amine which was used without further purification in the next coupling reaction with dimethyl squarate **22** to give the desired monosubstituted squaramides in good yield (entries 10-12). Lastly, ammonia was coupled with squarate **22** to yield the precursor **24m** (entry 13).

Table 3: Synthesis of squaramide precursors **24a-m**.



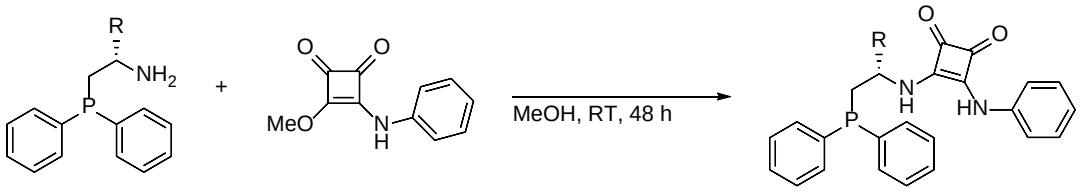
22 **23a-m** **24a-m**

entry	R	squaramide 24 (yield in %)	entry	R	squaramide 24 (yield in %)
1		**24a** (94)	8		**24h** (50)

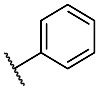
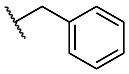
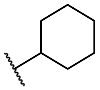
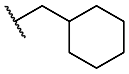
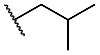
2		**24b** (17)	9		**24i** (54)
3		**24c** (79)	10		**24j** (87)
4		**24d** (75)	11		**24k** (73)
5		**24e** (12)	12		**24l** (59)
6		**24f** (63)	13	H	**24m** (56)
7		**24g** (48)			

In the last step of the catalyst synthesis, the squaramide precursor **24a** was coupled with amino phosphines **18a-f** by stirring in methanol. Fortunately, the product precipitated from the solution and therefore the catalyst was simply purified by filtration. For all amino phosphines with different chiral backbones the resulting organocatalysts **25a-f** were isolated in good yield (Table 4).

Table 4: Synthesis of squaramide-based organocatalysts **25a-f** derived from amino phosphines **18a-f**.

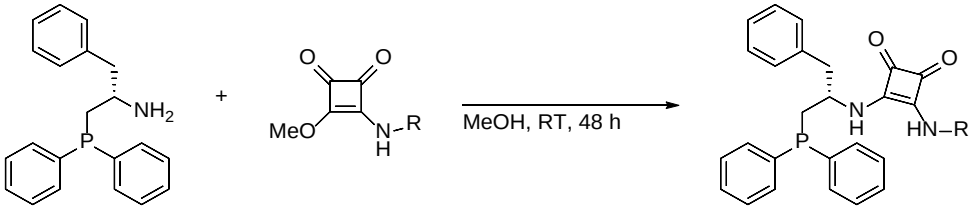


18a-f **24a** **25a-f**

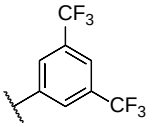
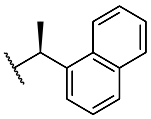
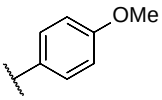
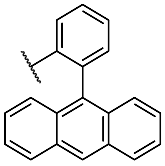
entry	R	catalyst 25 (yield in %)	entry	R	catalyst 25 (yield in %)
1		**25a** (78)	4		**25d** (85)
2		**25b** (84)	5		**25e** (79)
3		**25c** (70)	6		**25f** (66)

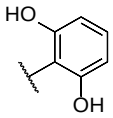
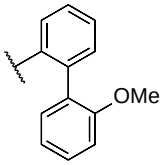
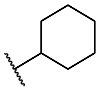
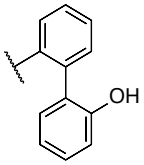
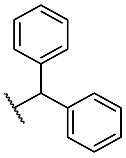
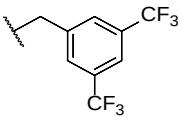
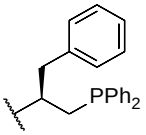
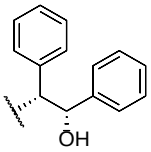
For studies regarding the effect of the *N*-residue of the squaramide unit, different precursors **24b-m** were coupled with the phenylalanine-derived amino phosphine **18d**. All bifunctional phosphines **26a-m** were isolated in moderate to excellent yield (Table 5). For the dimeric catalyst **26m** (entry 13), the synthetic protocol was slightly modified. Dimethyl squarate **22** and two equivalents of the amino phosphine **18d** were stirred to yield the dimeric phosphine catalyst **26m** after filtration.

Table 5: Synthesis of squaramide-based organocatalysts **26a-m** derived from amino phosphine **18d**.



18d **24b-m** **26a-m**

entry	R	catalyst 26 (yield in %)	entry	R	catalyst 26 (yield in %)
1		**26a** (25)	8		**26h** (91)
2		**26b** (99)	9		**26i** (54)

3		**26c** (82)	10		**26j** (33)
4		**26d** (73)	11		**26k** (77)
5		**26e** (71)	12	H	**26l** (92)
6		**26f** (98)	13		**26m** (55)
7		**26g** (82)			

2.2.3 Synthesis of 3rd Generation Catalysts

Compared to the previous catalyst generations, the third generation of bifunctional phosphines shown in Figure 8 has a more modular core structure. Four different positions can be derivatized, which permits the synthesis of a broader variety of catalysts.

This type of catalyst is derived from β-hydroxy amino acids such as threonine or phenylserine. Because of the additional hydroxy group, the synthesis of the resulting amino phosphine precursors has to been modified compared to the phosphine adducts from the first or second generation catalyst. In Figure 8 the retrosynthetic analysis of the lead structure is presented. This proposed seven-step synthesis starts from different inexpensive commercially available amino acids, which enables the formation of catalysts with various R^2 substituents. The key-intermediate is the mesyl *N*-Boc 2,2-dimethyl oxazolidine, since this adduct is the precursor to the amino phosphine synthesis. The use of different diaryl or dialkyl phosphides for the nucleophilic substitution of the mesyl intermediate gave catalysts modified at the R^4 positions. Interestingly, until today the effect of the residues on the phosphorus atom has not yet been investigated in terms of selectivity or reactivity for the MBH reaction. Further structural diversity of the catalyst can be achieved by modification of the secondary hydroxyl group with a wide variety of different silyl groups or by using different isothiourea precursors for the coupling with the amino group.

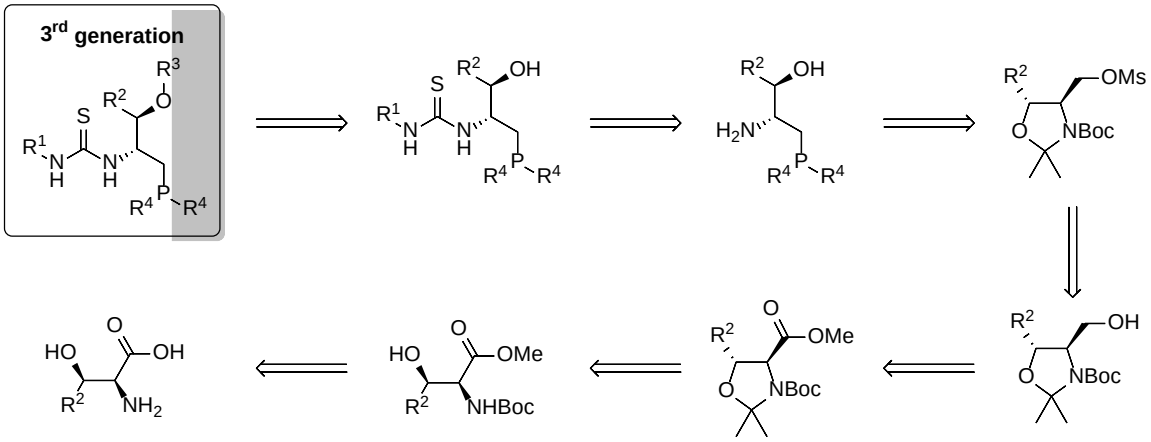
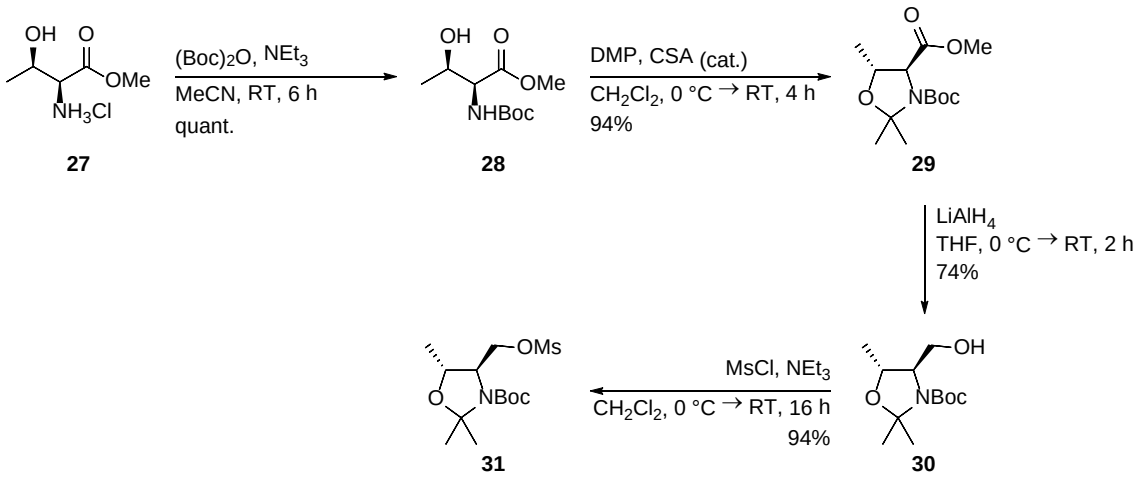


Figure 8: Retrosynthetic analysis of 3rd generation catalysts.

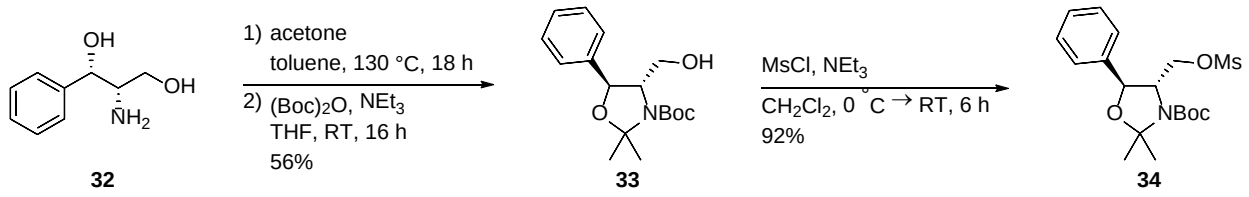
The threonine-derived mesyl oxazolidine was synthesized according to a slightly modified four-step procedure by Lu (Scheme 14).[49] *N*-Boc protected threonine methyl ester **28** was isolated in quantitative yield after treatment of the corresponding hydrochloride salt **27** with di-*tert*-butyl dicarbonate ($(Boc)_2O$) and triethylamine. Next, the Boc adduct **28** was converted to the

corresponding 2,2-dimethyl oxazolidine intermediate **29** by a camphorsulfonic acid (CSA) catalyzed cyclization reaction with 2,2-dimethoxy propane (DMP). After reduction of the ester group with lithium aluminum hydride the resulting alcohol **30** was mesylated to give mesyl oxazolidine **31** in 94% yield.



Scheme 14: Synthesis of mesyl oxazolidine **31** derived from L-threonine methyl ester hydrochloride **27**.

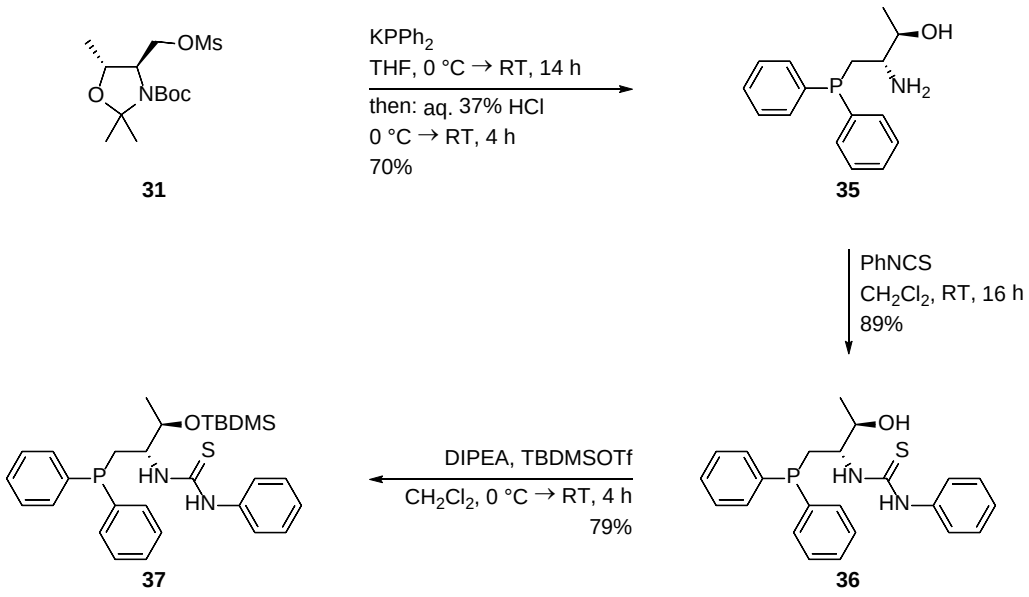
For the preparation of the phenylserine-derived mesyl oxazolidine **34** a different synthetic approach was used (Scheme 15). In the first step, (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol **32** and acetone were refluxed in a flask equipped with a Dean-Stark apparatus to form the resulting 2,2-dimethyl oxazolidine intermediate. Directly after the work-up, the free amine was Boc protected to form compound **33** in moderate yield over two steps. In the last step, the *O*-mesyl intermediate **34** was isolated in very good yield after treating alcohol adduct **33** with mesyl chloride and triethylamine.



Scheme 15: Synthesis of mesyl oxazolidine **34** derived from amino alcohol **32**.

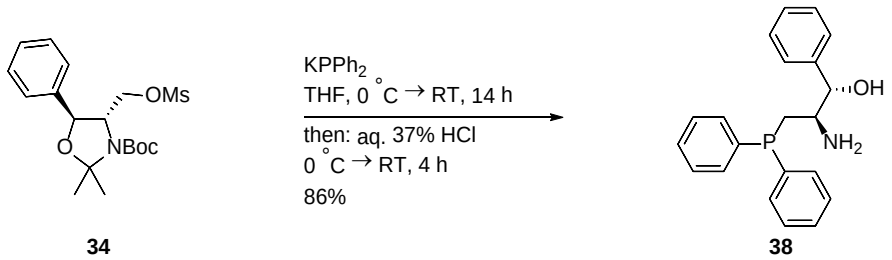
With the two mesyl intermediates **31** and **34** in hand, the nucleophilic substitution by potassium diphenylphosphide and the final steps for the catalyst synthesis were investigated. The threonine-

derived oxazolidine **31** was used for initial studies. The corresponding amino phosphine **35** was obtained in a two-step one-pot process. The mesylate group was displaced by diphenylphosphide in a nucleophilic substitution reaction. Afterwards, the *in situ* formed oxazolidine phosphine intermediate was hydrolyzed and Boc deprotected using concentrated hydrochloric acid to form the resulting amino phosphine **35** in 70% yield (Scheme 16). Then, the free amine was coupled with *N*-phenyl isothiocyanate to form thiourea intermediate **36**. After silylation of the secondary alcohol, the resulting bifunctional catalyst **37** was formed in good yield over two steps.



Scheme 16: Synthesis of threonine-derived catalyst **37**.

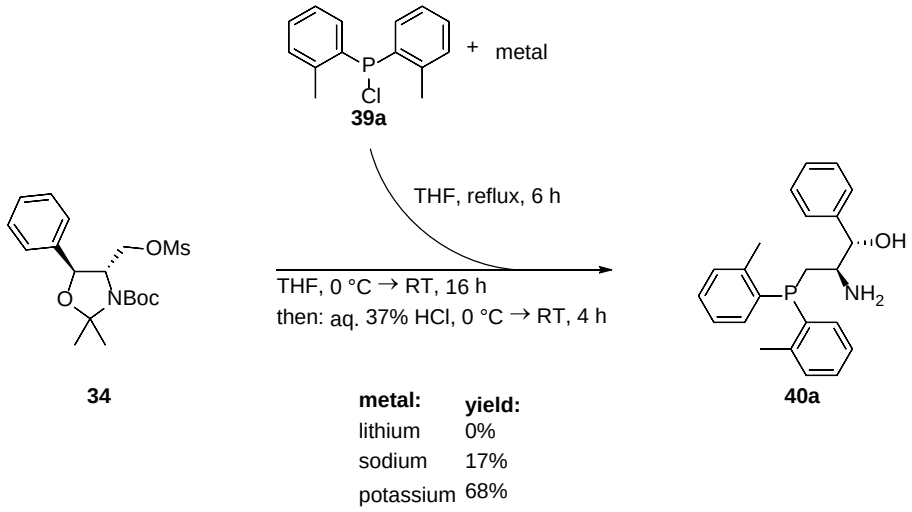
For the synthesis of the phenylserine-derived amino phosphine **38**, the same synthetic procedure as for phosphine **35** was applied. In the case of oxazolidine **34**, the resulting phosphine product **38** was isolated even in higher yield compared to the threonine-derived amino phosphine **35** (Scheme 17).



Scheme 17: Synthesis of amino phosphine **38**.

Another aim of the project was the synthesis of amino phosphines with various substituents at the phosphorus atom to investigate the effect of the phosphine residues on the MBH reaction. For this synthetic goal a new approach had to be developed using a nucleophilic phosphine source for the substitution of the mesyl group. As a test system, the nucleophilic substitution of oxazolidine **34** with chlorodi(*ortho*-tolyl)phosphine **39a** as a pronucleophile was investigated. The electrophilic diarylchlorophosphine can be reduced to the resulting nucleophilic diarylphosphide by stirring the precursor with a strong reductant such as lithium, sodium or potassium, according to literature known-procedures.[64–66] This synthetic strategy enabled the synthesis of a wide variety of phosphines because the required diarylchlorophosphines were either commercially available or could be easily prepared from the corresponding aromatic bromides.

Three different alkali di(*ortho*-tolyl)phosphides were freshly prepared by refluxing an excess of the corresponding alkali metal and **39a** in THF (Scheme 18). The formation of the resulting metal phosphide intermediate was observed by ^{31}P-NMR analysis of the crude reaction mixture and for all three metals the corresponding adduct was observed. Using lithium phosphide, the formation of the amino phosphine **40a** was not detected by either ^{31}P-NMR or ESI-MS analysis of the crude reaction mixture. When the metal was changed to sodium, conversion to the desired product **40a** was observed, and it was then isolated in low yield. The yield drastically improved using the corresponding potassium di(*ortho*-tolyl)phosphide.

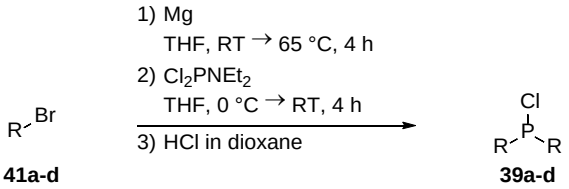


Scheme 18: Screening of different alkali metals for the nucleophilic substitution of **34** by alkali phosphide.

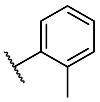
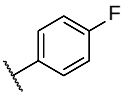
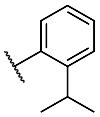
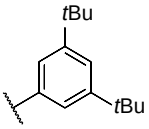
Various diarylchlorophosphines were synthesized by a slightly modified one-pot procedure of Wass.[67] *N*,*N*-Diethylphosphoramidous dichloride was treated with the Grignard reagent prepared from the corresponding aryl bromides **41a-d** to form the resulting diaryl diethylphosphoramidous

intermediate. This intermediate was converted into the corresponding diarylchlorophosphines displacing the diethylamine group by a chloride with hydrogen chloride. After purification by Kugelrohr distillation, all chlorophosphines **39a-d** were obtained in good to excellent yield (Table 6).

Table 6: Synthesis of diarylchlorophosphines **39a-d**.



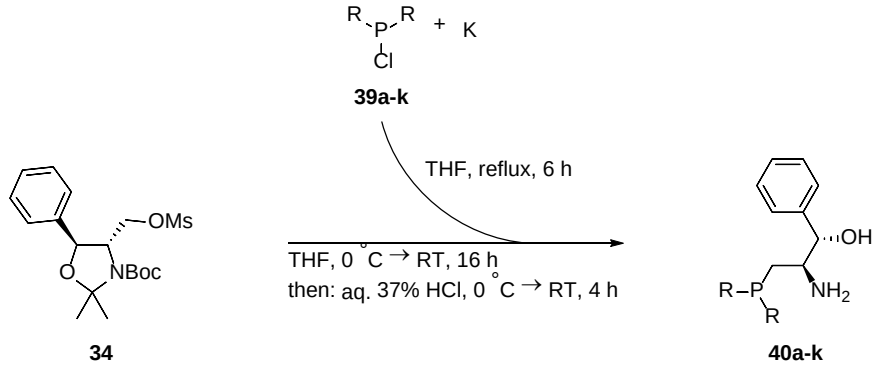
41a-d **39a-d**

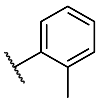
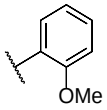
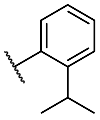
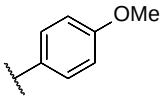
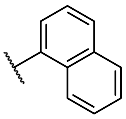
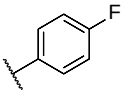
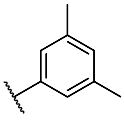
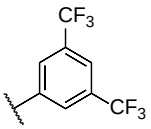
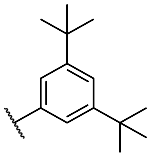
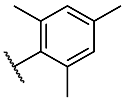
entry	R	chlorophosphine 39 (yield in %)	entry	R	chlorophosphine 39 (yield in %)
1		**39a** (84)	3		**39c** (90)
2		**39b** (52)	4		**39d** (95)

With the optimized conditions in hand, various diarylchlorophosphines **39a-d** were utilized in the synthesis of the resulting amino phosphines **40a-k** (Table 7). For all chlorophosphines with *ortho* alkyl substituted phenyl systems (entries 1-2), naphthyl groups (entry 3) or 3,5-dialkyl substituted phenyl systems (entries 4-5), the phosphide formation with potassium was detected by ^{31}P-NMR analysis of the crude reaction mixture. Then, these *in situ* generated phosphides were directly used for the nucleophilic displacement of the mesylate group in intermediate **34**. The resulting amino phosphines **40a-e** were isolated in low to good yield after hydrolysis of the oxazolidine and cleavage of the Boc group (entries 1-5). In the case of bis(2,4,6-trimethylphenyl)phosphorus chloride (entry 6) the nucleophilic phosphide intermediate was formed by potassium reduction but no conversion to the amino phosphine **40f** was detected by ESI-MS or ^{31}P-NMR analysis of the crude reaction mixture before hydrochloric acid addition. It is possible that the nucleophilic substitution of the mesylate group by the potassium dimesitylphosphide is disfavored due to the steric bulkiness of the phosphorus residues. With chlorophosphines that contain methoxy, fluorine or trifluoromethyl groups on the phenyl ring (entries 7-10) or 2-furyl groups (entry 11), the formation of the resulting amino phosphines **40j-k** was not detected. In these examples, the problematic

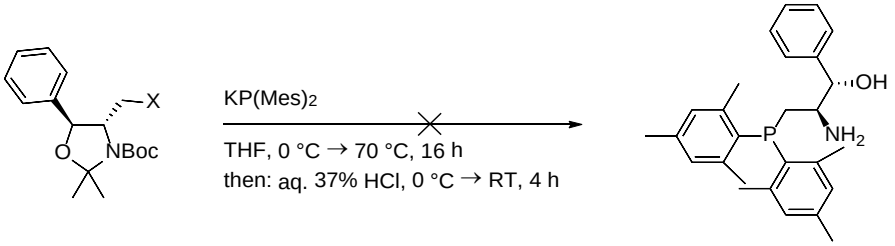
step was the formation of the potassium diarylphosphide adduct as crude ^{31}P-NMR analysis of the reduction step showed decomposition under the reaction conditions (entries 7-11).

Table 7: Synthesis of amino phosphines **40a-k**.



entry	R	amino phosphine 40 (yield in %)	entry	R	amino phosphine 40 (yield in %)
1		**40a** (68)	7		**40g** (0)
2		**40b** (38)	8		**40h** (0)
3		**40c** (79)	9		**40i** (0)
4		**40d** (32)	10		**40j** (0)
5		**40e** (29)	11		**40k** (0)
6		**40f** (0)			

The nucleophilic substitution with potassium dimesitylphosphide was further studied (Scheme 19) using different leaving groups or higher reaction temperatures. With mesyl oxazolidine **34** and an increased reaction temperature of 70 °C, formation of the resulting phosphine **40f** was not detected. Thus, oxazolidines with different leaving groups were synthesized by refluxing oxazolidine **34** with the corresponding lithium halide salt to form the resulting bromo or iodo oxazolidine intermediate **41** or **42**. Unfortunately, for both adducts conversion to the desired product **40f** was not observed using standard conditions or higher reaction temperatures. These results indicate that because of the steric hindrance of the phosphine and due to the steric environment of the oxazolidine a nucleophilic substitution with $KP(Mes)_2$ is impossible.



34 X = OMs
41 X = Br
42 X = I

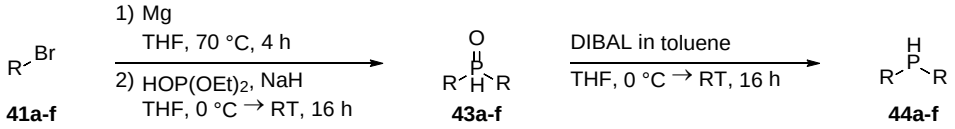
40f

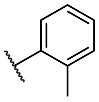
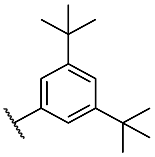
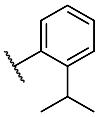
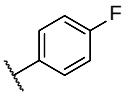
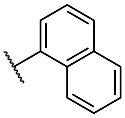
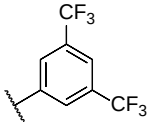
Scheme 19: Investigations towards the synthesis of amino phosphine **40f**.

Because of the limited reproducibility of the amino phosphine synthesis (yield between 15 and 79% for bisnapthylchlorophosphine-derived amino phosphine **40c**), the high costs for the corresponding chlorophosphines and the potential hazards associated with molten potassium on a large scale synthesis, a new synthetic strategy was investigated. Instead of alkali metal mediated reduction of the chlorophosphine the nucleophilic potassium phosphide intermediate can also be formed by deprotonation of the corresponding phosphine adduct with potassium hydride. The advantages of this approach are that many phosphines are commercially available and the prices per gram are lower compared to the corresponding chlorophosphines. Moreover, the phosphide is formed under milder reaction conditions which could extend the scope to methoxy- or fluorine substituted aryl phosphines.

For the synthesis of phosphines that were not commercially available, a two-step synthetic procedure developed by Busacca[68] was applied (Table 8). In the first step secondary phosphine oxides **43a-f** were synthesized by Grignard addition to diethyl phosphite. Almost all oxides **43a-f** were isolated in moderate to excellent yield after trituration of the crude reaction mixture in hexane/ether (entries 1-5). Only in the case of 3,5-bis(trifluoromethyl)phenylmagnesium bromide was product formation not detected by ^{31}P-NMR analysis of the crude mixture (entry 6). In the next step, the phosphine oxides were reduced with DIBAL to form the resulting phosphines **44a-f** with yields between 65 and 93% (entries 1-5). All phosphines were directly used in the next step after filtration of the crude reaction mixture over a pad of silica gel under inert gas.

Table 8: Synthesis of diarylphosphines **44a-f**.

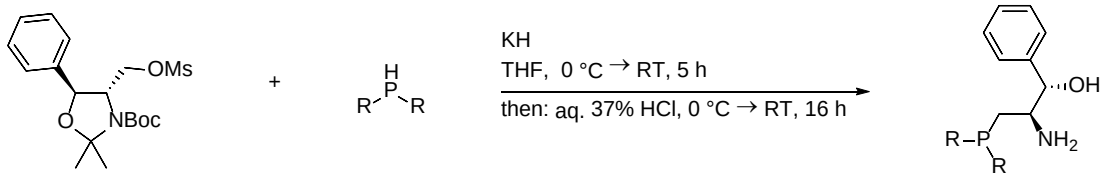


entry	R	phosphine oxide 43 (yield in %)	phosphine 44 (yield in %)	entry	R	phosphine oxide 43 (yield in %)	phosphine 44 (yield in %)
1		**43a** (87)	**44a** (93)	4		**43d** (43)	**44d** (80)
2		**43b** (73)	**44b** (76)	5		**43e** (56)	**44e** (65)
3		**43c** (96)	**44c** (87)	6		**43f** (0)	**44f** (-)

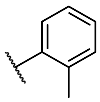
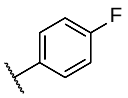
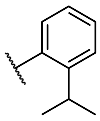
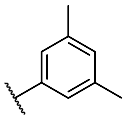
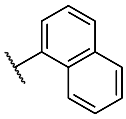
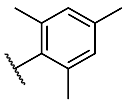
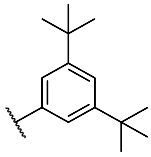
With phosphines **44a-e** in hand, the new synthetic approach that employed secondary phosphines for the synthesis of amino phosphines was investigated (Table 9). In all cases the resulting potassium diarylphosphide was formed by deprotonation of the corresponding phosphine with potassium hydride and the resulting red reaction solution was directly treated with oxazolidine **34** followed by a hydrochloric acid induced oxazolidine opening and Boc deprotection. To our satisfaction, phosphines **44a-d/f** (entries 1-4 and 6) gave the corresponding amino phosphines

40a-d/f in much higher yield compared to the previous methodology (Table 7, entry 3). Moreover, the yields were more reproducible between different batches and for amino phosphine **40c** the scale could be increased from 0.4 mmol to 3.0 mmol without any problems. Unfortunately, for bis(2,4,6-trimethylphenyl)phosphine and for bis(4-flurophenyl)phosphine (Table 9, entries 5 and 7) no product formation was detected.

Table 9: Synthesis of amino phosphines **40a-g** starting from phosphines **44a-g**.

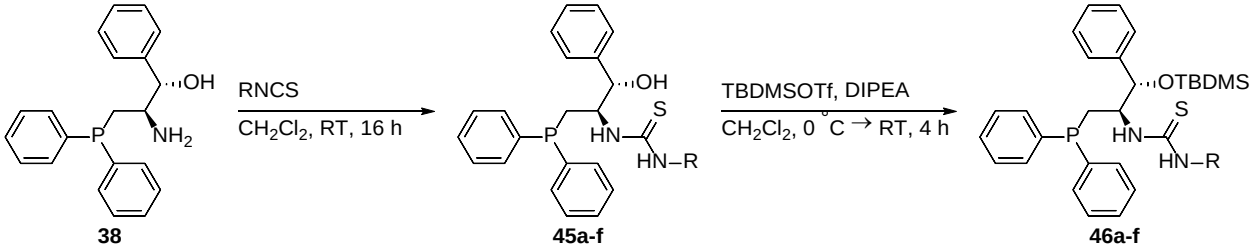


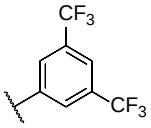
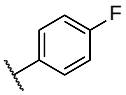
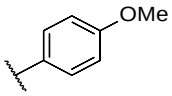
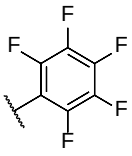
34 **44a-g** **40a-g**

entry	R	amino phosphine 40 (yield in %)	entry	R	amino phosphine 40 (yield in %)
1		**40a** (78)	5		**40e** (0)
2		**40b** (72)	6		**40f** (79)
3		**40c** (89)	7		**40g** (0)
4		**40d** (64)			

With all of the desired amino phosphines in hand, the last two-steps of the catalyst synthesis were investigated using the same synthetic procedure as described for catalyst **37** in Scheme 16. In the first step the amino group in **38** was coupled with different commercially available isothiocyanate precursors to yield the thiourea intermediate **45a-f** (Table 10, entries 1-5). Only in the case of cyclohexyl isothiocyanate a low yield was observed due to its lower reactivity (entry 6). Next, the secondary benzylic alcohol was silylated with *tert*-butyldimethylsilyl trifluoro-methanesulfonate (TBDMSOTf) and DIPEA as a base. All bifunctional catalysts **46a-f** were isolated with yield between 65-90% for the silylation step (entries 1-6).

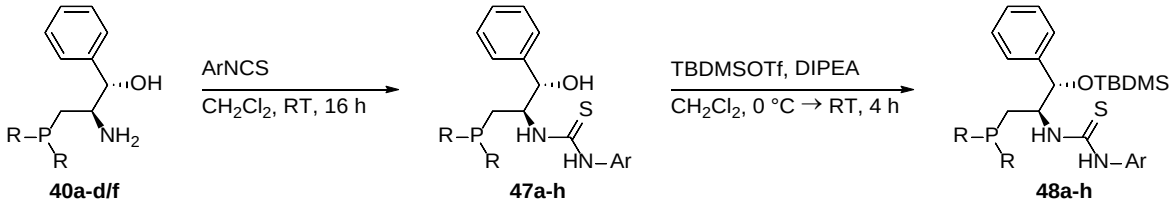
Table 10: Synthesis of bifunctional organocatalyst **46a-f** with differnet thiourea units.



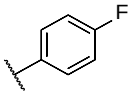
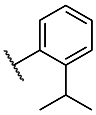
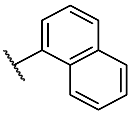
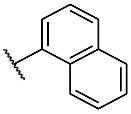
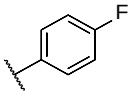
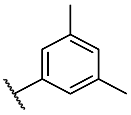
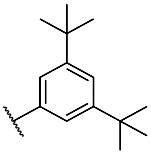
entry	R	thiourea 45 (yield in %)	catalyst 46 (yield in %)	entry	R	thiourea 45 (yield in %)	catalyst 46 (yield in %)
1		**45a** (84)	**46a** (90)	4		**45d** (87)	**46d** (80)
2		**45b** (91)	**46b** (77)	5		**45e** (91)	**46e** (65)
3		**45c** (58)	**46c** (72)	6		**45f** (39)	**46f** (68)

In Table 11 the catalyst synthesis starting from differently substituted phosphines **40a-d/f** is presented. All bifunctional phosphines **47a-g** were synthesized using the standard two-step procedure and the desired organocatalysts **48a-g** were isolated in moderate to good overall yield.

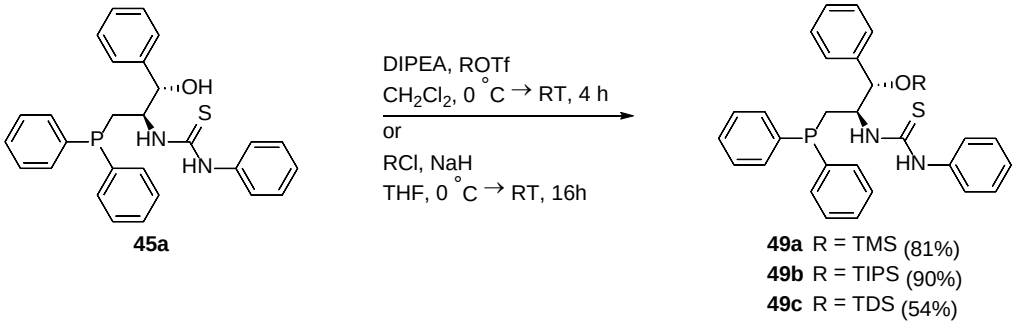
Table 11: Synthesis of bifuntional organocatalysts **48a-g** with different phosphine residues.



40a-d/f **47a-h** **48a-h**

entry	R	Ar	thiourea 47 (yield in %)	catalyst 48 (yield in %)
1			**47a** (55)	**48a** (53)
2			**47b** (73)	**48b** (72)
3			**47c** (75)	**48c** (91)
4			**47d** (83)	**48d** (69)
5			**47e** (98)	**48e** (76)
6			**47f** (95)	**48f** (88)
7			**47g** (36)	**48g** (71)

Next organocatalysts derived from phosphine thiourea precursor **45a** with various silyl groups were synthesized using two different strategies (Scheme 20). For trimethyl (TMS)- and triisopropyl (TIPS) silyl protected alcohols, the method using the corresponding triflates was applied and the catalysts **49a** and **49b** were isolated in high yield. The dimethylthexylsilyl (TDS) catalyst **49c** was formed using a different strategy. In this approach, the benzylic alcohol was deprotonated by sodium hydride followed by addition of chlorodimethylthexylsilane to form the desired catalyst **49c** in 54% yield after purification by column chromatography.

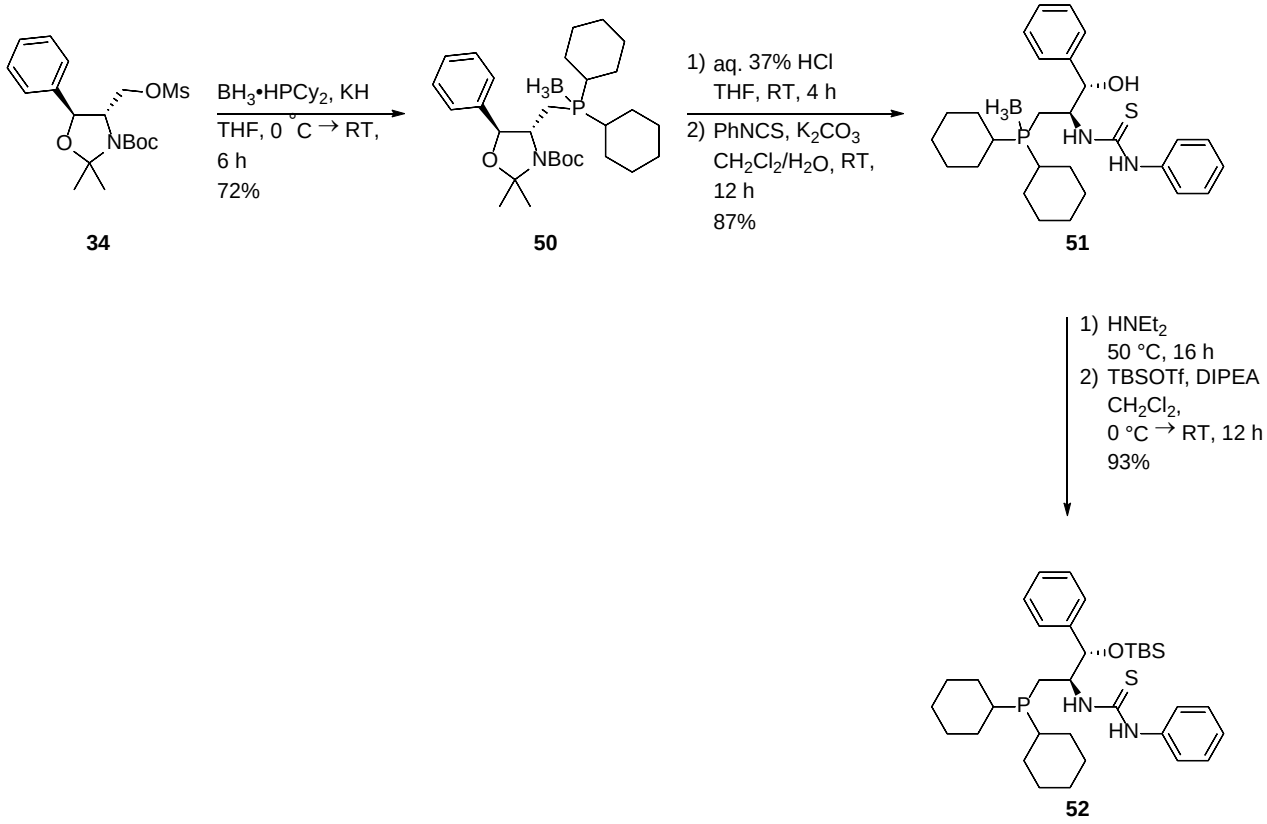


45a

49a R = TMS (81%)
49b R = TIPS (90%)
49c R = TDS (54%)

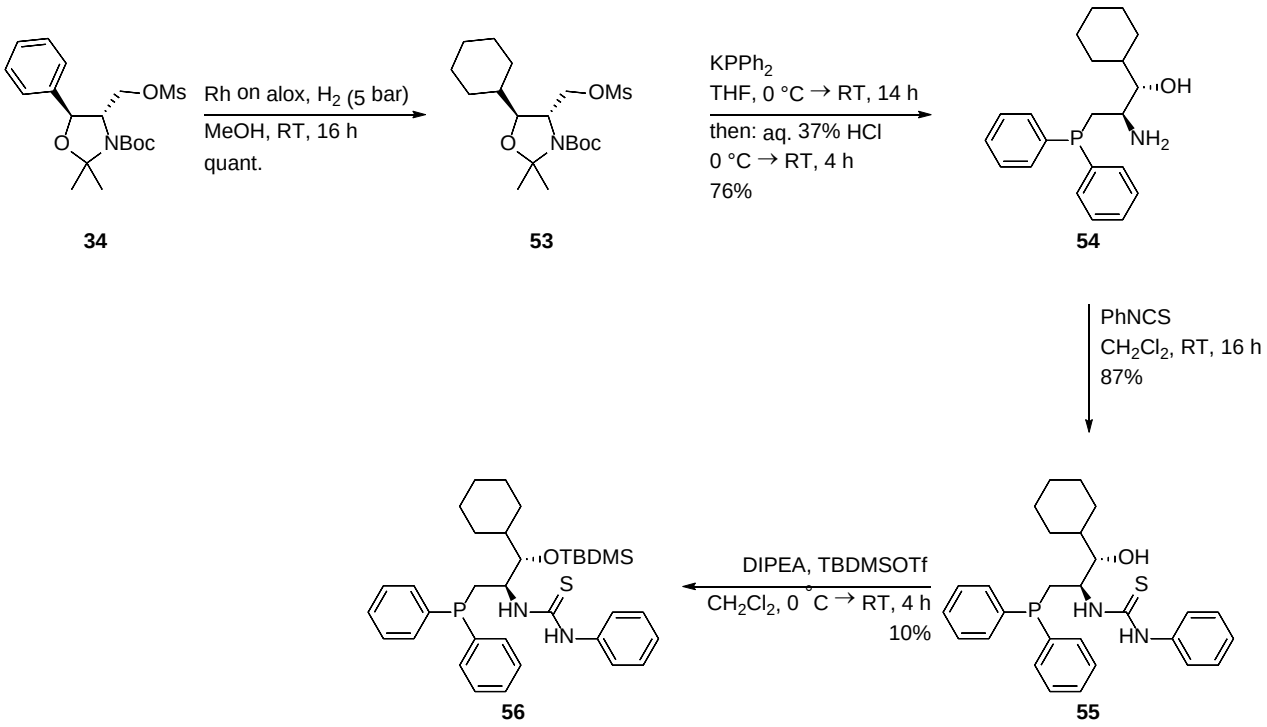
Scheme 20: Synthesis of bifunctional organocatalysts **49a-c** with different siyl groups.

For the synthesis of dicyclohexyl phosphine-based organocatalyst **52** a different synthetic procedure was developed due to the sensitivity towards oxidation of the alkylphosphine moiety. In the first step, the borane-protected phosphine oxazolidine intermediate **50** was formed by nucleophilic substitution of the corresponding mesyl intermediate **34**. Next, the oxazolidine ring was opened and the Boc group was cleaved using HCl, followed by phenyl isothiocyanate coupling in a biphasic solvent system with potassium carbonate. This sequence gave thiourea intermediate **51** in a 3:1 ratio of deprotected to protected phosphine. The mixture of phosphine **51** was stirred overnight in diethylamine at 50 °C to deprotect the phosphine, and after silylation the resulting bifunctional catalyst **52** was isolated in moderate overall yield (Scheme 21).



Scheme 21: Synthesis of dicyclohexyl phosphine based organocatalyst **52**.

To investigate the effect of the chiral backbone on the enantioselectivity of the MBH reaction, catalyst **56**, which contained a cyclohexyl residue in the chiral backbone was synthesized. Mesyl intermediate **53** was synthesized by rhodium on activated alumina catalyzed reduction of the phenyl group in **34** under hydrogen atmosphere. Next, the amino phosphine **54** was formed using the standard synthetic procedure. After phenylthiourea coupling and silylation the desired organocatalyst **56** was isolated in a low overall yield (Scheme 22). The problematic step was the introduction of the TBDMS group due to the steric hindrance of the secondary alcohol.



34 **53** **54** **55** **56**

Scheme 22: Synthesis of bifunctional organocatalyst **56**.

2.2.4 Synthesis of 4th Generation Catalysts

In the 4th catalyst generation, the match-mismatch effect for each diastereomer of the catalyst in the asymmetric MBH reaction was investigated by inverting the stereogenic center at the secondary alcohol position to get the *like*-diastereomer of the bifunctional phosphine (Figure 9).

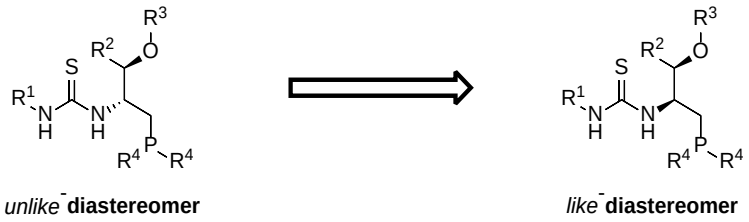
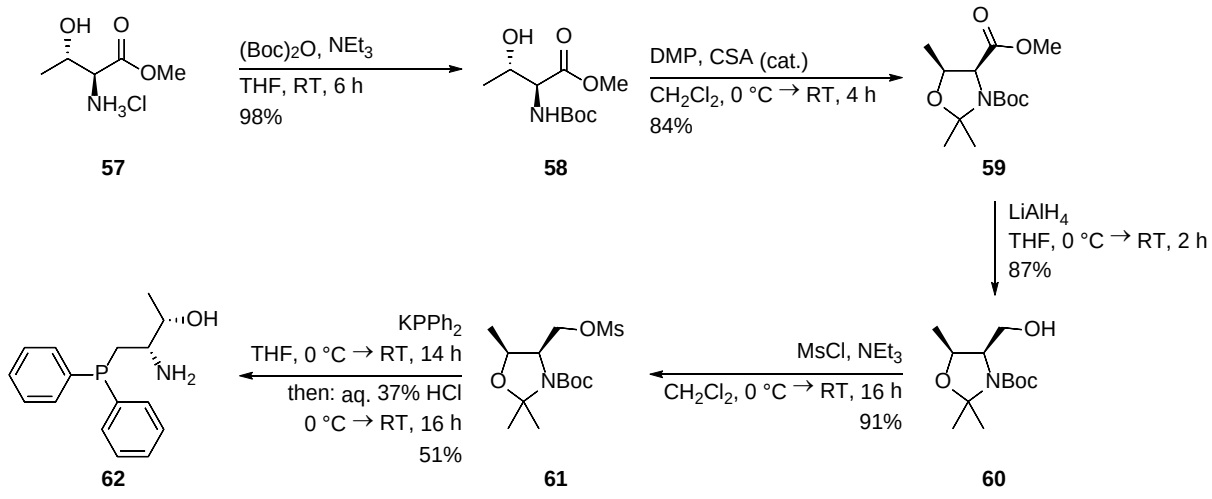


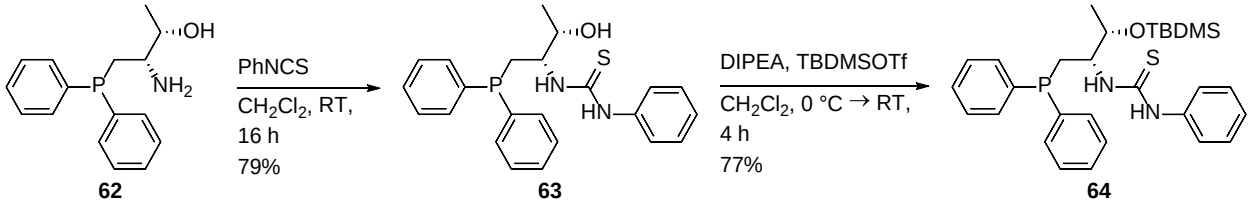
Figure 9: Lead structure of the fourth catalyst generation.

First, the threonine-based amino phosphine **62** was synthesized through a five-step process which began with commercially available (2*S*,3*R*)-threonine hydrochloride methyl ester **57**. In the initial step, Boc-protection of threonine methyl ester **57** followed by camphoricsulfonic acid (CSA) catalyzed oxazolidine formation with 2,2-dimethoxypropane (DMP) gave the resulting 2,2-dimehtyl oxazolidine intermediate **59** in good yield. Next, the ester was reduced using lithium aluminium hydride and the resulting alcohol **60** was mesylated to obtain *O*-mesyl adduct **61**. Installation of the phosphine followed by oxazolidine hydrolysis gave the resulting amino phosphine **62** in moderate yield (Scheme 23).



Scheme 23: Synthesis of (*S,S*)-amino phosphine **62**.

Afterwards, (*S*,*S*)-catalyst **64** was synthesized through a two-step sequence in which the amino group was first coupled with phenyl isothiocyanate and then silylated to yield the bifunctional phosphine **64** in moderate overall yield (Scheme 24).



Scheme 24: Synthesis of (*S*,*S*)-catalyst **64**.

Unfortunately, for phenylserine-derived phosphines the (*R*,*S*)-diastereomer **65** of the precursor is not commercially available. In Figure 10 two possible retrosynthetic analyses are presented. In strategy **A**, the synthesis starts from the commercially available ethyl cinnamate **68**. Enantioselective Sharpless dihydroxylation with AD-mix-β should form the chiral diol intermediate **67**. Then, the hydroxy group next to the ethyl ester moiety has to been converted into a leaving group which afterwards can be displaced by an azide under inversion of configuration to form azide adduct **66**. Reduction of the azide, then leads to amino alcohol **65**. A shorter synthetic approach is based on strategy **B**. In this synthetic sequence the starting point is the commercially available (*S,S*)-diastereomer of amino alcohol **32**. In the first steps, the primary alcohol and the amino group have to be protected to form intermediate **69**. Inversion of the benzylic hydroxyl group through a Mitsunobu reaction should give the desired (*R*,*S*)-product **65**.

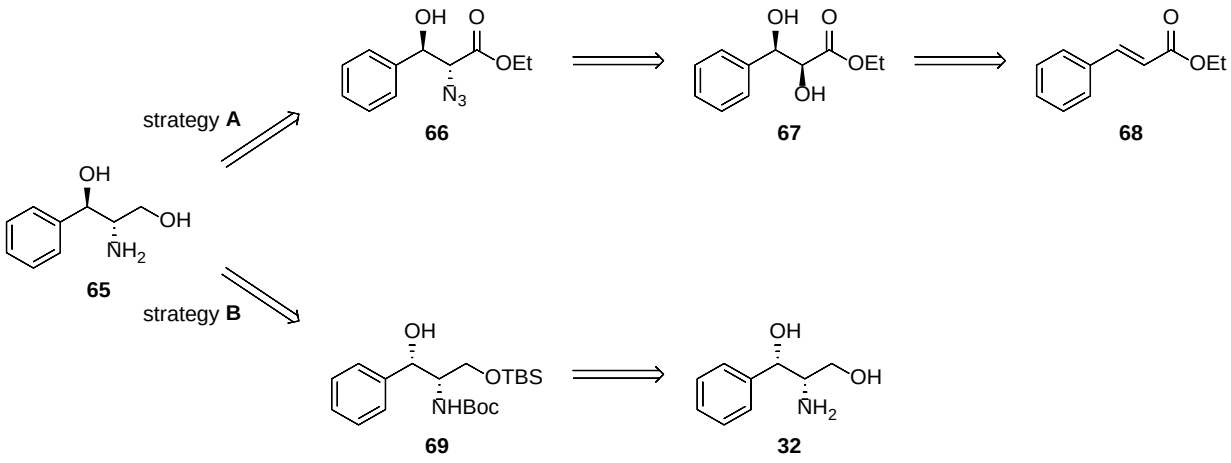
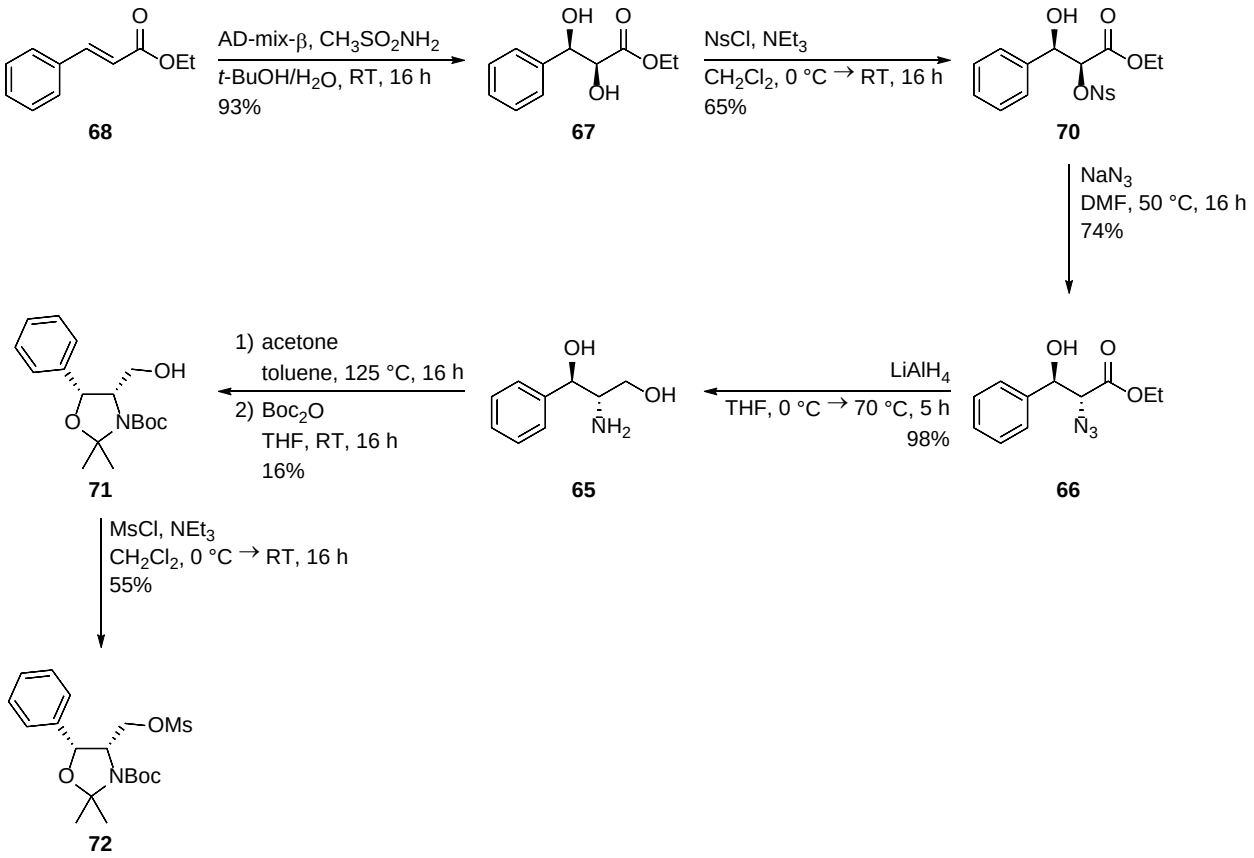


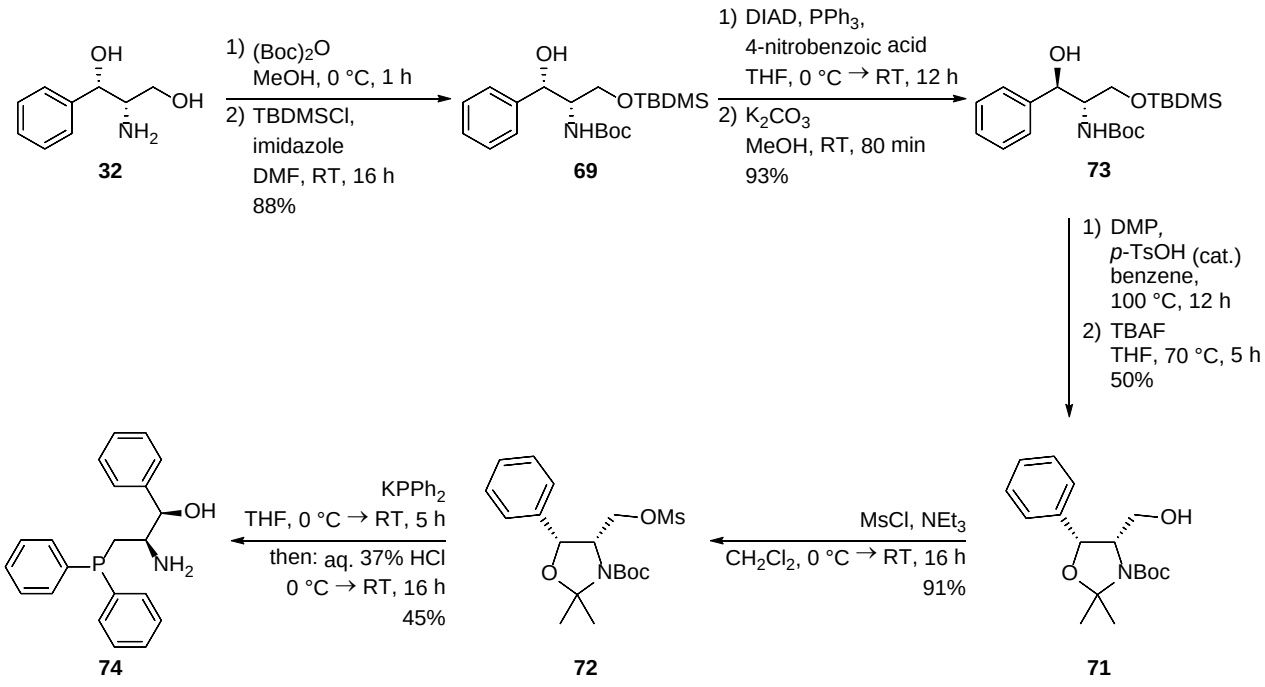
Figure 10: Retrosynthetic analysis of (1*R*,2*S*)-2-amino-1-phenylpropane-1,3-diol **65**.

Following strategy **A**, the *unlike*-diol **67** was synthesized from ethyl cinnamate **68** according to a procedure of Hormi (Scheme 25).[69] After Sharpless asymmetric dihydroxylation using AD-mix-beta in combination with methansulfonamide as general acid catalyst, the product **67** was isolated in excellent yield and high enantioselectivity (>99% *ee*) as only one diastereomer (confirmed by ^{1}H-NMR analysis using a chiral shift reagent). Next, the hydroxy group adjacent to the ester functionality was selectively converted into a 4-nitrobenzenesulfonyl group by treatment of the diol **67** with nosyl chloride and triethylamine.[70] This gave compound **70** in 65% yield. Then, the *O*-nosyl group was substituted by an azide to form the resulting intermediate **66** with inversion of configuration. Reduction of the azide and ester group by lithium aluminum hydride gave the desired (1*R*,2*S*)-amino alcohol **65** in quantitative yield. The Boc 2,2-dimethyl oxazolidine intermediate **71** was synthesized from the crude alcohol **65** through a condensation reaction with acetone under reflux conditions. After subsequent Boc-protection of the oxazolidine adduct, intermediate **71** was isolated in very low yield compared to the synthesis starting from the (1*S*,2*S*)-amino alcohol **32**. Moreover, also for the mesylation step a lower yield was obtained in the synthesis of adduct **72** when compared to the preparation of diastereomer **34** (see Scheme 15).



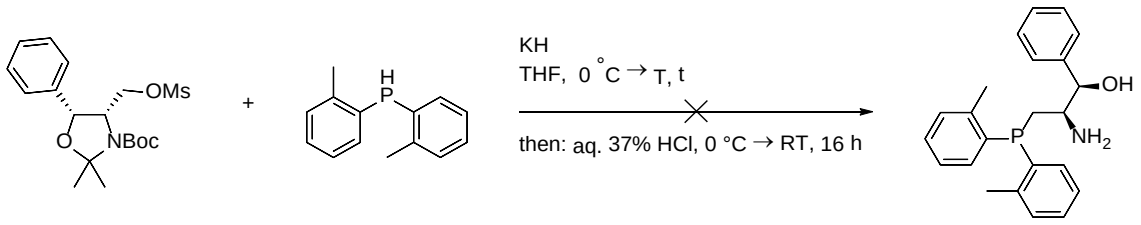
Scheme 25: Synthesis (4*S*,5*R*)-mesyl oxazolidine **72**.

Due to the low yield in the last two steps of strategy **A** (Scheme 25), strategy **B** was investigated for the synthesis of diastereomer **72**. In this process, the primary alcohol and the amino group of (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol were protected using a stepwise one-pot procedure to form intermediate **69** in very good yield. Afterwards, the secondary alcohol was inverted in a Mitsunobu reaction with diisopropyl azodicarboxylate (DIAD), triphenylphosphine and 4-nitrobenzoic acid as a pronucleophile. This gave the corresponding ester adduct which was then hydrolyzed to the alcohol product **73** with potassium carbonate in methanol. Next, oxazolidine **71** was synthesized according to a one-pot procedure of Yokomatsu and Shimeno.[71] In this sequence, compound **73** was cyclized to the resulting TBDMS-protected oxazolidine in a *p*-toluenesulfonic acid (*p*-TsOH) catalyzed condensation with 2,2-dimethoxypropane (DMP) followed by desilylation with TBAF yielded the alcohol **71** in 50% yield over two steps. After mesylation, the intermediate **72** was subjected to the standard protocol for the synthesis of amino phosphines using potassium diphenylphosphide followed by hydrolysis with concentrated hydrochloride acid. The resulting amino phosphine product **74** was isolated in 45% yield (Scheme 26).



Scheme 26: Synthesis of (1*R*,2*R*)-amino phosphine **74**.

With the mesyl oxazolidine **72** in hand, the nucleophilic substitution with diarylphosphides was investigated using di(*ortho*-tolyl)phosphine **44a** as a test reagent. Using the previous reaction conditions (Scheme 17), conversion to the desired amino phosphine product **75a** was not detected by ESI-MS analysis of the crude reaction mixture. Also after longer reaction times or at higher reaction temperatures the nucleophilic displacement of the mesylate group was not observed (Scheme 27). In the *(4S,5R)*-diastereomer the methylene position is blocked by the phenyl- and Boc groups, explaining the lack of reactivity of compound **72**.

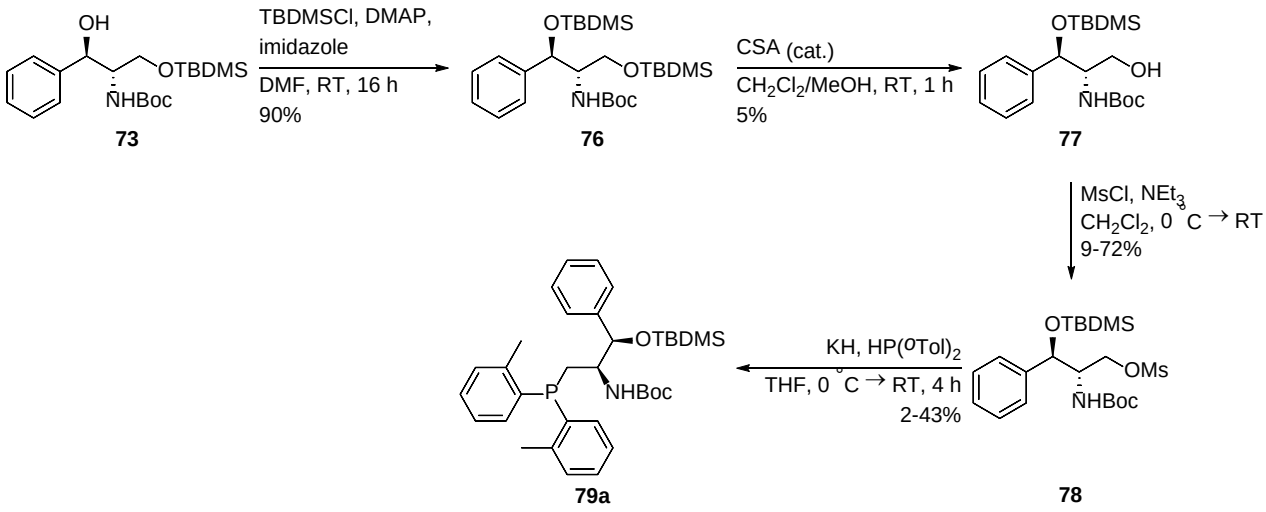


72 **44a** **75a**

conditions (T, t):	**conversion:**
25 °C, 5 h	no
25 °C, 16 h	no
75 °C, 16 h	no

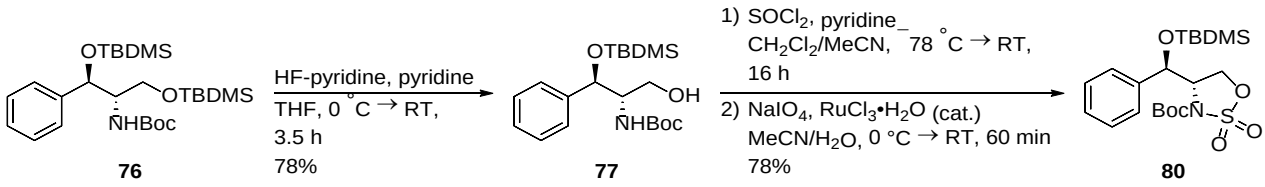
Scheme 27: Investigations towards the synthesis of amino phosphine **75a**.

Due of the problem in the substitution step using oxazolidine **72**, a new approach *via* the less rigid mesyl adduct **78** was investigated (Scheme 28). In the first step of the synthesis, the hydroxy group of the inverted protected product **73** was silylated using TBDMS chloride, DMAP and imidazole to give fully protected intermediate **76**. In the following step, the primary alcohol was deprotected using a catalytic amount of camphoricsulfonic acid (CSA) in a CH_2Cl_2/MeOH mixture to form primary alcohol intermediate **77** in only 5% yield. Afterwards, the alcohol group in **77** was mesylated using mesyl chloride and triethylamine but, unfortunately, this step was not reproducible. This could be due to intramolecular aziridine formation as a possible undesired side reaction. In this case the nucleophilic substitution of the *O*-mesyl group by potassium di(*ortho*-tolyl)phosphide was indeed observed but nevertheless the yield of *N*-Boc-protected amino phosphine product **79a** fluctuated between different batches. In this step, aziridine formation might also be a possible side reaction.



Scheme 28: Synthesis of *N*-Boc-protected amino phosphine **79a**.

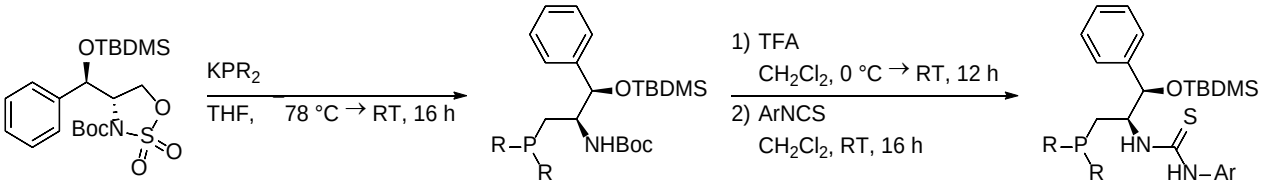
Because of problems with the reproducibility in two last steps of the amino phosphine synthesis presented in Scheme 28, a different synthetic protocol was investigated in which an *N*-protected cyclic sulfamidates was utilized as an electrophile for the nucleophilic substitution step. Fully protected intermediate **76** was selectively deprotected at the primary alcohol position using HF-pyridine complex as fluoride donor to yield the resulting alcohol intermediate **77** in good yield. Afterwards, sulfonamidate adduct **80** was formed in a two-step one pot procedure. First, *N*-Boc protected amino alcohol intermediate **77** was treated with thionyl chloride to form an oxathiazolidin-2-oxide intermediate which was subsequently oxidized with $RuCl_3$ and sodium periodate. The final product **80** was isolated in 78% yield (Scheme 29).



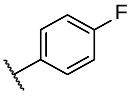
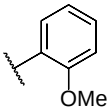
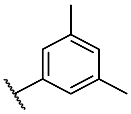
Scheme 29: Synthesis of *N*-protected cyclic sulfonamidate **80**.

Next, the nucleophilic ring-opening of **80** was investigated using potassium diarylphosphide followed by hydrolysis with diluted sulfuric acid. For all tested phosphine precursors (Table 12, entries 1-5) the resulting *N*-Boc protected amino phosphines **79a-d** were isolated in moderate to good yield. Using this strategy, it was finally possible to synthesize an amino phosphine-derived from bis(2-methoxyphenyl)phosphine (entry 4). Afterwards the Boc group was removed using trifluoroacetic acid (TFA) in dichloromethane and after basic aqueous work-up the crude mixture was directly used in the next step. In the last synthetic step, the amino group was coupled with different *N*-aryl isothiocyanates and after column chromatography the resulting bifunctional organocatalysts **81a-e** were isolated in very good yield (entries 1-5).

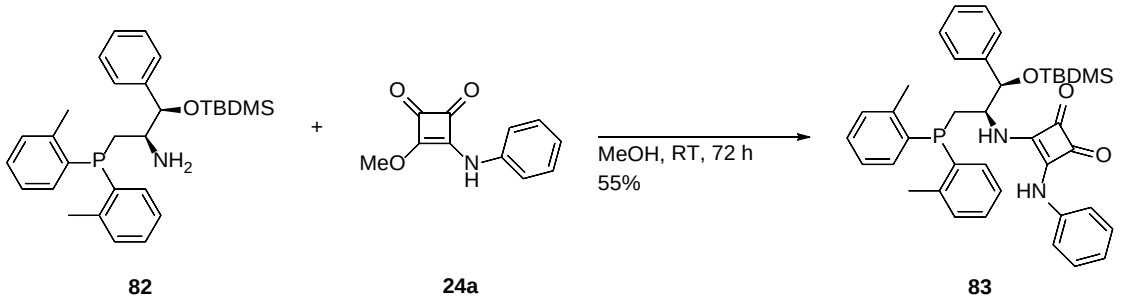
Table 12: Synthesis of (*R,R*)-catalysts **81a-e.**



80 **79a-d** **81a-e**

entry	R	Ar	**Boc-amino phosphine 79** (yield in %)	**catalyst 81** (yield in %)
1			**79a** (58)	**81a** (88)
2			**79b** (80)	**81b** (80)
3			**79b** (80)	**81c** (86)
4			**79c** (66)	**81d** (89)
5			**79d** (54)	**81e** (86)

Additionally, squaramide-catalyst **83** was synthesized to evaluate whether the enantioselectivity of the MBH reaction could be improved by replacing the hydrogen-bonding subunit. The bifunctional catalyst **83** was isolated in moderate yield after mixing squaramide precursor **24a** with amino phosphine **82** in methanol for three days.

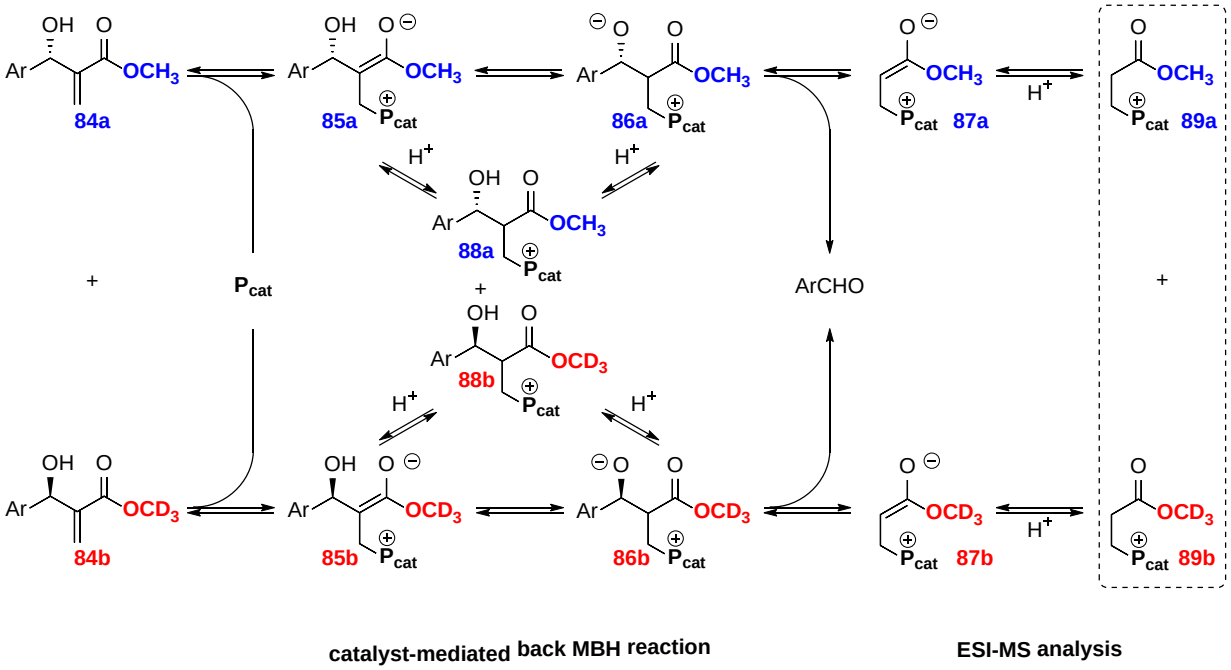


82 **24a** **83**

Scheme 30: Synthesis of squaramide-based organocatalysts **83.**

2.3 Catalyst Evaluation by ESI-MS Back Reaction Screening

The principle behind our screening methodology for the MBH reaction is depicted in Scheme 31. Starting from a 1:1 mixture of mass-labelled quasi-enantiomeric MBH products **84a** and **84b**, a catalyst-mediated back reaction via intermediates **85a** and **85b** is induced, which then undergo cleavage to the aromatic aldehyde (in the present study 4-nitrobenzaldehyde) and the mass-labelled catalyst-substrate adducts **87a** and **87b**. If we assume that a fast equilibrium is established between intermediates **84a** and **84b** and the corresponding catalyst adducts **85a** and **85b**, followed by a slow rate-determining C–C bond cleavage (Curtin-Hammet conditions), the ratio **87a**/**87b** will be identical to the enantiomeric ratio produced in the MBH reaction in the forward direction according to the principle of microscopic reversibility. The ratio **87a**/**87b** can be reliably determined even at very low concentration by electrospray ionization mass spectrometry (ESI-MS). Under the conditions of ESI-MS analysis, intermediates **87a** and **87b** are protonated and their ratio is determined from the signal ratio of the corresponding cationic species **89a** and **89b**.



Scheme 31: Principle of the back reaction screening methodology for the MBH reaction.

The results obtained during my master thesis showed that upon treatment of MBH adducts derived from acrylic esters and 4-nitrobenzaldehyde with triphenylphosphine, signals of catalyst adducts resulting from C–C bond cleavage could be detected by ESI-MS. During my master studies a

suitable pair of quasi-enantiomeric MBH products was developed. Alkyl esters which differed in the number of carbon atoms, which we evaluated first, gave unsatisfactory results as they slightly differed in reactivity. This reactivity difference resulted in unequal ratios of catalyst-substrate adducts with an achiral catalyst. We eventually found that the methyl and trideuteromethyl esters **84a** and **84b** proved to be optimal as they possessed identical reactivity and gave rise to easily detectable signal pairs.

Successful application of back reaction screening requires the C–C bond forming step to be rate- and enantioselectivity-determining. However, in several studies the proton transfer after the aldol step was found to be, at least in part, rate-determining.[53,58] We therefore conducted preliminary experiments with chiral bifunctional phosphine-based catalyst during my master studies. We were pleased to find that the ratios **89a/89b** produced in the back reaction closely matched the enantiomeric ratios determined for the preparative forward reaction. This implied that our screening protocol should indeed be applicable (see Figure 11 for representative examples). Encouraged by these results, we started a systematic evaluation of chiral MBH catalysts based on the screening protocol shown in Scheme 31.

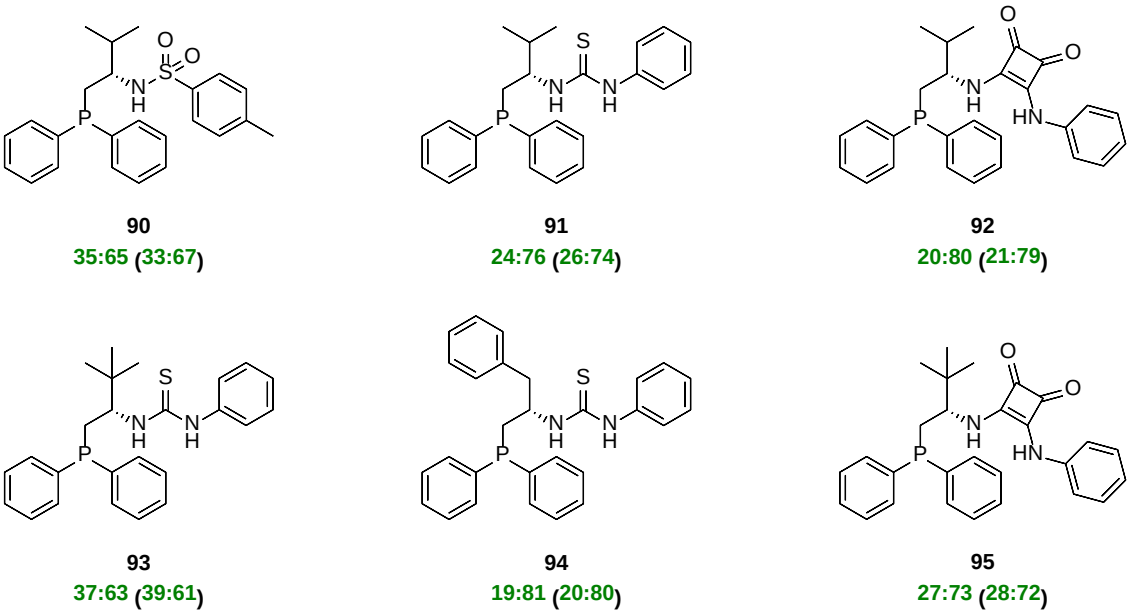


Figure 11: Catalyst overview of my master thesis (enantiomeric ratio determined in the forward reaction is given in brackets).

2.3.1 Single Catalyst Screening of Bifunctional Phosphines

First, purified first generation catalysts with different chiral backbones were subjected to the single back reaction screening protocol for the evaluation of the intrinsic enantioselectivities. For back reaction screening an equimolar mixture of quasi-enantiomers **84a** and **84b** was allowed to react with 10 mol% of catalyst in CH_2Cl_2 at room temperature. After 30 minutes, the reaction mixture was diluted ten-fold with CH_2Cl_2 and a sample was then immediately injected into the spectrometer. The signals of the positively charged *retro*-MBH products **89a** and **89b** as well as the cationic species **88a** and **88b** generated by protonation of intermediates **85a**/**86a** and **85b**/**86b** were all clearly visible with high intensity (see Figure 12 for a representative ESI-MS spectrum with triphenylphosphine as catalyst).

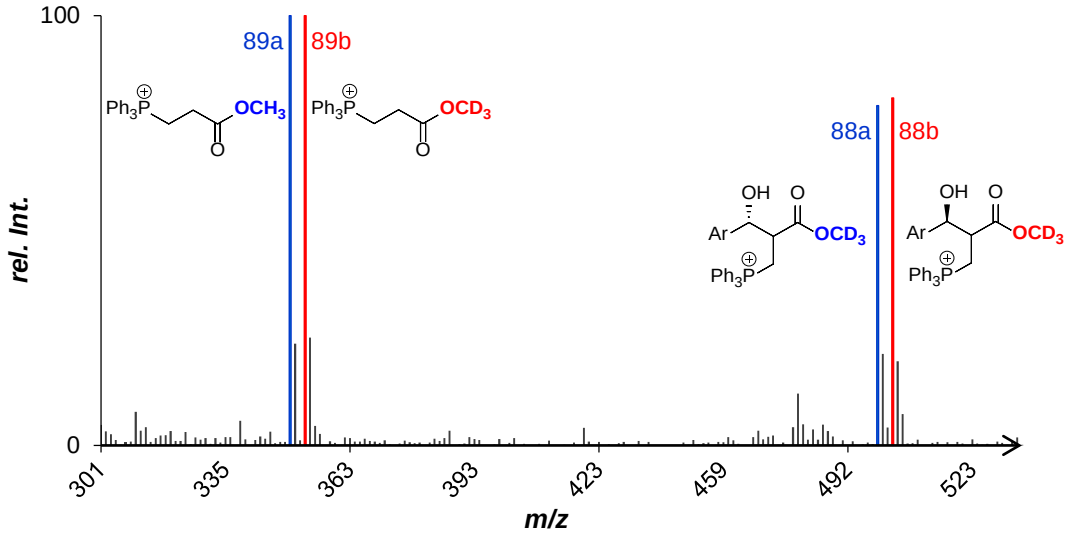
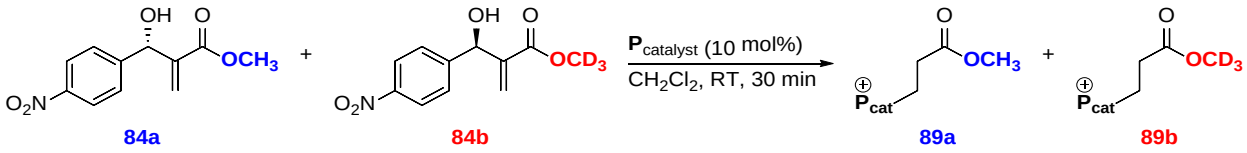


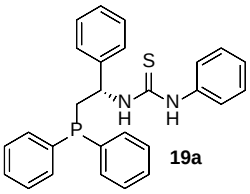
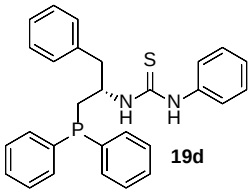
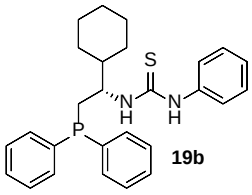
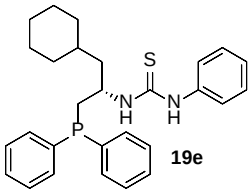
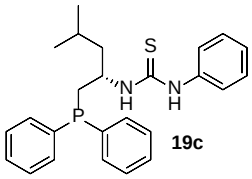
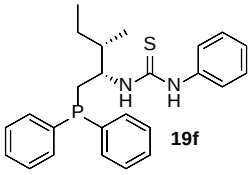
Figure 12: ESI-MS spectrum with triphenylphosphine as catalyst for back reaction screening.

To validate the screening results, the ratios **89a**/**89b** measured by ESI-MS were compared to the enantiomeric ratios (e.r.) determined for the forward reaction by HPLC on a chiral stationary phase. To our satisfaction the results from the back reaction screening and from the corresponding preparative MBH reactions closely matched each other. In some cases, the e.r. of the preparative reaction was significantly lower than the selectivity of the back reaction. However, this divergence was caused by slow catalyst-induced racemization of the MBH products under the reaction conditions. After a short reaction time of 30 minutes the selectivities of the back and forward reaction matched again.

The effect of the chiral backbone of thiourea-based organocatalysts from different amino phosphines for the selectivity of the MBH reaction is summarized in Table 13. For catalyst **19a** derived from phenyl glycine only a low *ee* of 22% was measured. The enantioselectivity was improved by increasing the steric hindrance at the α-position of the amino phosphine as in catalyst **19b.** Moreover, a slightly higher enantiomeric ratio was observed for the isoleucine based catalyst **19f**. Catalysts **19c** with an *iso*-butyl group in the backbone gave an enantiomeric excess of 42% and the selectivity was increased to 54% *ee* by replacing the butyl group by a phenyl residue as in phosphine **19d**. A further increase of the steric hindrance in catalyst **19e** with the cyclohexyl moiety resulted in a decrease of selectivity from 23:77 to 26:74. To conclude, the best selectivities were observed for catalysts derived from phenylalanine (catalyst **19d**) or isoleucine (catalyst **19f**).

Table 13: Screening results for the first catalyst generation – investigation of the effect of the chiral backbone on the enantioselectivity.

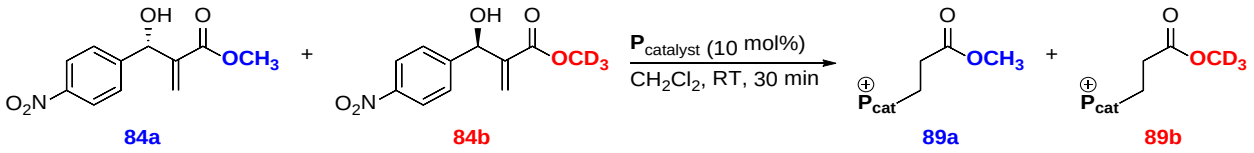


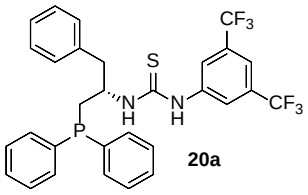
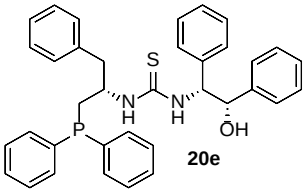
$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])	$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])
 **19a**	39:61 (38:62[b])	 **19d**	23:77 (23:77)
 **19b**	23:77 (22:78[b])	 **19e**	26:74 (25:75)
 **19c**	29:71 (28:72)	 **19f**	21:79 (20:80[b])

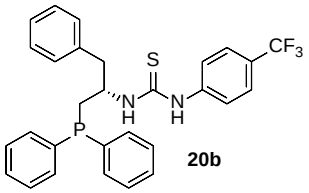
[a]: Reaction conditions: 4-nitrobenzaldehyde (1.0 eq.), methyl acrylate (1.5 eq.), 10 mol% catalyst, CH_2Cl_2, RT, 18 hours. Determined by HPLC on a chiral stationary phase. [b]: Ratio determined after 30 minutes.

Based on the results of the single catalyst screening in Table 13, (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine was chosen as a core structure to study the influence of the thiourea group on the enantioselectivity of the MBH reaction (Table 14). Introduction of electron-withdrawing (catalyst **20a** or **20b**) or electron-donating (catalyst **20c**) substituents attached to the *N*-phenyl group had only a marginal effect on the enantioselectivity. The selectivity was slightly improved by installing a bulkier diphenylmethane unit at the thiourea moiety (catalyst **20d**). Next, the influence of a chiral hydroxyl group attached to the thiourea unit was investigated to test if the proton transfer step could be accelerated. An additional hydrogen-bonding donor could help in the orientation of the substrate by non-covalent interactions. Indeed, compared to *N*-phenyl thiourea-derived catalyst **19d** (see Table 13) the enantiomeric excess increased to 68% which could be an indication for the positive effect of the chiral alcohol group in catalyst **20e** (Table 14) on the selectivity. With an e.r. of 20:80 the selectivity obtained with catalyst **20g** containing a *N*-benzyl residue was similar to phosphine **19d** (see Table 13). For the dimeric catalyst **20f** (Table 14) a marginally higher enantioselectivity was observed. For all catalysts with an *N*-alkyl group at the thiourea unit a catalyst induced product racemization was observed over time which reflected the high reactivity of these catalysts. Only after short reaction times, a match between the ratio **89a/89b** and the e.r. of the forward reaction was achieved.

Table 14: Screening results for the first catalyst generation – investigation of the effect of the *N*-residue at the thiourea group on the enantioselectivity.

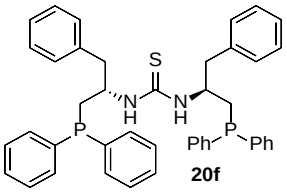


$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])	$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])
 **20a**	23:77 (23:77)	 **20e**	16:84 (14:86[b])



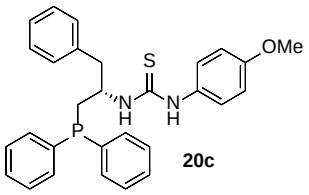
20b

23:77 (25:75)



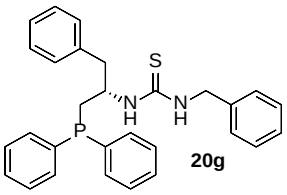
20f

16:84 (14:86[b])



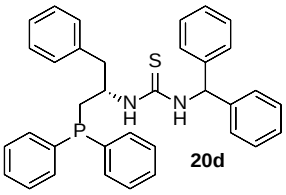
20c

22:78 (24:76)



20g

20:80 (21:79[b])



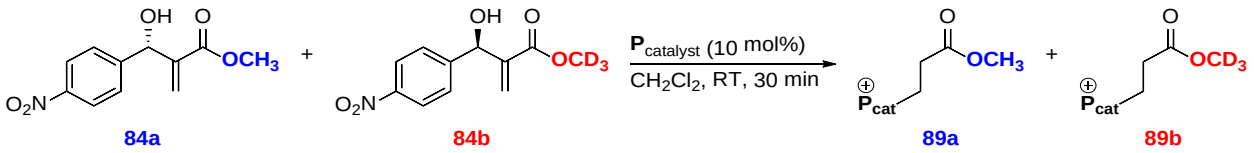
20d

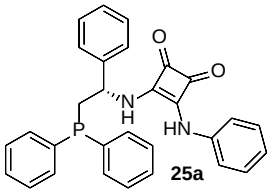
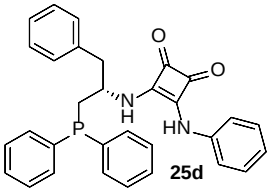
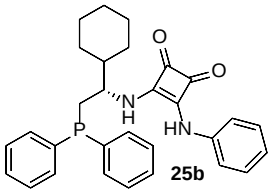
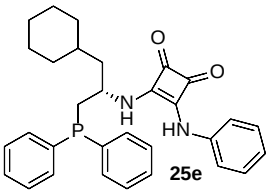
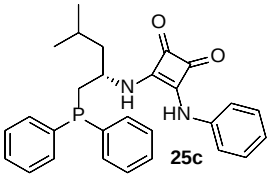
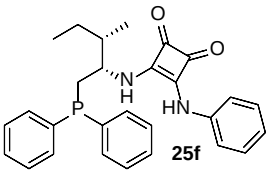
16:84 (17:83[b])

[a]: Reaction conditions: 4-nitrobenzaldehyde (1.0 eq.), methyl acrylate (1.5 eq.), 10 mol% catalyst, CH_2Cl_2, RT, 18 hours. Determined by HPLC on a chiral stationary phase. [b]: Ratio determined after 30 minutes.

Next, the second catalyst generation was screened using the back reaction screening protocol. Replacement of the thiourea group by a squaramide unit led to improved e.r. values for all catalysts when compared to the corresponding thiourea derivatives (see Table 15 vs Table 13). The enantioselectivity was lowered by increasing steric hindrance in the chiral backbone with a cyclohexyl group (catalyst **25b** or catalyst **25e**) compared to phenyl substituted bifunctional phosphines **25a** and **25d**. For catalyst structures with an isobutyl group (catalyst **25c**) or isoleucine-derived catalyst **25f** no further improvement of the intrinsic selectivity was achieved. In conclusion, the best selectivities were observed for the phenylalanine and phenyl glycine-derived organocatalysts **25d** and **25a**, respectively.

Table 15: Screening results for the second catalyst generation – investigation of the effect of the chiral backbone on the enantioselectivity.

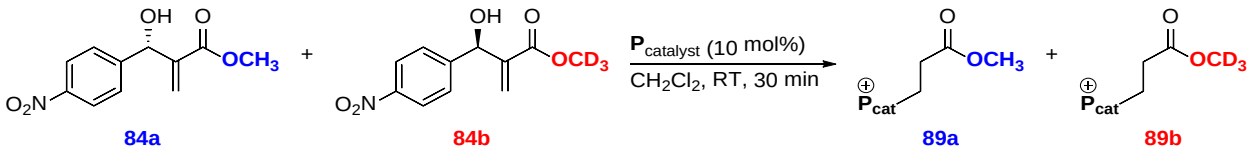


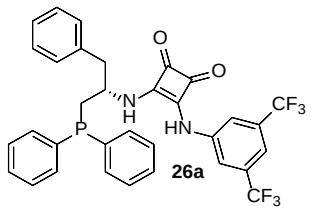
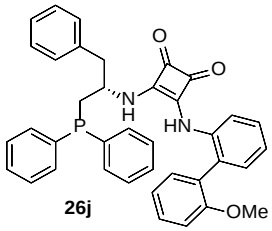
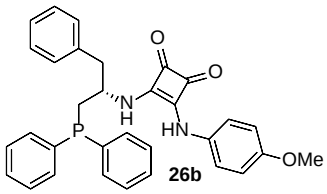
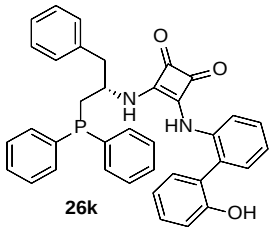
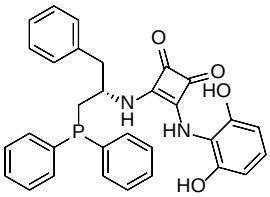
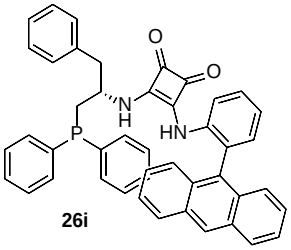
$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])	$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])
 **25a**	14:86 (12:88)	 **25d**	15:85 (15:85)
 **25b**	18:82 (19:81)	 **25e**	18:82 (19:81)
 **25c**	18:82 (18:82)	 **25f**	17:83 (15:85)

[a]: Reaction conditions: 4-nitrobenzaldehyde (1.0 eq.), methyl acrylate (1.5 eq.), 10 mol% catalyst, CH_2Cl_2, RT, 18 hours. Determined by HPLC on a chiral stationary phase.

In a next step the influence of the *N*-substituent on the squaramide unit on the selectivity was investigated. The results in Table 16 show the effect of various *N*-aryl groups. Trifluoromethyl (catalyst **26a**) or methoxy (catalyst **26b**) residues on the *N*-phenyl substituent did not have any effect on the stereoselectivity of the reaction. For catalyst **26c** with two phenolic hydroxyl groups, only low conversion in the preparative reaction was detected by TLC. This could be due to the possible protonation of the enolate intermediate by the acidic phenol groups which reduced the reactivity of the bifunctional phosphine **26c**. Next, squaramide catalyst **26j** with a *N*-2-methoxybiphenyl residue gave a lower enantiomeric ratio. Moreover, catalyst **26k** with 2-hydroxybiphenyl gave similar selectivity compared to the *O*-methylated catalyst **26j** but was likely due to racemization as indicated by the detected higher selectivity by ESI-MS. The installation of an anthracene unit at the *ortho* position of the *N*-phenyl residue as a steric shield did not influence the e.r. of the catalyst **26i**.

Table 16: Screening results for the second catalyst generation – investigation of the effect of the *N*-aryl substituent at the squaramide group on the enantioselectivity.



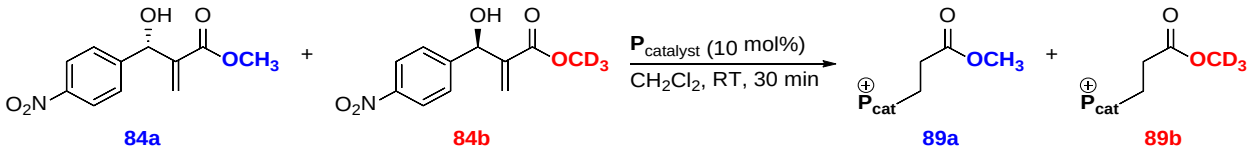
$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])	$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])
 **26a**	16:84 (17:83)	 **26j**	23:77 (25:75)
 **26b**	14:86 (14:86)	 **26k**	24:76 (25:75[b])
 **26c**	15:85 (11:89)	 **26i**	16:84 (16:84)

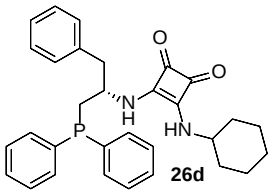
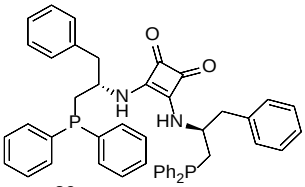
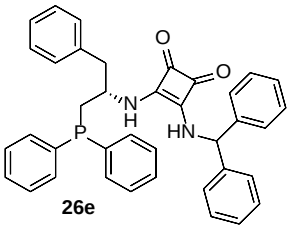
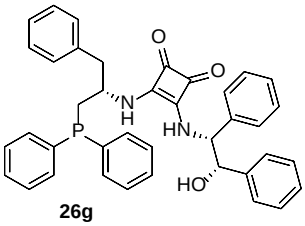
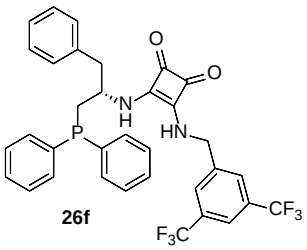
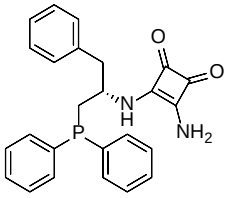
[a]: Reaction conditions: 4-nitrobenzaldehyde (1.0 eq.), methyl acrylate (1.5 eq.), 10 mol% catalyst, CH_2Cl_2, RT, 18 hours. Determined by HPLC on a chiral stationary phase. [b]: Ratio determined after 30 minutes.

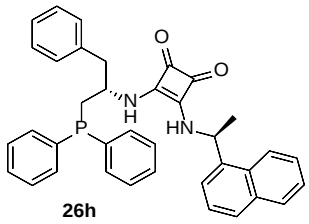
The effect of an *N*-alkyl substituent on enantioselectivities obtained with squaramide catalysts is presented in Table 17. The e.r. decreased from 15:85 to 20:80 when a cyclohexyl group was attached to the squaramide unit in catalyst **26d** compared to catalyst **25d** (see

Table 15). For catalysts with a diphenylmethane (catalyst **26e**) or (*S*)-naphthylethyl (catalyst **26h**) (Table 17) substituted squaramide moiety only a marginal influence of the steric hindrance was detected compared to the sterically less demanding catalysts **25d** (Table 15). Moreover, catalyst **26f** (Table 17) derived from 3,5-bis(trifluoromethyl)-benzylamine substituted squaramide did not increase the enantioselectivity compared to catalyst **25d** (Table 15). The dimeric catalyst **26m** or organocatalysts **26g** (Table 17) with an additional chiral hydroxyl group did not improve the e.r. Interestingly, the bifunctional phosphine **26l** with an amino group attached to the squaramide gave slightly higher enantioselectivity but racemization occurred during the preparative reaction.

Table 17: Screening results for the second catalyst generation – investigation of the effect of the *N*-alkyl substituent at the squaramide group on the enantioselectivity.



$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])	$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])
 **26d**	20:80 (20:80)	 **26m**	18:82 (15:85)
 **26e**	15:85 (15:85)	 **26g**	16:84 (16:84[b])
 **26f**	19:81 (18:82)	 **26l**	12:88 (15:85[b])



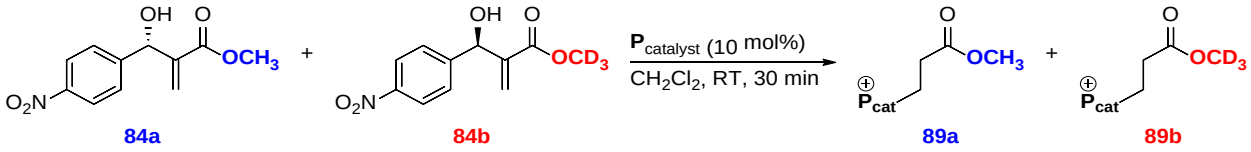
26h

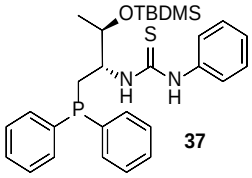
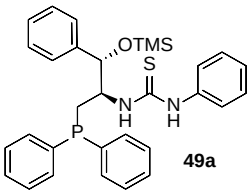
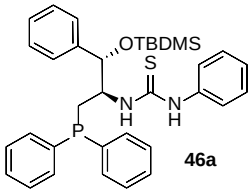
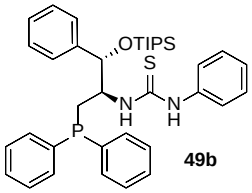
16:84 (16:84)

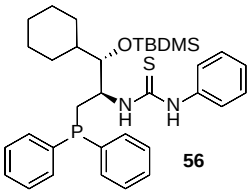
[a]: Reaction conditions: 4-nitrobenzaldehyde (1.0 eq.), methyl acrylate (1.5 eq.), 10 mol% catalyst, CH_2Cl_2, RT, 18 hours. Determined by HPLC on a chiral stationary phase. [b]: Ratio determined after 30 minutes.

The effect of the chiral backbone of the third catalyst generation on the enantioselectivity is shown in Table 18. Threonine-derived catalyst **37** gave a moderate enantiomeric excess of 54%. A more pronounced increase of the e.r. resulted when the methyl group of catalyst **37** was replaced by a phenyl group (catalyst **46a**). In contrast, a lower selectivity was detected for catalyst **56** with a cyclohexyl group in the backbone. Catalyst **45a** which lacked a silyl protecting group gave racemic product. A smaller silyl group like TMS or bigger groups such as TIPS or TDS resulted in a decreased e.r. of the MBH product compared to TBDMS-protected phosphine **46a**.

Table 18: Screening resutls for third generation catalysts – investigation of the effect of the chiral backbone on the enantioselectivity.

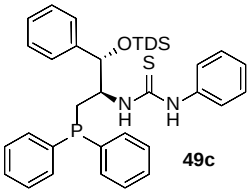


$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])	$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])
 **37**	23:77 (24:76)	 **49a**	85:15 (83:17)
 **46a**	91:9 (90:10)	 **49b**	82:18 (81:19)



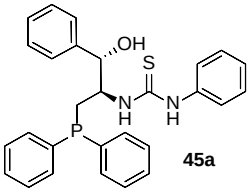
56

70:30 (80:20)



49c

83:17 (84:16)



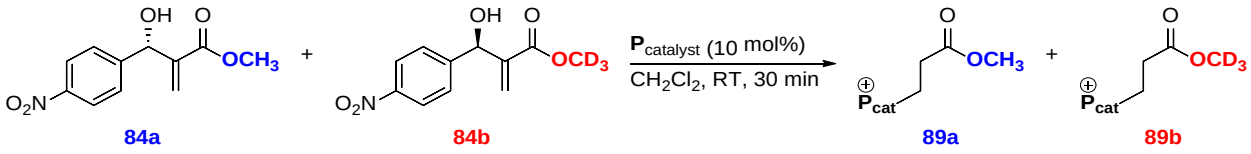
45a

52:48 (50:50)

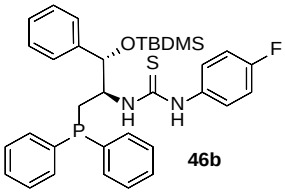
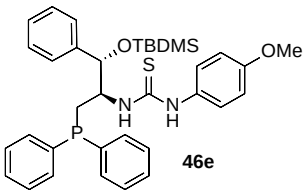
[a]: Reaction conditions: 4-nitrobenzaldehyde (1.0 eq.), methyl acrylate (1.5 eq.), 10 mol% catalyst, CH_2Cl_2, RT, 18 hours. Determined by HPLC on a chiral stationary phase.

The screening results in Table 18 show that the TBDMS and the phenyl group are crucial for the selectivity of the MBH reaction. The next task was to study the effect of the *N*-substituent of the thiourea unit for the best catalyst **46a** on the stereoselectivity of the MBH reaction (Table 19). When different electron-donating (catalyst **46e**) or electron-withdrawing substituents (catalyst **46d**) were installed next to the thiourea group only a marginal effect on the selectivity was detected. In contrast, an *N*-cyclohexyl substituent (catalyst **46f**) lowered the enantiomeric ratio from 90:10 to 80:20. Furthermore, in the case of the *N*-pentafluorophenyl-based catalyst **46c** a racemization process over time was observed. Ultimately, the *N*-phenyl group was found to be the best residue in terms of enantioselectivity.

Table 19: Screening resutls for third generation catalysts – investigation of the effect of the thiourea group on the enantioselectivity.

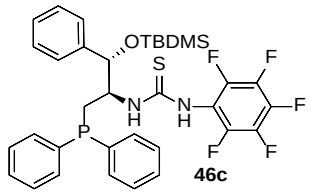


84a 84b 89a 89b

$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])	$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])
	88:12 (87:13)		87:13 (87:13)

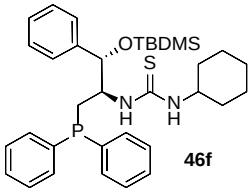
46b

46e



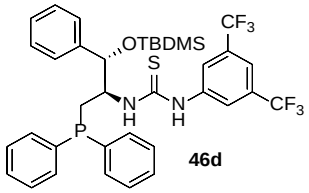
46c

91:9 (90:10[b])



46f

83:17 (80:20)



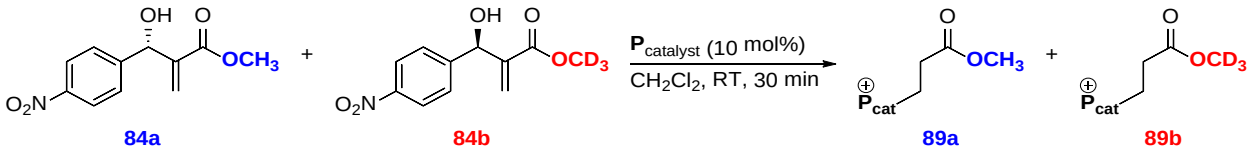
46d

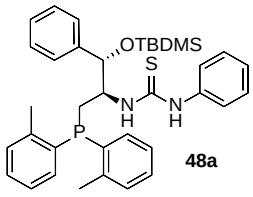
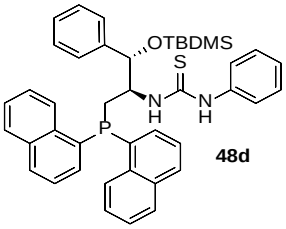
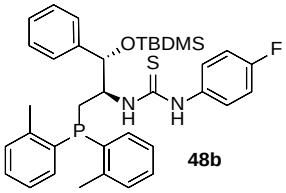
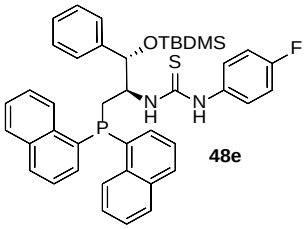
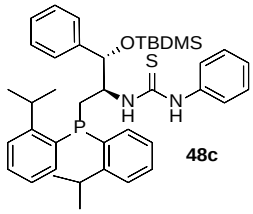
89:11 (87:13)

[a]: Reaction conditions: 4-nitrobenzaldehyde (1.0 eq.), methyl acrylate (1.5 eq.), 10 mol% catalyst, CH_2Cl_2, RT, 18 hours. Determined by HPLC on a chiral stationary phase. [b]: Ratio determined after 30 minutes.

Next, the influence of the phosphine residue on the intrinsic selectivity were studied by investigating various phosphines in the back reaction screening. A significant increase in enantioselectivity was achieved by replacing the *P*-phenyl groups with bulkier *ortho*-tolyl (catalyst **48a,b**), *ortho-i*Pr-phenyl (catalyst **48c**), or 1-naphthyl (catalyst **48d**,**e**) groups (Table 20). In contrast, the *N*-aryl residue did not affect the selectivity of the MBH reaction. These screening results demonstrated the importance that steric hindrance at the *ortho* position of the aromatic residue on the phosphorus center has for the stereoselectivity of the reaction. The reactivity drops with increasing steric hindrance from *ortho*-tolyl to 1-napthyl to *ortho-i*Pr-phenyl substituted phosphines-based on analysis of the detected intensities of the catalyst-substrate adducts by ESI-MS.

Table 20: Screening resutls for third generation catalysts – investigation of the effect of aryl substituted phosphines on the enantioselectivity.

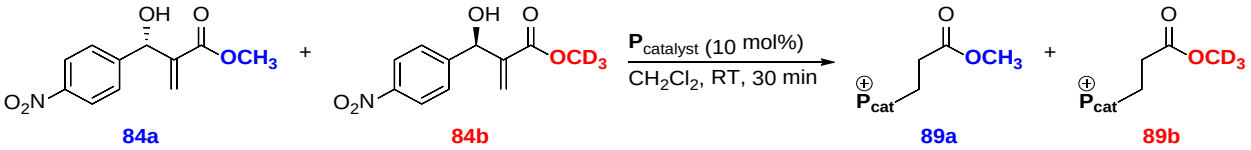


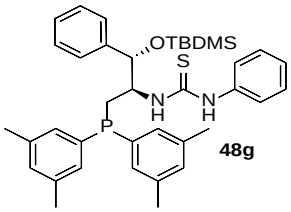
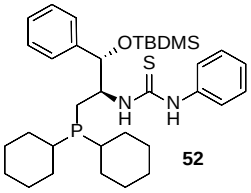
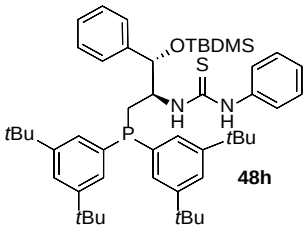
$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])	$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])
 **48a**	94:6 (94:6)	 **48d**	96:4 (95:5)
 **48b**	93:7 (94:6)	 **48e**	95:5 (95:5)
 **48c**	94:6 (93:7)		

[a]: Reaction conditions: 4-nitrobenzaldehyde (1.0 eq.), methyl acrylate (1.5 eq.), 10 mol% catalyst, CH_2Cl_2, RT, 18 hours. Determined by HPLC on a chiral stationary phase.

Next, the electronic and the steric effects of 3,5-substituted aryl phosphines were investigated. Catalysts **48g** and **48h** with 3,5-dialkyl-substituted *P*-phenyl groups gave inferior results (Table 21). A more drastic effect was observed for the dicylcohexyl phosphine-derived catalyst **52** which gave racemic product mixtures. Electron-rich phosphine-based organocatalysts were very reactive but unfortunately gave only low enantioselectivities.

Table 21: Screening resutls for third generation catalysts – investigation of the effect of electron-rich phosphines on the enantioselectivity.



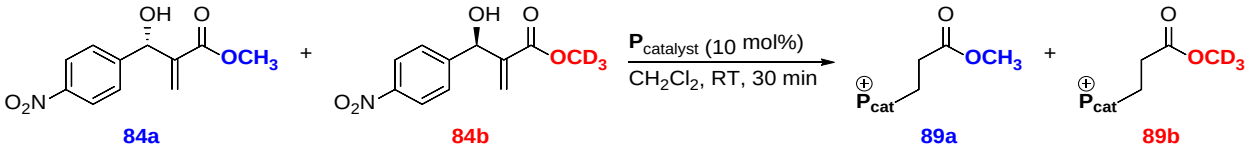
$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])	$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])
 **48g**	79:21 (79:21)	 **52**	50:50 (49:51)
 **48h**	80:20 (81:19)		

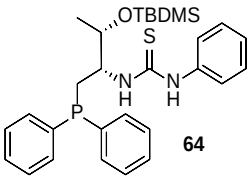
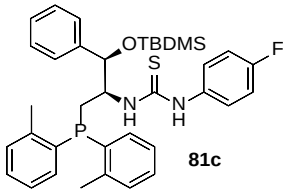
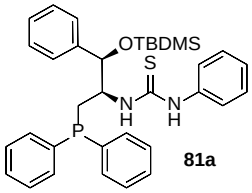
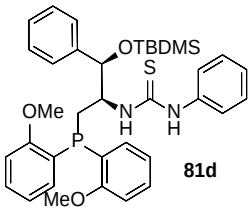
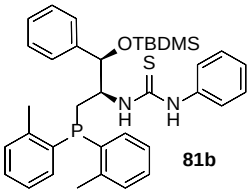
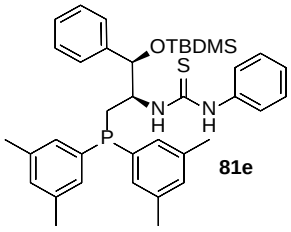
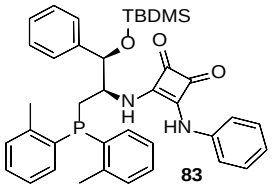
[a]: Reaction conditions: 4-nitrobenzaldehyde (1.0 eq.), methyl acrylate (1.5 eq.), 10 mol% catalyst, CH_2Cl_2, RT, 18 hours. Determined by HPLC on a chiral stationary phase.

In the fourth catalyst generation the effect of the stereogenic center at the secondary alcohol position was studied (Table 22). In the case of the threonine-based organocatalysts **64**, the e.r. was improved from 23:77 to 13:87 by switching from the (*R*,*S*)- to the (*S*,*S*)-diastereomer. Motivated by this result, various *like*-diastereomers of phenyl serine-derived organocatalysts were screened and we were pleased to see that for each catalyst a higher selectivity was observed (see Tables 18-21 for the (*R*,*S*)-analogs). Again, electron rich phosphines such as the 3,5-dimethylphenyl (catalyst **81e**) or the 2-methoxyphenyl (catalyst **81d**) substituted phosphines gave

lower selectivities. Moreover, for catalyst **81e** racemization was observed during the preparative MBH reaction. Unfortunately, no further improvement of the selectivity was detected by replacing the thiourea unit by a squaramide group (catalyst **83**). These results show that the stereogenic center at the alcohol position can influence the selectivity of the catalyst and that the *like*-diastereomer is the preferred diastereomer.

Table 22: Screening resutls for forth generation catalysts – investigation of the effect of the chiral backbone and phosphine residue on the enantioselectivity.



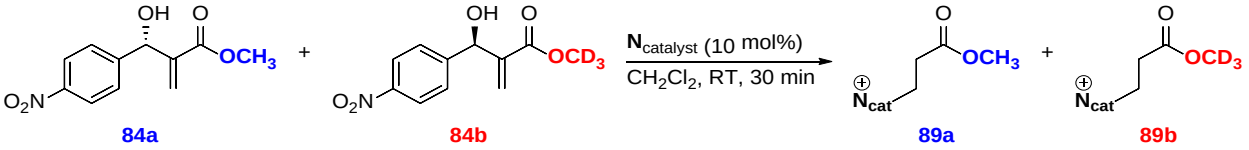
$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])	$P_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])
 **64**	13:87 (13:87)	 **81c**	95:5 (95:5)
 **81a**	93:7 (94:6)	 **81d**	71:29 (71:29)
 **81b**	95:5 (95:5)	 **81e**	89:11 (89:11[b])
 **83**	93:7 (92:8)		

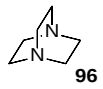
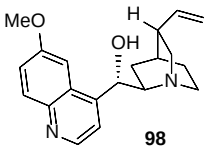
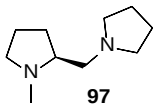
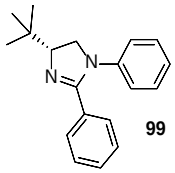
[a]: Reaction conditions: 4-nitrobenzaldehyde (1.0 eq.), methyl acrylate (1.5 eq.), 10 mol% catalyst, CH_2Cl_2, RT, 18 hours. Determined by HPLC on a chiral stationary phase. [b]: Ratio determined after 30 minutes.

2.3.2 Single Catalyst Screening of Tertiary Amine Catalysts

Herein, tertiary amines were applied to the back reaction screening protocol. Unfortunately, back reaction was not detected by ESI-MS for DABCO **96**, chiral diamine catalyst **97**, chiral quinine catalyst **98** or chiral imidazole-based catalyst **99** using the standard screening conditions (Table 23). For all catalyst the corresponding forward reaction was observed and for the chiral amine-based organocatalysts some levels of enantioselectivity were determined by HPLC analysis on a chiral stationary phase.

Table 23: Screening results for amine-based catalysts.



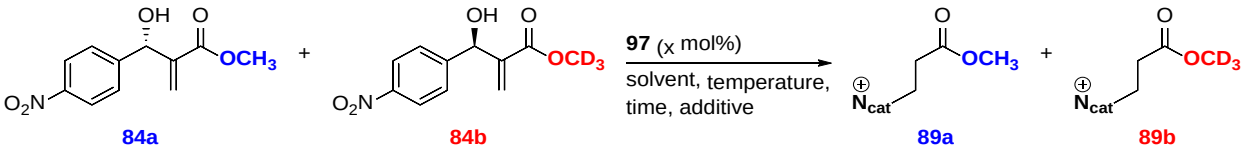
$N_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])	$N_{catalyst}$	**ESI-MS screening 89a/89b** (e.r. prep.[a])
 **96**	n.d.[b] (50:50)	 **98**	n.d.[b] (70:30)
 **97**	n.d.[b] (63:37)	 **99**	n.d.[b] (55:45)

[a]: Reaction conditions: 4-nitrobenzaldehyde (1.0 eq.), methyl acrylate (1.5 eq.), 10 mol% catalyst, CH_2Cl_2, RT, 18 hours. Determined by HPLC on a chiral stationary phase. [b]: No back reaction intermediates detected by ESI-MS analysis.

For the diamine catalyst **97** the reaction parameters for the back reaction screening were investigated (Table 24). When dichloromethane was used as the solvent, the back reaction was not observed using longer reaction times (entries 1-2), higher temperature (entry 3) or higher catalyst loading (entry 4). One explanation might be that the proton transfer is too high in energy and therefore the back MBH reaction cannot take place. The proton transfer could be accelerated by the addition of protic additives which in principle might have a positive effect on the *retro*-activity. Unfortunately, for all additives tested, formation of back reaction intermediates (entries 5-

6) was not detected by ESI-MS analysis. Also when the solvent was changed to *iso*-propanol the formation of catalyst-substrate adducts **89a**/**89b** was not observed under various screening conditions (entries 8-10). Moreover, even the intermediate which should be formed after nucleophilic attack of the catalyst to the MBH adduct was not detected by ESI-MS. Compared to phosphines, amines are less nucleophilic and therefore the nucleophilic attack to the substrate might be disfavored.

Table 24: Screening of reaction parameters for back reaction screening.



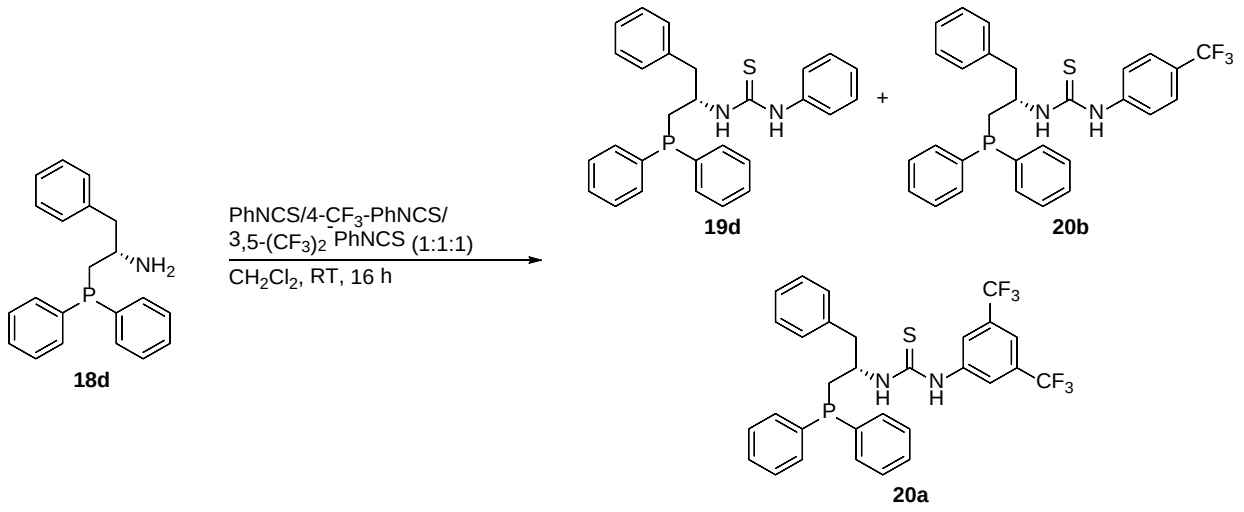
entry	x mol%	solvent	temperature [°C]	time [min]	additive	ESI-MS screening 89a/89b
1	10	CH_2Cl_2	25	30	no	n.d.[a]
2	10	CH_2Cl_2	25	120	no	n.d.[a]
3	10	CH_2Cl_2	50	30	no	n.d.[a]
4	10	CH_2Cl_2	50	120	no	n.d.[a]
5	30	CH_2Cl_2	25	30	no	n.d.[a]
6	10	CH_2Cl_2	25	30	PNP (10 mol%)	n.d.[a]
7	10	CH_2Cl_2	25	30	water (10 mol%)	n.d.[a]
8	10	iPrOH	25	30	no	n.d.[a]
9	10	iPrOH	25	120	no	n.d.[a]
10	10	iPrOH	50	30	no	n.d.[a]

[a]: No back reaction intermediates detected by ESI-MS analysis.

2.3.3 Multi-Catalyst Screening

Conventional determination of catalyst selectivities relies on product analysis by HPLC or GC on a chiral stationary phase. Using the back reaction screening methodology, evaluation of several catalysts with different molecular masses in a single experiment should be possible because each phosphine will form mass-labelled adducts, that appear at different positions in the mass spectrum. Moreover, in principle, crude mixtures of phosphines could be applied in the multi-catalyst ESI-MS screening because potential catalytically active impurities should not influence the ratios of the detected phosphine intermediates. The only requirements for the multi-catalyst screening are that all catalysts in the crude mixture should have a similar activity in the back MBH reaction and that the signals of the mass-labelled substrate-catalyst intermediates should not overlap.

First, a crude mixture of the first generation catalysts was synthesized to investigate the effect of the *N*-aryl residue at the thiourea moiety on the stereoselectivity of the reaction. For that purpose, amino phosphine **18d** was reacted for 16 hours with an equimolar mixture of three different aromatic isothiocyanates. After evaporation of the solvent under high vacuum, a crude mixture which contained three catalysts was obtained (Scheme 32).



Scheme 32: Synthesis of the crude catalyst mixture for the first catalyst generation.

This mixture was subjected to the standard back reaction screening protocol and after 30 minutes all three catalyst-substrate adducts were detected with high intensity (Figure 13). Moreover, the ratios perfectly matched with the results from the single catalyst screening protocol (ratio in brackets).

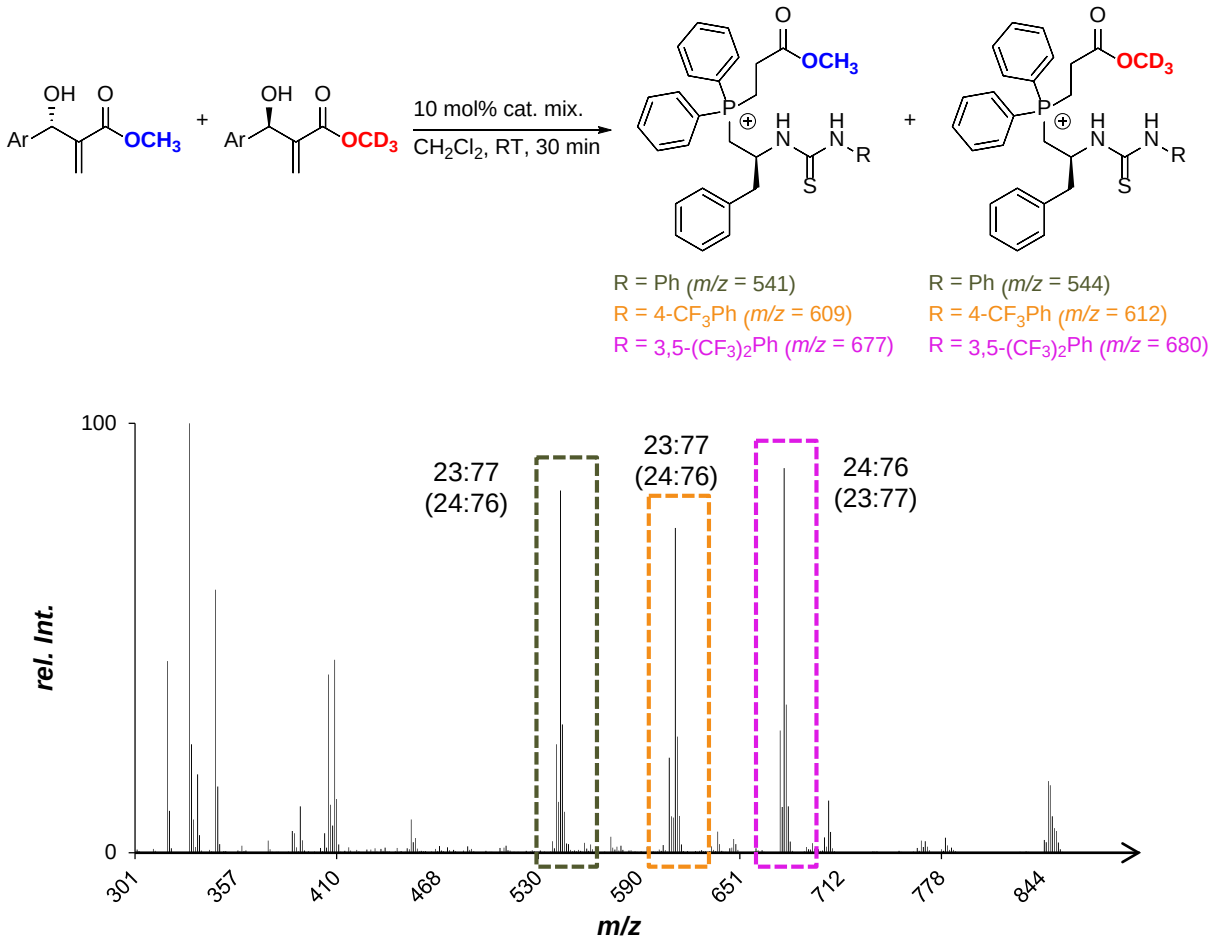
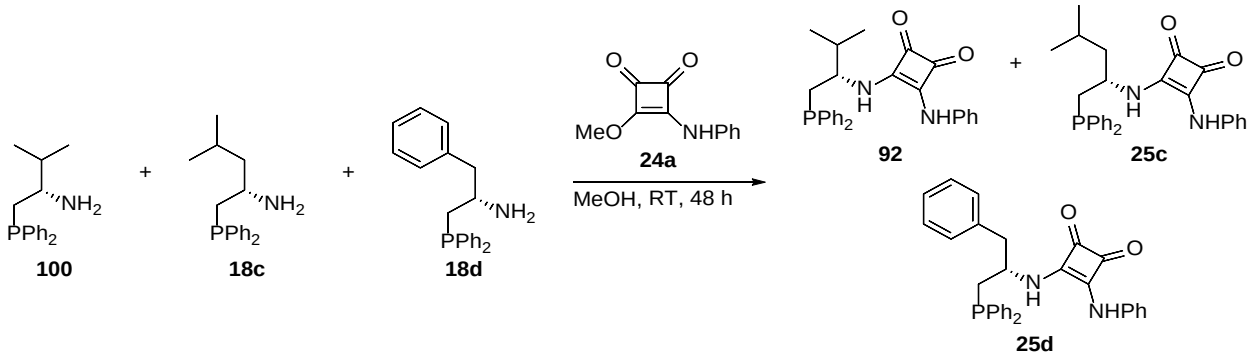


Figure 13: Results of the catalyst mixture screening of first generation catalyst.

Next, the one-batch crude mixture screening was extended to the second catalyst generation. An equimolar mixture of three different amino phosphines was treated with squaramide precursor **24a** and after two days the precipitated catalyst mixture was filtered off (Scheme 33). With this approach only one screening experiment is needed for the investigation of the effect of the chiral backbone on the enantioselectivity of the MBH reaction



Scheme 33: Synthesis of the crude catalyst mixture for the second catalyst generation.

For all catalysts the corresponding key-intermediates were detected by ESI-MS analysis. However, compared to thiourea-based catalysts the intensity was lower due to the lower reactivity of the squaramide-based phosphines. Again the most selective catalyst could be directly identified from the crude mixture (Figure 14).

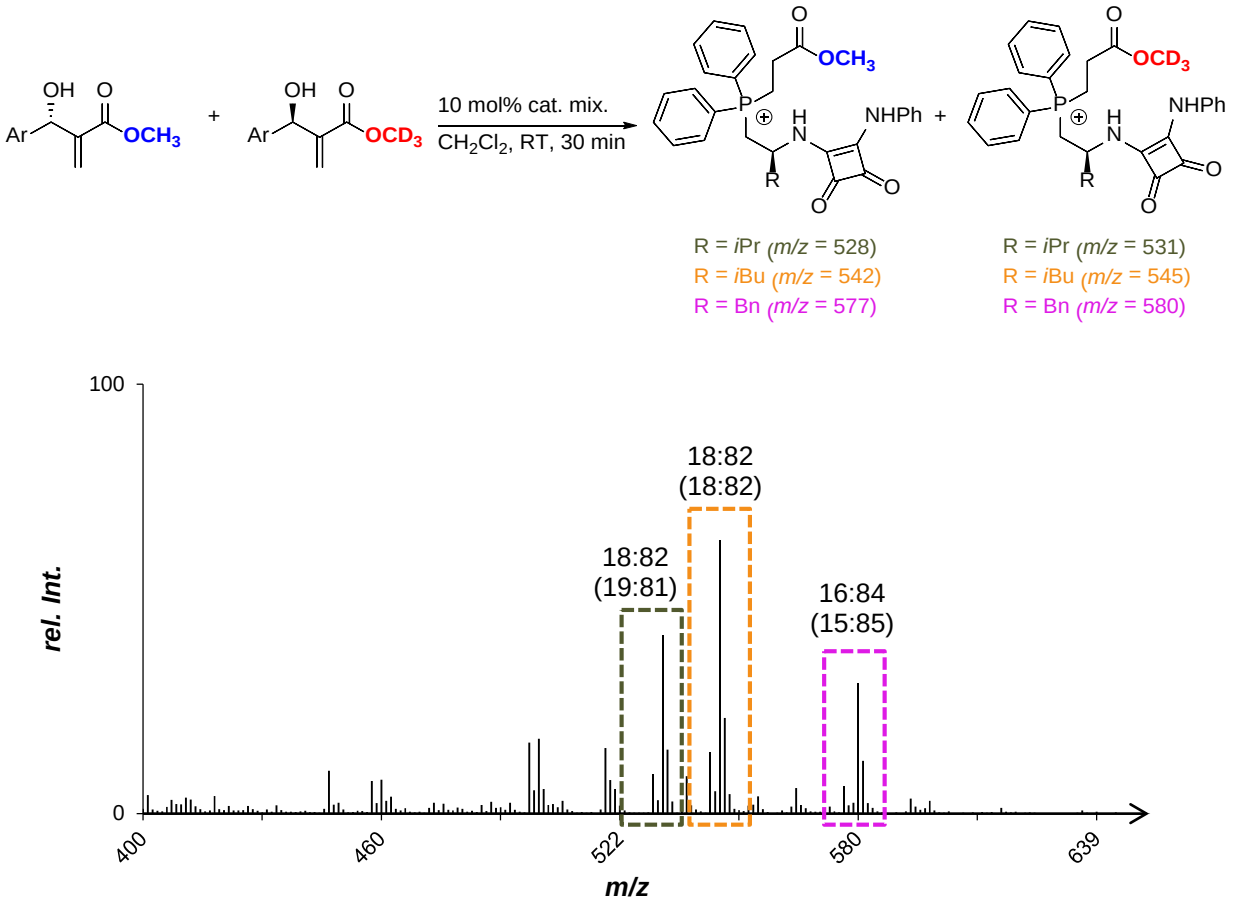
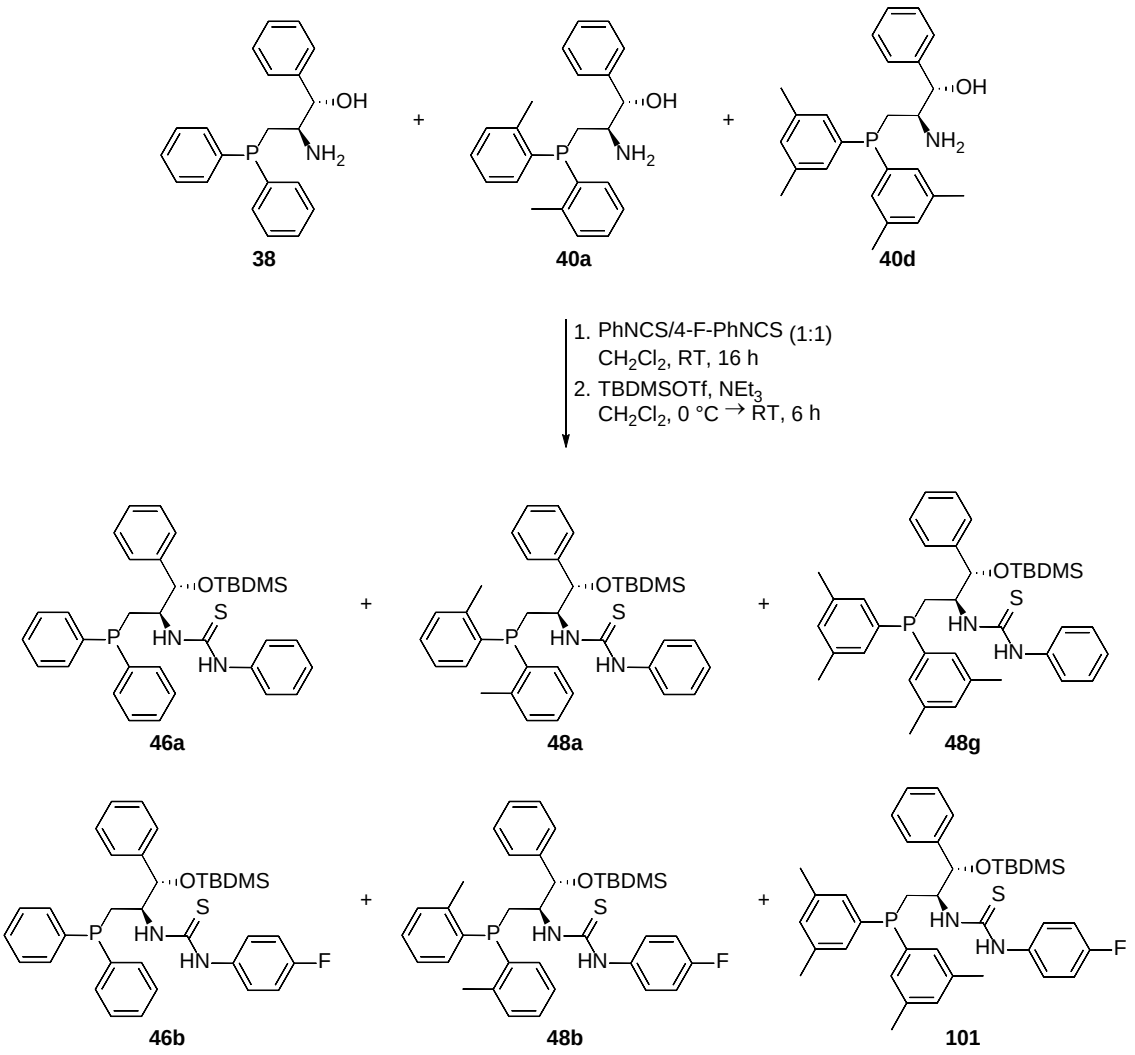


Figure 14: Results of the catalyst mixture screening of second generation catalyst.

The modular structure of third generation catalyst seemed to be ideal for the crude catalyst mixture screening protocol due to the two different positions that can be derivatized during the synthesis. In this case a library of six catalysts was synthesized following a two-step procedure. Three different amino phosphines were mixed with a one to one mixture of two aryl isothiocyanate precursors to form the resulting six thiourea intermediates *in situ*. Afterwards, the crude mixture was dried under high vacuum for four hours, the secondary alcohol was TBDMS protected and after aqueous workup the crude catalyst mixture was obtained (Scheme 34).



Scheme 34: Synthesis of crude catalyst mixture for the third catalyst generation.

By using the catalyst mixture from above, the effect of the phosphine substituents and the influence of the *N*-aryl substituent was investigated in one experiment. Thus, the resulting crude mixture was directly subjected to back reaction screening. For all catalysts the corresponding

signals of intermediates **89a** and **89b** were detected. Although the selectivities obtained by multi-catalyst screening were somewhat lower than the e.r. values from single catalyst screening, the selectivity order among the six catalysts was correctly displayed by the data. Thus, the most selective catalysts in a combinatorial library can be readily identified using this screening protocol (Figure 15). The deviation of the ratios **89a**/**89b** from the actual e.r. values is likely caused by the high catalyst loading (30 mol%) that had to be used in order to obtain satisfactory signal to noise ratios. Under these conditions the assumption of a rapid pre-equilibrium between **85a** and **86a**, and **85b** and **86b**, is no longer valid.

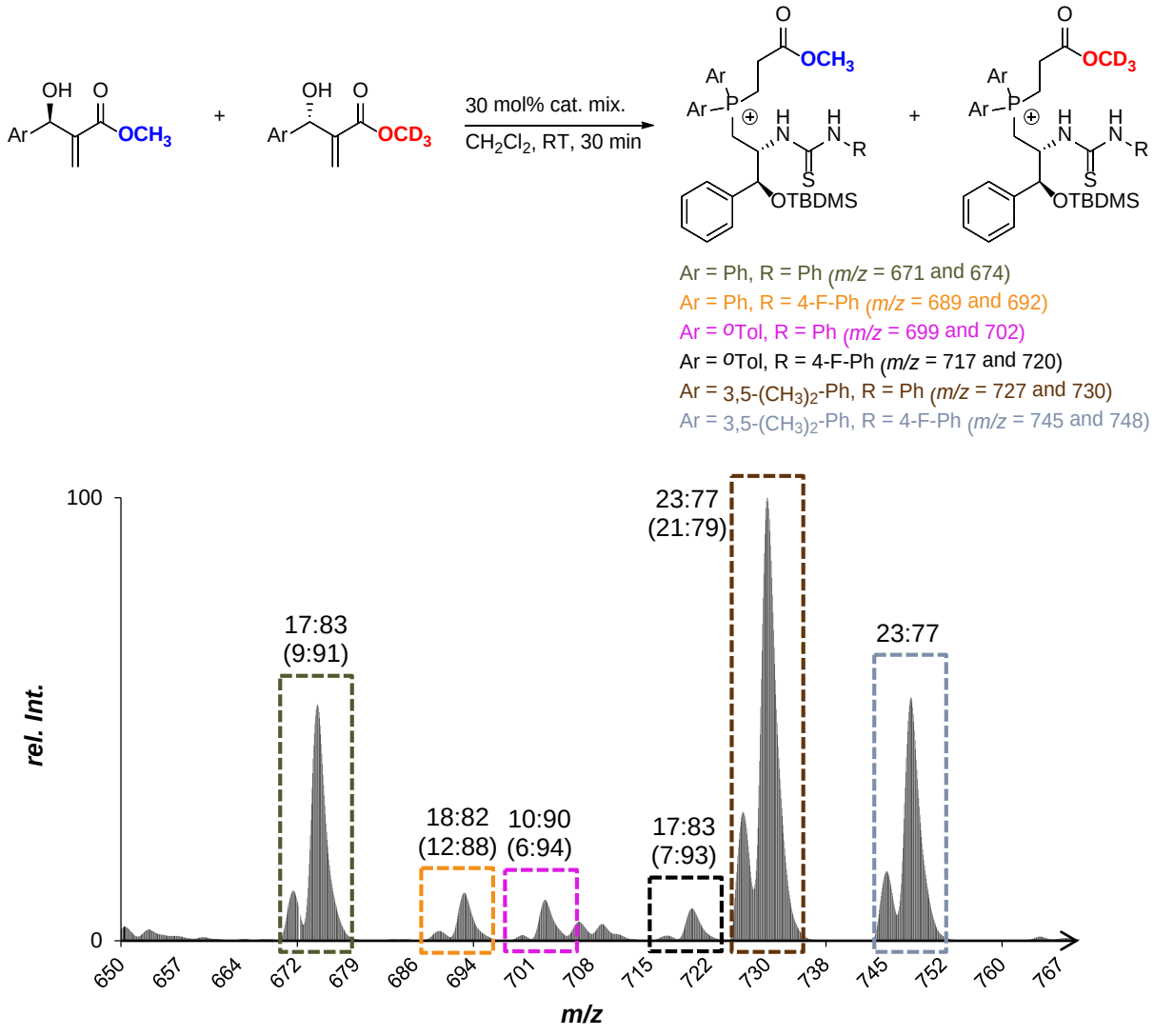
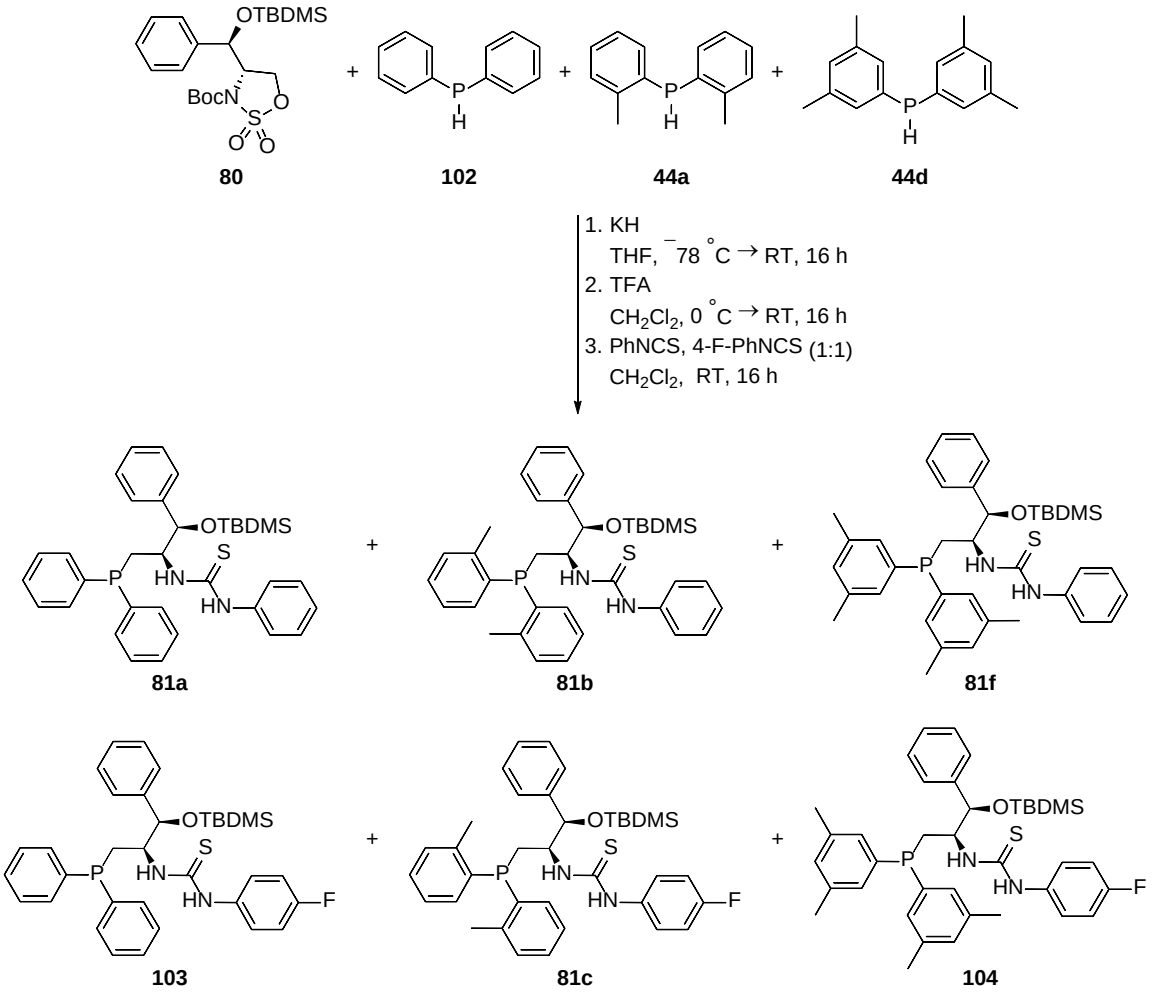


Figure 15: Results of the catalyst mixture screening of third generation catalyst.

For the fourth generation catalysts a crude catalyst synthesis was developed which began from the *N*-Boc protected cyclic sulfonamidate **80**. The advantage of this method is, that no amino phosphine precursor has to be isolated in advance. In the first step, the amino phosphine intermediates were formed by nucleophilic attack of the sulfonamidate by an equimolar mixture of a phosphide solution prepared from phosphines **102**, **44a** and **44d**. After hydrolysis and aqueous work up the crude mixture was directly used in the Boc deprotection step with TFA. Then, the crude reaction mixture from the deprotection step was washed with saturated aqueous sodium carbonate solution and the crude amine mixture was used without purification. A subsequent coupling reaction with two different isothiocyanate precursors gave six different bifunctional phosphines (Scheme 35).



Scheme 35: Synthesis of crude catalyst mixture for the fourth catalyst generation.

The catalyst mixture was then directly subjected to back reaction screening and after 30 minutes all intermediate ratios could be determined by ESI-MS analysis. The most selective catalyst was clearly identified, but again a slight variation of the ratios between multiple and single catalyst screening was observed. These results demonstrate the potential of the screening protocol for combinatorial catalyst development.

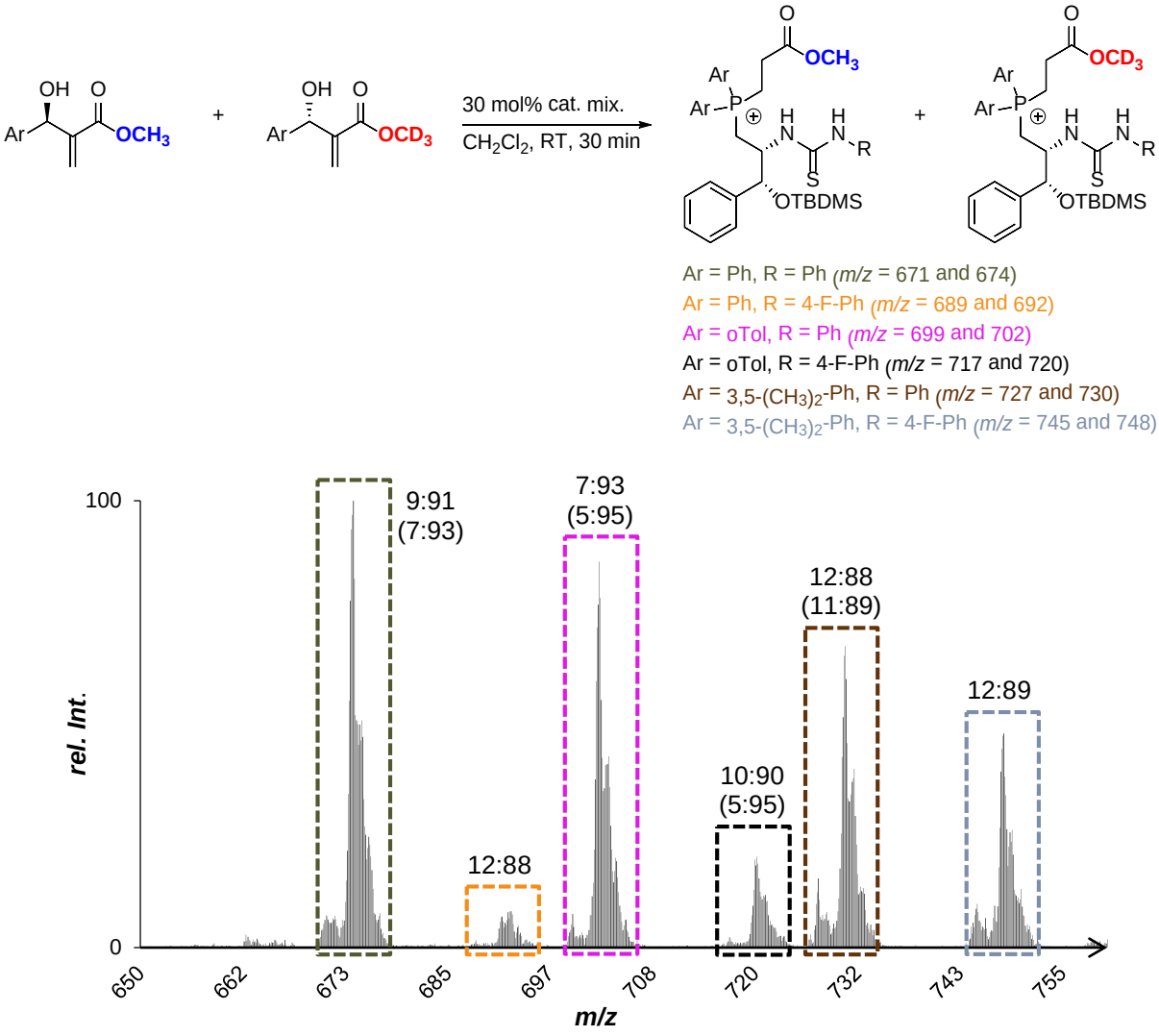


Figure 16: Results of the catalyst mixture screening of fourth catalyst generation.

2.4 Mechanistic Investigations

The results obtained from the back reaction screening also provided insights into the catalytic cycle. Mechanistic studies of amine-catalyzed MBH reactions have shown that C–C bond formation and the subsequent proton transfer have similar activation barriers and, depending on the reaction conditions, one or the other step may become primarily rate-limiting. For phosphine-based catalysts only a computational study was reported, which predicted the proton transfer step to be rate-determining. However, Plata and Singleton have recently demonstrated that at present computational methods are unable to cope with the complex multi-step catalytic cycle of MBH reactions and, therefore, fail to produce reliable results.[53]

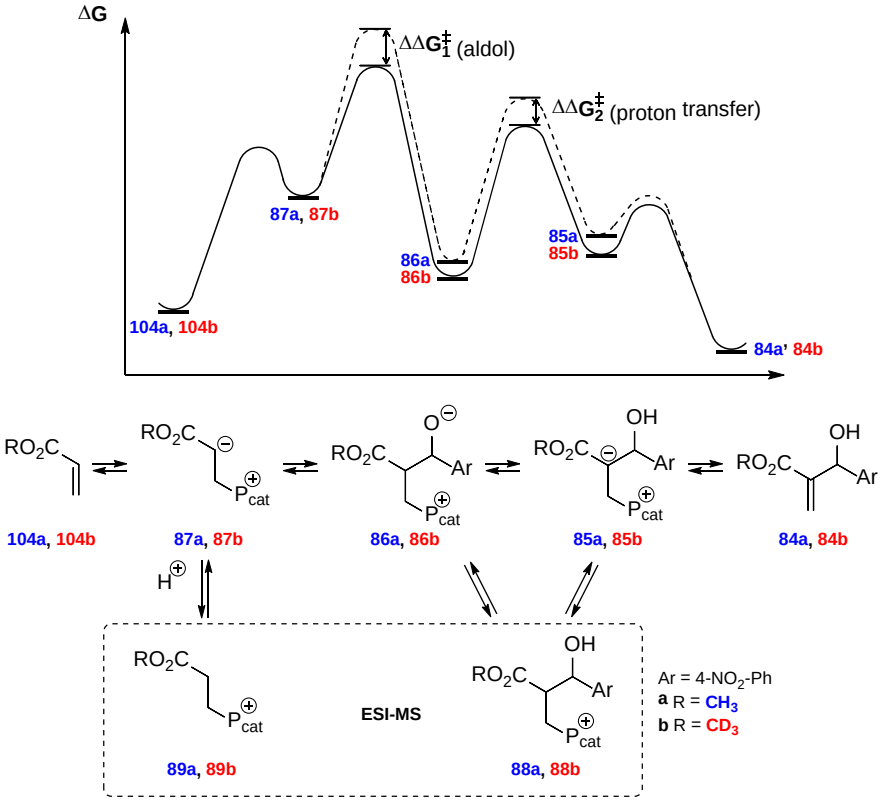


Figure 17: Estimated qualitative energy profiles based on the results from the ESI-MS back reaction screening.

The close match between the selectivities obtained from the back reaction screening and the preparative forward reaction indicates that C–C bond formation is the rate- and enantioselectivity-determining step. A qualitative reaction coordinate consistent with the selectivity data is shown in Figure 17. The consensus between the product e.r. of the forward reaction and the ratio **87a**/**87b**

determined from the ESI-MS signals of intermediates **89a** and **89b** in the back reaction implies that both ratios depend on the same transition state. This is the case if the aldol step is the step with the highest energy barrier. If the proton transfer were rate-determining (Figure 18), equilibration between intermediates **86a**/**86b** and **87a**/**87b** would occur, due to the now reversible aldol step. Thus, the ratio **89a**/**89b** would depend on both $\Delta\Delta G^{\ddagger}$ of the proton transfer and the equilibrium constants $K_{(\mathbf{86a/87a})}$ and $K_{(\mathbf{86b/87b})}$, which differ because of the unequal relative energies of **86a** and **86b**, while the enantioselectivity of the forward reaction would be determined solely by $\Delta\Delta G^{\ddagger}$ of the proton transfer. Accordingly, the ratio **89a**/**89b** would be expected to deviate from the e.r of the forward reaction, in contradiction to the observed match between the forward and back reaction.

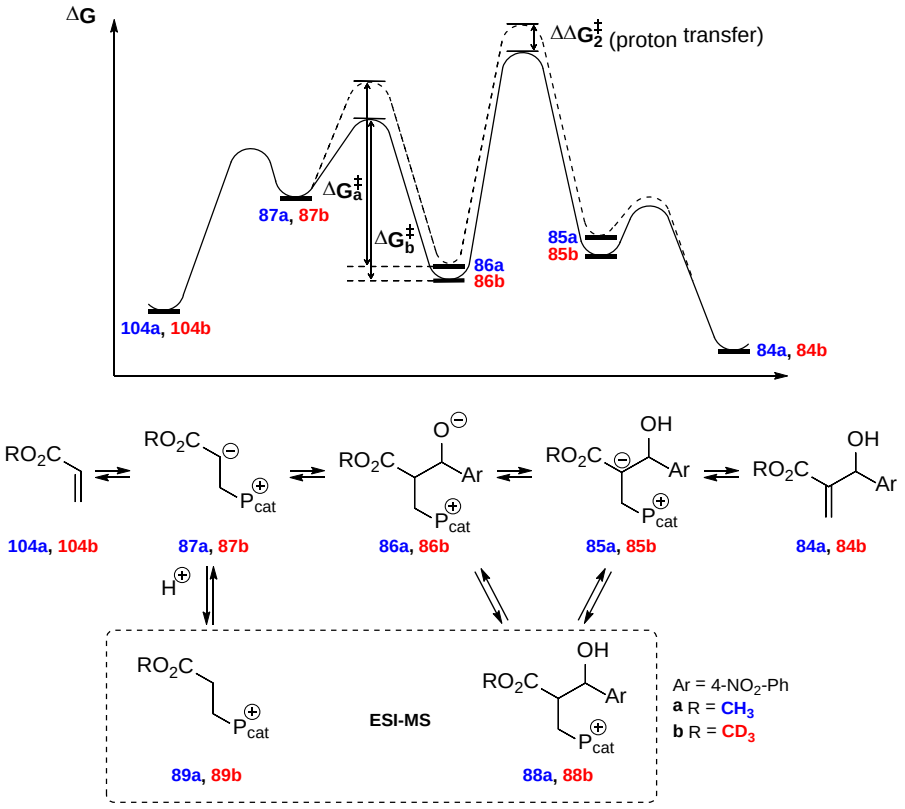


Figure 18: Estimated qualitative energy profiles based on the results from the ESI-MS back reaction screening.

In addition, kinetic measurements were carried out to determine the reaction order in aldehyde by *in situ* ^{1}H-NMR analysis of reaction process based on the signals of the methyl ester group of acrylate **104a** (3.73 ppm) and MBH adduct **84a** (3.71 ppm). Data were taken from four reactions, in which the aldehyde/acrylate ratio was varied from 0.5 to 3.0. The results clearly showed the reaction to be first order in aldehyde, providing further evidence that the aldol step is rate-limiting (Figure 19).

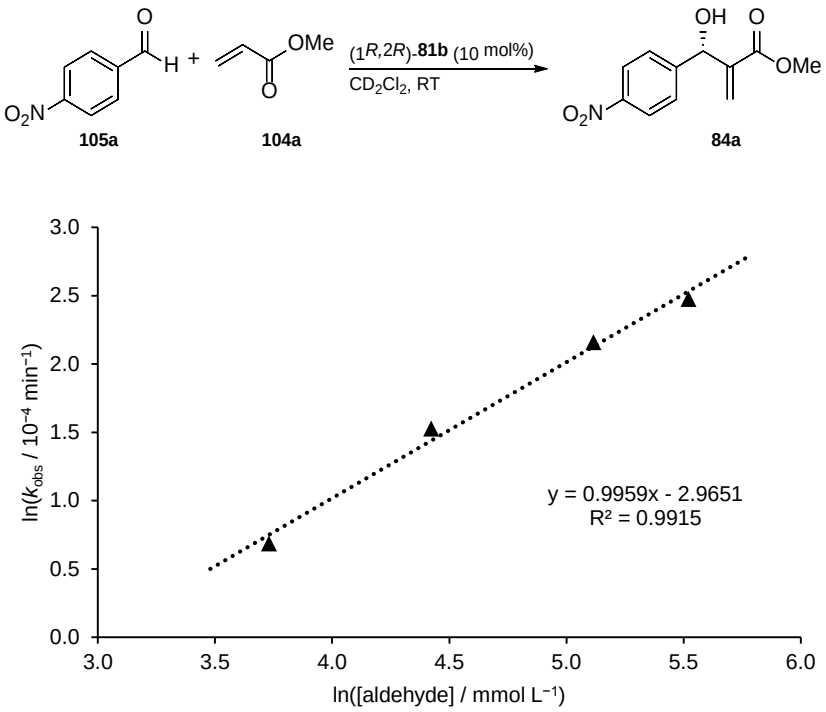
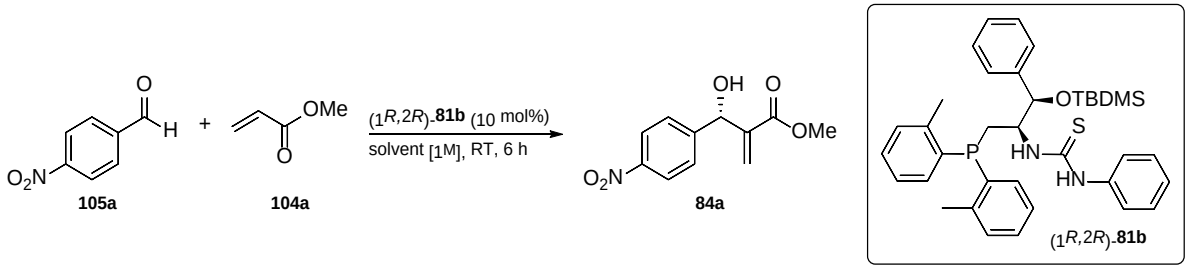


Figure 19: Kinetic analysis of the MBH reaction of methyl acrylate with 4-nitrobenzaldehyde. Double logarithmic plot of the dependence of the reaction rate on the initial aldehyde concentration. The data points correspond to aldehyde concentrations of 41.7, 83.3, 166.7, and 250.0 mmol/L and a constant acrylate concentration of 83.3 mmol/L. Linear fit for **105a**: y = 0.9959x –12.175 (R^2 = 0.99), consistent with first order in **105a**.

2.5 Optimization of the Preparative Reaction

From our screening experiments with 62 catalysts, three efficient catalysts (1*R*,2*R*)-**81b**, (1*S*,2*R*)-**48a**, and (1*S*,2*R*)-**48d**, have emerged which all induce an e.r. of 95:5 in the reaction of methyl acrylate with 4-nitrobenzaldehyde. For further studies addressing the reaction parameters, (1*R*,2*R*)-**81b** was chosen because of its higher reactivity. First, the effect of different solvents was investigated. Using aprotic-polar solvents such as THF or Me-THF high yield and very good enantioselectivities were achieved (Table 25, entries 1-2). When the solvent system was changed to non-polar dichloromethane the enantiomeric excess was reduced by 4% (entry 3). On the other side, the same result like for THF was observed for toluene (entry 4). For protic solvents such as hexafluoro-2-propanol (HFIP) no conversion or for methanol low yield and enantioselectivity were detected (entries 5-6). Because of the acidity of HFIP, the enolate intermediate might be protonated which would quench the reactivity. In the case of MeOH, the hydrogen-bonding network of the catalyst-substrate intermediate could be disturbed which would influence the selectivity. Also the polar solvents acetonitrile and propylene carbonate gave only poor results (entries 7-8).

Table 25: Screening of different solvents for the MBH reaction with 4-nitrobenzaldehyde **105a**.[a]

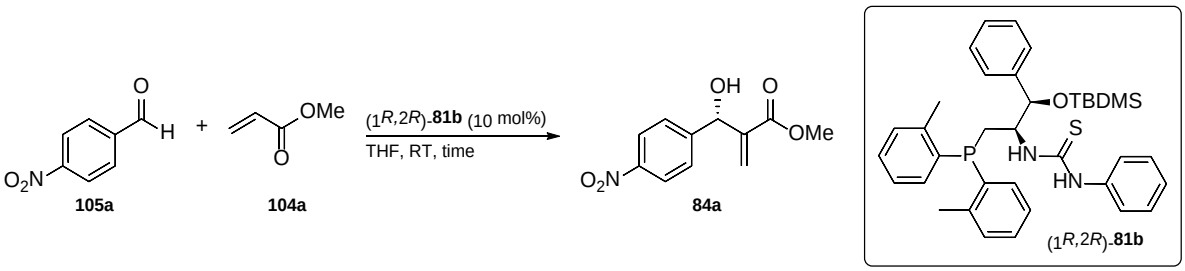


entry	solvent	yield [%][b]	*ee* [%][c]	entry	solvent	yield [%][b]	*ee* [%][c]
1	THF	92	94 (*S*)	5	HFIP	n.d.[d]	-
2	Me-THF	90	93 (*S*)	6	MeOH	60	64 (*S*)
3	CH_2Cl_2	91	90 (*S*)	7	MeCN	70	80 (*S*)
4	Toluene	92	94 (*S*)	8	PC	74	80 (*S*)

[a]: 0.1 mmol **105a**, 0.2 mmol **104a** in 0.1 mL solvent. [b]: After purification by preparative TLC. [c]: Determined by HPLC on a chiral stationary phase. [d]: No conversion to the product was observed by ^{1}H-NMR analysis of the crude mixture.

Next, the influence of reaction time, ratio of the two starting materials, concentration, catalyst loading and addition of molecular sieves were investigated. Using a 5:1 acrylate to aldehyde ratio the MBH adduct was obtained with high yield and enantiomeric excess after both eight hours and six hours reaction time (Table 26, entries 1-2). When, the amount of methyl acrylate was lowered from five to two equivalents no loss of reactivity was observed (entry 4). Slightly higher enantioselectivity was obtained when the reaction solution was more diluted, however a lower yield was obtained (entry 5). With the use of activated molecular sieves the yield was further improved (entry 6). With a lower catalyst loading (5 mol%), lower yield and enantioselectivity were obtained using the standard conditions (entry 7).

Table 26: Screening of different reaction parameters for the MBH reaction with 4-nitrobenzaldehyde.

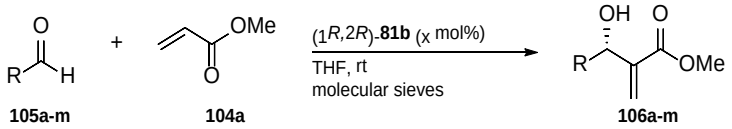


entry	105 [mmol]	104a [mmol]	time [h]	THF [µL]	yield [%][a]	*ee* [%][b]
1	0.1	0.5	8	50	98	93 (*S*)
2	0.1	0.5	6	50	96	93 (*S*)
3	0.1	0.5	4	50	93	93 (*S*)
4	0.1	0.2	6	50	95	93 (*S*)
5	0.1	0.2	6	100	92	94 (*S*)
6[c]	0.1	0.2	6	100	98	94 (*S*)
7[c,d]	0.1	0.2	6	100	84	92 (*S*)

[a]: After purification by preparative TLC. [b]: Determined by HPLC on a chiral stationary phase. [c]: 50 mg Activated molecular sieves were used. [d]: 5 mol% Organocatalysts was used.

After the reaction conditions were optimized, the substrate scope was analyzed. Under the optimized conditions a wide range of aromatic and heteroaromatic aldehydes afforded the resulting chiral MBH products with high enantioselectivities and yield in the preparative reaction (Table 27, entries 1-12), with the exception of 4-methylbenzaldehyde **105k**, which showed lower reactivity (entry 11) and cyclohexane carbaldehyde **105l**, which gave only low enantiomeric excess and yield. Overall, catalyst (1*R*,2*R*)-**81b** clearly outperformed the best literature-known catalysts such as (2*R*,3*S*)-**37** in terms of enantioselectivity and yield.

Table 27: Substrate scope.[a]



entry	R	product	x	t [h]	yield [%][b]	*ee* [%][c]
1	4-NO_2-C_6H_4 (**105a**)	**106a**	10	6	98	94 (*S*)
2	2-NO_2-C_6H_4 (**105b**)	**106b**	10	6	88	80 (*S*)
3	4-CN-C_6H_4 (**105c**)	**106c**	10	18	93	92 (*S*)
4	3,5-(CF_3)-C_6H_3 (**105d**)	**106d**	10	18	98	92 (*S*)
5	4-F-C_6H_4 (**105e**)	**106e**	20	48	69	90 (*S*)
6	4-Cl-C_6H_4 (**105f**)	**106f**	20	48	89	90 (*S*)
7	4-Br-C_6H_4 (**105g**)	**106g**	20	48	90	92 (*S*)
8	C_6H_5 (**105h**)	**106h**	20	72	82 (73)[d]	90 (*S*) (90)[d]
9	2-pyridine (**105i**)	**106i**	20	72	95	90 (*S*)
10	2-furfural (**105j**)	**106j**	20	72	83	80 (*S*)
11	4-Me-C_6H_4 (**105k**)	**106k**	20	96	42	85 (*S*)
11	C_6H_{11} (**105l**)	**106l**	20	96	36	30 (*S*)

[a]: 0.1 mmol **105a-m**, 0.2 mmol **104a** in 0.1 mL THF. [b]: After purification by preparative TLC. [c]: Determined by HPLC on a chiral stationary phase. [d]: 1 mmol scale.

2.6 Conclusion

In conclusion, the synthesis of four different catalyst generations starting from commercially available amino acids was described in this chapter (Figure 20). The effect of the chiral backbone, the H-bond donor moiety and the phosphine residue on the enantioselectivity of the MBH reaction was investigated by evaluating these catalysts.

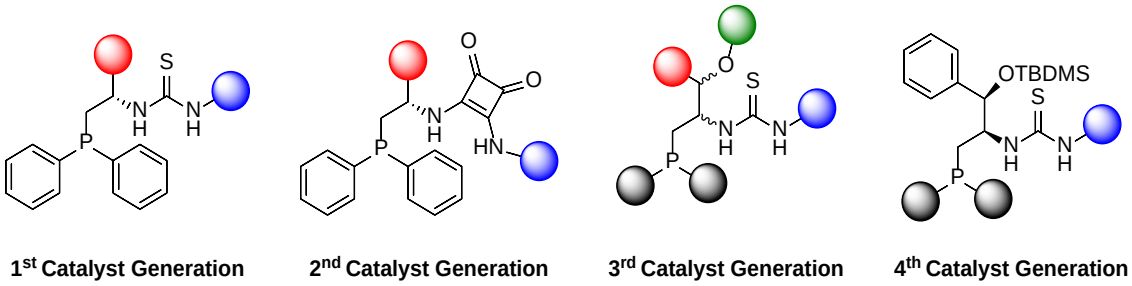


Figure 20: Overview about synthesized catalyst generations.

Moreover, the potential of mass spectrometric back reaction screening for the evaluation of catalysts for asymmetric MBH reactions was demonstrated. Screening of 62 bifunctional phosphines has led to an efficient catalyst for the reaction of methyl acrylate with aldehydes, showing improved enantioselectivity and scope compared to previously reported catalysts (Figure 21). Finally, the back reaction screening protocol was successfully extended to multi-catalyst screening of crude catalyst mixtures containing up to six bifunctional phosphines.

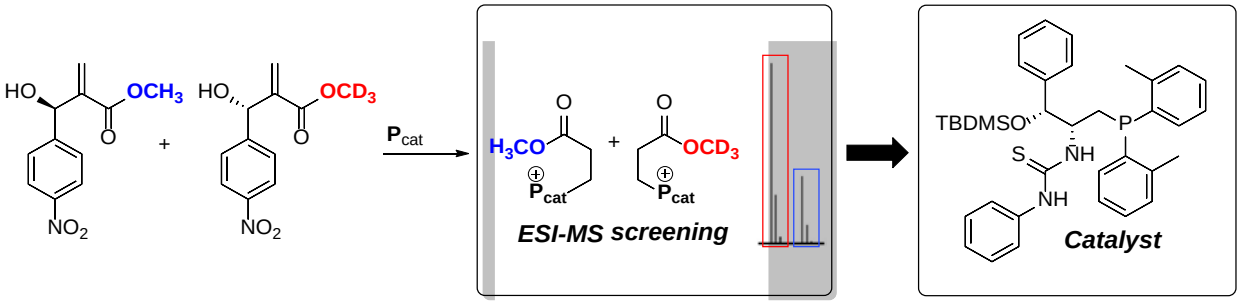


Figure 21: Evaluation of chiral bifunctional phosphines by back reaction screening.

In addition, the results from back reaction screening and additional kinetic studies have provided evidence that the enantioselectivity is determined in the C–C bond-forming step which is turnover-limiting.

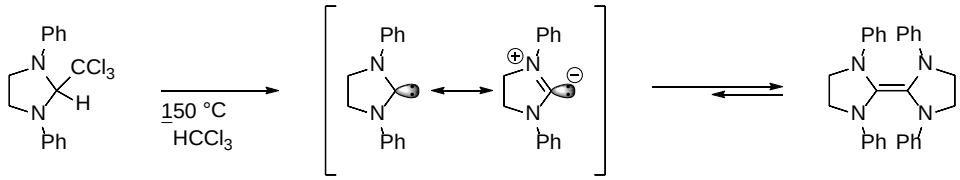
Chapter 3

Asymmetric Cross-Benzoin Reaction

3.1 Introduction

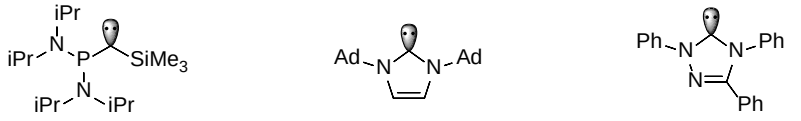
3.1.1 *N*-Heterocyclic Carbenes

Carbenes are neutral carbon-based molecules that contain a divalent carbon atom with an electron sextet.[72] Their existence was first postulated by Dumas in 1835.[73] In the early stages of carbene research, it was assumed that carbenes were reactive intermediates that could not be isolated. For example, Wanzlick prepared an *N*-heterocyclic carbene upon vacuum pyrolysis of the corresponding trichloromethyl dihydroimidazole. However, they were only able to isolate the resulting dimeric carbene intermediate due to the high reactivity of the carbene. The equilibrium between the free and the dimeric carbene forms is now referred to as the Wanzlick equilibrium (Scheme 36).[74,75]



Scheme 36: *N*-heterocyclic carbene by Wanzlick.[74]

Years later, after the pioneering reports by Bertrand in 1988[76] and Arduengo in 1991[77] (Figure 22) in which isolable heteroatom-stabilized carbenes were described, the research field which pertains to practical use of carbenes as catalysts for several organo- or metal-catalyzed transformations has grown tremendously.[78] For example, Enders and Teles developed the first triazolium-derived carbene which was the first commercially available *N*-heterocyclic carbene (NHC) catalyst.[79]



Bertrand in 1988[76] **Ardunengo** in 1991[77] **Enders** in 1995[79]

Figure 22: Stable carbenes by Bertrand[76], Arduengo[77] and Enders[79].

The different NHC precursors can be divided into five key categories (Figure 23) depending on the number and nature of the heteroatoms in the ring structure. However, all categories contain at least one nitrogen atom in the ring system as a common element.[80] For organocatalysis, only triazolium-, imidazoline-, imidazole- and thiazole-derived precatalysts are used while cyclic alkyl amino carbenes (CAAC)[81] are predominantly utilized in metal-catalyzed transformations.

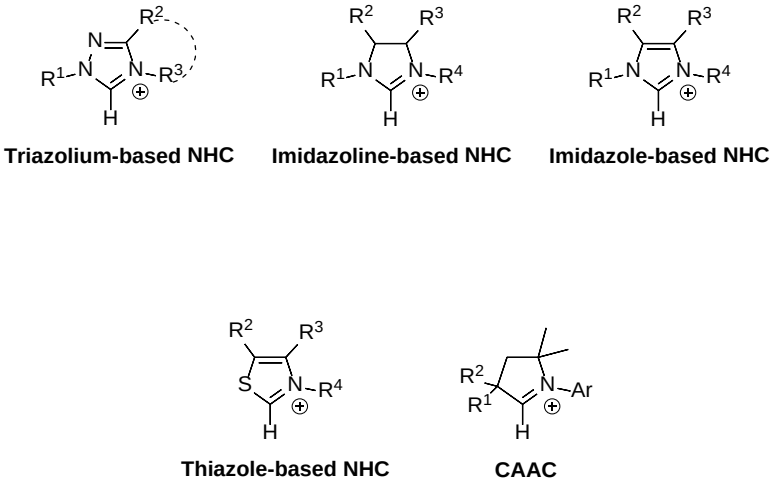


Figure 23: Overview different structure types of NHC precatalysts.

The most common lead structure used in asymmetric organocatalytic carbene-catalyzed reactions contains a triazolium ring system. The modular nature of this type of core structure permits the synthesis of a variety of chiral precatalysts. Furthermore, these type of azoles are easily accessible by many literature-described synthetic procedures.[80] Very often the active carbene is formed upon deprotonation of the azolium precursor by a base. The thermodynamic stability and the reactivity[82] of the resulting nucleophilic carbene is influenced by the different substituents on the triazolium unit (R^1 to R^3) and by heteroatoms in the ring structure. Compared to classical carbenes, NHC's have a singlet ground-state configuration in which the carbene carbon has an sp^2-hybridized lone pair (HOMO) and a *p*-orbital which is part of a π-system with a low lying unoccupied antibonding orbital. The two nitrogen heteroatoms stabilize the free carbene through a π-donating interaction of the *N*-lone pairs with the *p*-orbital. In addition, a σ-withdrawing effect of the C-N bonds exists (Figure 24).[83] The acidity of the different azole-based carbene precursor was investigated by Smith and O'Donoghue, who showed that the most acidic precursor contains a triazolium ring and the acidity can be further increased by installing electron-withdrawing *N*-aryl

substituents.[84] Mayr evaluated the effect of the azole ring and the *N*-substituents on the nucleophilicity experimentally and found that imidazoline-based carbenes are more nucleophilic compared to the triazolium-derived carbenes.[82]

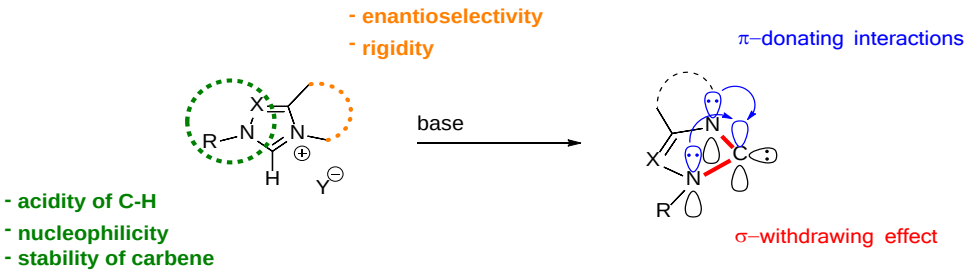
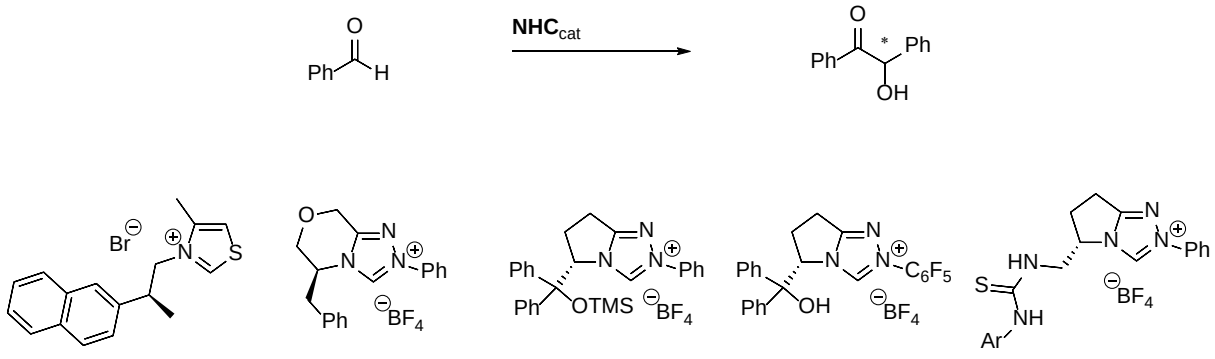


Figure 24: Lead structure for the triazolium-based organocatalysts.

3.1.2 Benzoin Reaction

The most studied carbene-catalyzed reaction is the benzoin reaction in which two aldehydes are coupled to give the so-called homo-benzoin product.[78,80] The first example of a benzoin reaction was discovered by Wöhler and Liebig in 1832 which employed cyanide as catalyst.[85] Much years later the first carbene-based pathway was developed by Ukai using thiazolium salts in combination with a base.[86] After these seminal discoveries were reported many research groups around the world began to design chiral *N*-heterocyclic carbenes for the asymmetric benzoin-coupling (see Scheme 37 for representative reactions of benzaldehyde). The first chiral thiazolium-based catalyst **106** was developed by Sheenan in 1974, from which the chiral benzoin product was obtained in very low yield and moderate enantioselectivity.[87] Years later, Leeper introduced chiral triazolium salt-based precatalysts **107** for the asymmetric aldehyde coupling, and with this new carbene a higher enantiomeric excess and moderate yield was observed.[88] This lead structure was further optimized by the Enders group and from this work precatalyst **108** was developed.[89] This was the first time excellent selectivities and high yield were obtained with a chiral NHC catalyst. One year later, Connon and Zeitler introduced the bifunctional triazolium salt **109** as a powerful catalyst for the asymmetric benzoin reaction showing high reactivity and enantioselectivity.[90] In 2010, the Waser group developed a thiourea-based triazolium salt **110** and they observed high enantioselectivity but low yield in the benzoin coupling.[91]



106

Sheehan in 1974[87] with 9.5 mol% cat-**106**, NEt_3 in MeOH

yield 6%, *ee* 52%

107

Leeper in 1998[88] with 30 mol% cat-**107**, NEt_3 in MeOH

yield 45%, *ee* 80%

108

Enders in 2008[89] with 10 mol% cat-**108**, KHMDS in toluene

yield 66%, *ee* 95%

109

Zeitler in 2009[90] with 4 mol% cat-**109**, Rb_2CO_3 in THF

yield 90%, *ee* 99%

110

Waser in 2010[91] with 5 mol% cat-**110**, K_2CO_3 in THF

yield 17%, *ee* 90%

Scheme 37: Representative examples of carbene-catalyzed asymmetric benzoin reaction.

After more than half a century since the cyanide-catalyzed benzoin condensation mechanism was postulated by Lapworth,[92] the mechanism of thiazolium-catalyzed benzoin reactions was proposed by Breslow in 1958.[93] In this proposal, the thiazolium salt is first deprotonated by an external base to form the active nucleophilic carbene which can then react in the catalytic cycle presented in Figure 25. In the first step, the electrophilic carbonyl carbon is nucleophilically attacked by the carbene, thereby generating the resulting zwitterionic thiazolium-aldehyde intermediate. After a proton shift, the nucleophilic and neutral Breslow intermediate is formed which has an inverted reactivity compared to the aldehyde. Recently, the diamino enol species (Breslow intermediate) derived from imidazoline-based carbene and aromatic aldehydes was characterized by Berkessel using NMR studies.[94] Moreover, the investigations have shown that this intermediate can react as a nucleophilic acyl anion equivalent. In the next step of the catalytic cycle, a second aldehyde molecule is attacked by the Breslow intermediate to form a zwitterionic adduct. The final benzoin product is released after elimination of the carbene catalyst. Very recent computational studies have shown that the proton-transfer step for the formation of the Breslow intermediate is the rate-limiting step.[95,96]

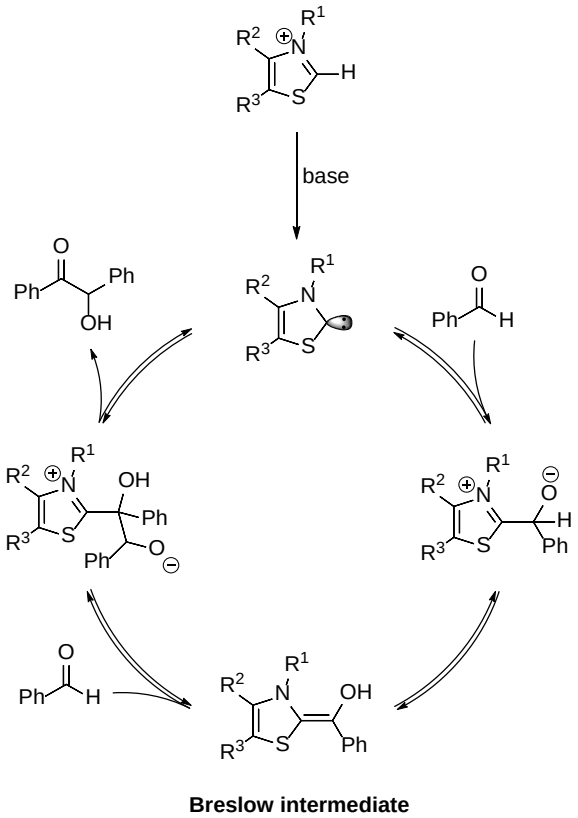


Figure 25: Catalytic cycle of the benzoin reaction proposed by Breslow.[93]

In 2004, the Houk group investigated the stereoselectivity of the asymmetric benzoin reaction. Therein they used computational methods in order to determine the transition state for the enantioselectivity-determining C-C bond formation step.[97] As a model system they studied the benzoin condensation of benzaldehyde catalyzed by a triazolium-based catalyst developed by Enders.[98] The lowest-energy transition state is depicted in Figure 26. Because of steric interactions, the phenyl substituent of the aldehyde in the Breslow intermediate adopts an *anti*-configuration to the *tert*-butyl group of the catalyst to generate an *E*-enolamine intermediate. The aromatic system of the second aldehyde molecule is situated *anti* to the phenyl group of the Breslow intermediate and *anti* to the *N*-phenyl substituent of the catalyst. From the structure of the transition state a distance between the iminium ion and the aromatic system of benzaldehyde of ≈3.4 Å was calculated which is consistent with π-aryl-iminium ion interactions. Therefore, together with the steric shielding of one side by the *tert*-butyl group of the catalyst, the corresponding *re* transition state is favored.

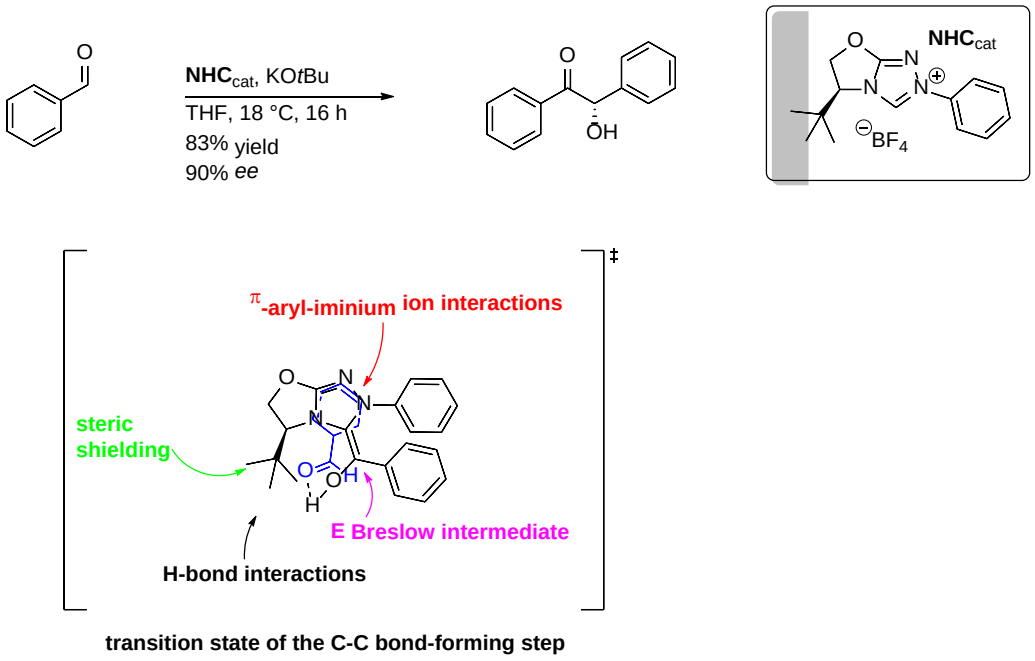
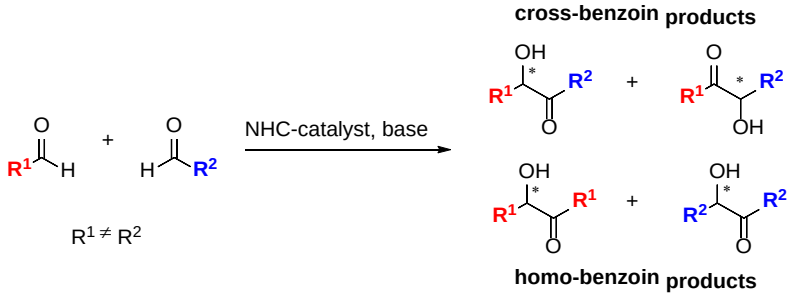


Figure 26: Transition state of the C-C bond-forming step.

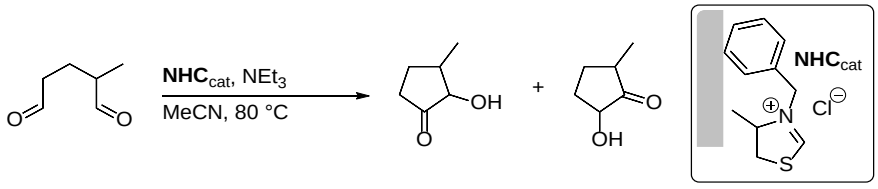
3.1.3 Cross-Benzoin Reaction

The benzoin-type coupling reaction of two different electrophiles catalyzed by a NHC-catalyst is known as the cross-benzoin reaction (with two aldehydes a representative example is shown in Scheme 38). Because of the use of a different second aldehyde, four possible hydroxyl ketone products can be formed. Therefore, the challenging problem in this scenario is to obtain the desired cross-benzoin product chemoselectively in high yield and prevent the formation of to the undesired homo-benzoin products. One strategy which promotes formation of the cross-product is to tune the reactivity of one aldehyde such that the Breslow intermediate is preferably formed with the sterically less demanding or more electrophilic aldehyde. When both aldehydes have similar sterical and electronic chemical properties, a statistical or thermodynamic product mixture is observed. To further complicate this process, the reversibility of the cross-benzoin reaction hampers the chemoselective formation of the kinetic products.[80]



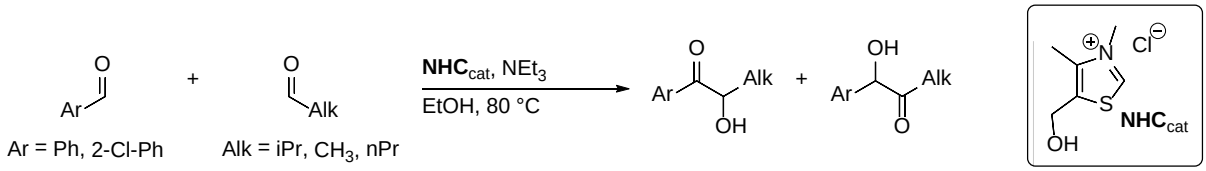
Scheme 38: Cross-benzoin reaction of two aldehydes.

In 1976, the first intramolecular cross-benzoin reaction was developed by Cookson and coworkers. [99] In this approach, the two aldehyde functions of pentanedials were coupled to form a racemic cyclic α-ketol. This transformation was catalyzed by a thiazolium salt, but unfortunately the desired cross-product was not formed chemoselectively and a mixture of both hydroxyl ketones was isolated (Scheme 39).



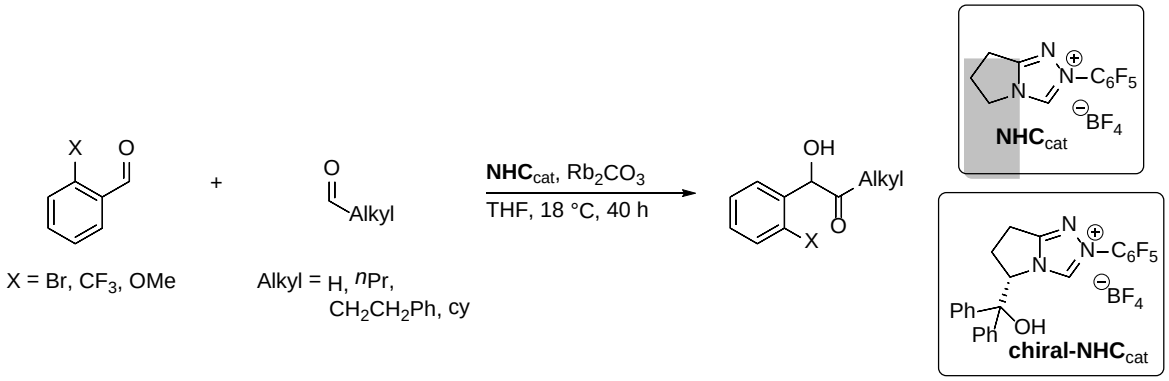
Scheme 39: First intramolecular cross-benzoin reaction by Cookson[99].

In the same year, Stetter introduced the first intermolecular cross-benzoin reaction between aromatic and aliphatic aldehydes catalyzed by a thiazolium derived carbene (Scheme 40). Good chemoselectivity towards the cross-benzoin products was achieved by using an excess (three equivalents) of the aliphatic aldehyde. Nevertheless, only with *ortho* substituted aromatic aldehydes was good selectivity to one cross-acyloin product observed, showing that this reaction was mainly controlled by the substrate.[100]



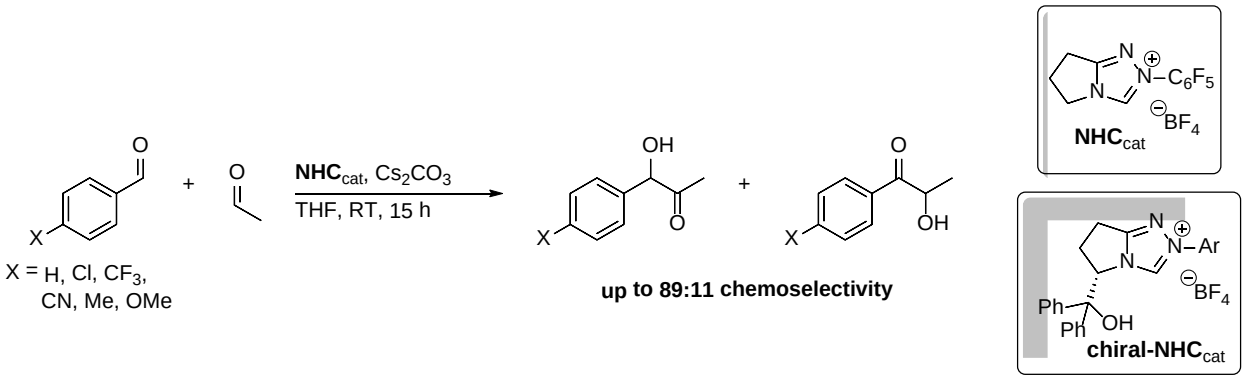
Scheme 40: First intermolecular cross-benzoin reaction by Stetter.[100]

Inspired by the work of Stetter, in 2011 Zeitler and Connon developed a cross-acyloin condensation between aliphatic and *ortho* substituted aromatic aldehydes using a triazolium salt with an *N*-pentafluorophenyl substituent.[101] The resulting cross-benzoin product was isolated with high chemoselectivity and in good yield from a wide variety of substituted aromatic and aliphatic aldehydes (Scheme 41). In this case, high chemoselectivity was achieved because of the selective Breslow intermediate formation with the alkyl aldehyde due to steric hindrance of the *ortho* substituent of the aryl aldehyde. Moreover, *retro*-benzoin reactivity was prevented by steric shielding of the *ortho* residue in the cross-acyloin, which prevented the attack of the NHC catalyst on the product. Finally, an asymmetric cross-benzoin reaction between *ortho* trifluoromethyl benzaldehyde and propionaldehyde was achieved in high yield and 77% *ee* using a bifunctional chiral triazolium salt.



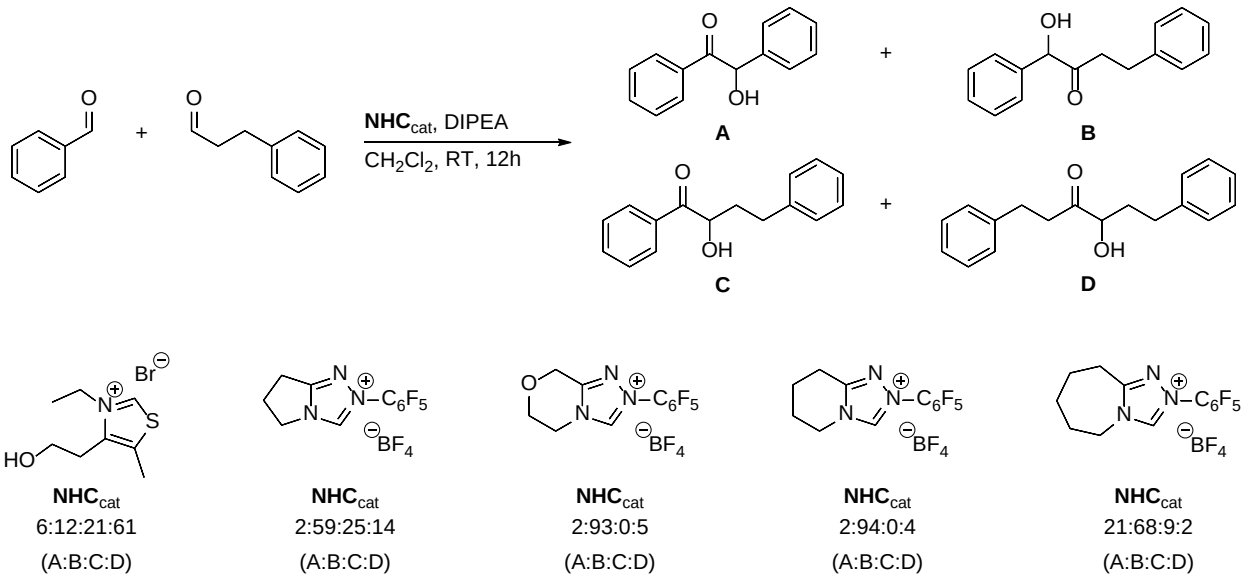
Scheme 41: Cross-benzoin reaction between aryl and alkyl aldehydes by Zeitler and Connon.[101]

The effect of the aldehyde ratio on the chemoselectivity of the cross-benzoin reaction was further investigated by Yang in 2011.[102] In this approach, a large excess (10 equivalents) of acetaldehyde was used in the cross-benzoin condensation with different *para*-substituted aryl aldehydes. The precatalyst used contained a core structure which was identical to that of Zeitler and Connon. This species gave the resulting products in high chemoselectivity and in high yield. In one example thy carried out a cross-benzoin condensation between 4-chlorobenzaldehyde and acetaldehyde catalyzed by a chiral bifunctional precatalyst. This reaction gave the chiral hydroxyl ketone product in excellent chemoselectivity, moderate yield and enantioselectivity.



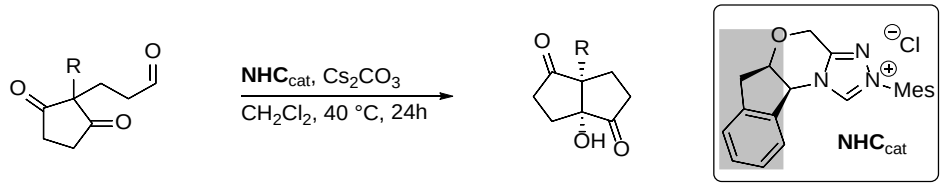
Scheme 42: Cross-benzoin reaction between aryl and acetaldehyde by Yang.[102]

In 2014, the Gravel group introduced a new concept for the synthesis of cross-acyloin products between aliphatic and aromatic aldehydes.[103] In their approach, the chemoselectivity of the reaction was achieved by catalyst design rather than substrate control. The chemoselectivities obtained after the screening of various triazolium salts indicated that the size of the fused ring system is crucial for the selective formation of the cross-benzoin product (Scheme 43). More specifically, they found that precatalysts with a six-membered fused ring system gave the best chemoselectivities. With the reaction conditions optimized, they investigated the substrate scope and a wide variety of different aldehydes were coupled. By using a chiral triazolium salt, moderate enantioselectivities were obtained. In all cases, the resulting cross-benzoin products were isolated in high yield and with excellent chemoselectivity.



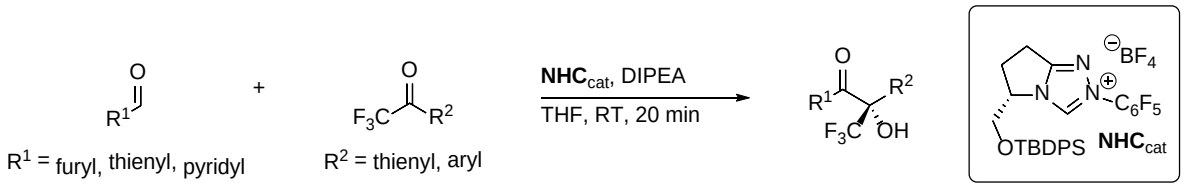
Scheme 43: Catalyst screening for the cross-benzoin reaction by Gravel.[103]

In a different approach to the cross-benzoin reaction, ketones were coupled with aldehydes to give aldehyde-ketone cross-benzoin products. One example of an intramolecular aldehyde-ketone cross-benzoin reaction was developed by Ema and Sakai[104,105] for the synthesis of chiral bicyclic tertiary alcohols from the corresponding cyclic diketone. High enantioselectivies and moderate to good yield were achieved on a wide variety of different six- or five-membered cyclic starting materials when the chiral triazolium salt was used (Scheme 44).



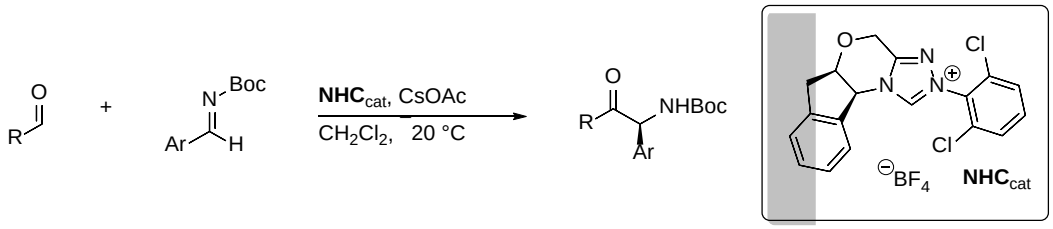
Scheme 44: Cross-aldehyde-ketone benzoin reaction by Ema and Sakai.[104]

In 2009 the Enders group developed an intramolecular coupling of aromatic aldehydes with trifluoromethyl ketones to form racemic α-hydroxy-α-trifluoromethyl ketones catalyzed by an achiral triazolium salt.[106] One year later, the same research group extended the synthetic protocol towards an asymmetric version using a chiral precatalyst (Scheme 45). The resulting chiral hydroxyl ketones were isolated in good to excellent yield and with enantioselectivities of up to 83% *ee*.[107]



Scheme 45: Intermolecular cross-benzoin reaction of aldehydes with ketones by Enders.[106]

One example of a synthetically useful extension of the cross-benzoin reaction is the coupling of Breslow intermediates with imines to obtain chiral amine products. In 2001, the first cross-*aza*-benzoin reaction was introduced by Murry and Frantz. In their approach, α-amido ketones were synthesized via a thiazolium-catalyzed coupling of aldehydes with acylimines.[108] Recently, the Rovis group developed a more synthetically useful asymmetric *aza*-benzoin reaction between alkyl aldehydes and *N*-Boc protected aromatic imines which gave highly enantioenriched Boc-protected amines. All amines were isolated in high yield and with excellent enantioselectivities (Scheme 46).[109]



Scheme 46: Asymmetric cross-aza-benzoin reaction by Rovis.[109]

3.1.4 Mechanistic Investigations

Recently, Gravel and coworkers investigated the mechanism of the piperidone-based carbene catalyzed cross-benzoin reaction through experimental and computational studies.[110] In the proposed catalytic cycle (Figure 27), first the active carbene is formed by deprotonation followed by nucleophilic attack to generate a zwitterionic intermediate, which is in agreement with the mechanism of Breslow (Figure 25). A carbene-aldehyde adduct is formed after intermolecular protonation, followed by a second deprotonation to create a resonance-stabilized zwitterion, respectively Breslow intermediate. Then, the carbonyl center of a second aldehyde molecule is attacked by the nucleophilic acyl intermediate, and after catalyst regeneration the final cross-benzoin product is released.

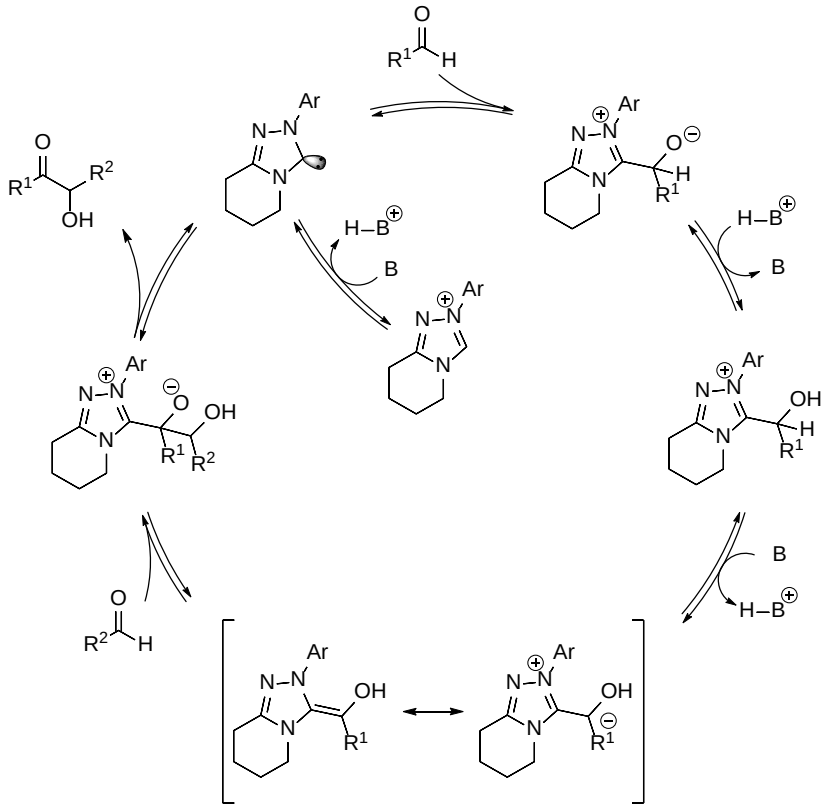


Figure 27: Mechanism of the cross-benzoin reaction proposed by Gravel.[110]

In the mechanistic investigations by Gravel the reaction coordinate of the cross-benzoin reaction was calculated and compared for every possible aldehyde combination. According to these calculations, the Breslow intermediate was preferably formed with the aliphatic aldehyde

compared to the aromatic aldehyde, because the Breslow intermediate derived from aryl aldehyde was found to be 5.7 kcal/mol higher in energy. Because of stabilizing π-stacking and π-cation interactions of the phenyl ring with the triazolium ring, the nucleophilic attack from the Breslow intermediate to the aryl aldehyde was favored for the cross-benzoin condensation. Modulation of the transition state for the rate-limiting carbon-carbon bond-forming step showed that the *Z*-Breslow adduct is generated which then attacks the aldehyde on the *si* face. Additionally, the reversibility of the cross-benzoin reaction was studied by ^{1}H-NMR analysis of cross-over experiments in which either cross- or homo benzoin products were mixed with aldehyde and catalyst. In case of the cross-benzoin products, the results showed that this reaction was fully reversible. Only with the alkyl-alkyl benzoin product no crossed products were detected, which indicated that this benzoin reaction is irreversible. Based on the results of the DFT calculations and experimental studies, the chemoselectivity is governed by kinetic control. Last, the effect of the fused-ring system of the catalyst on the chemoselectivity was studied. For carbenes with a five, six or seven membered ring system the corresponding transition state for the carbon-carbon formation step was calculated. Based on the comparison of the energies of these three transition states the authors suggested that steric interactions of the fused-ring system might control the chemoselectivity of the reaction. If the ring system was too small, a thermodynamic mixture of the products was obtained because all steps were found to be reversible. According to computational studies, the energy barriers in the reaction profile were found to be lower compared to the six-membered catalyst. Moreover, if the fused-ring system was too big, the energy of the C-C forming step would be increased by 2.7 kcal/mol which is reflected by the lower reactivity of this type of catalyst with a seven-membered ring.

3.2 Catalyst Synthesis

The precatalyst lead structure for the asymmetric cross-benzoin reaction is presented in Figure 28. Its modular structure seemed to be ideal for catalyst development because the effect of several structural units can be investigated. For example, by varying the *N*-aryl residue at the triazolium ring system the effect of the acidity of the carbene C-H proton or the nucleophilicity can be studied. Moreover, starting from different chiral building blocks the role of the chiral back bone can be investigated. In addition to steric hindrance, the effect of hydrogen-bonding units has to be considered. The influence of rotation of the chiral backbone on the chemo- and enantioselectivity of the reaction can be studied installing groups next to the stereogenic center. Studies by Gravel[103] have shown that six-membered fused ring systems are crucial for the chemoselectivity of the cross-benzoin reaction. Thus, morpholine- (X=O) or piperidine ($X=CH_2$) -based catalysts can be prepared to investigate this phenomenon.

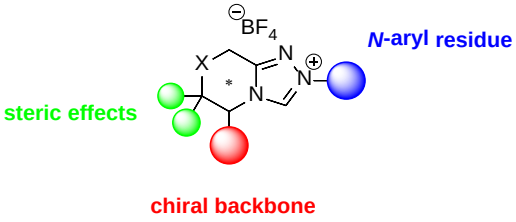


Figure 28: Catalyst lead structure for the asymmetric cross-benzoin reaction.

3.2.1 Synthesis of Morpholine-Based Triazolium Salts

The retrosynthetic analysis of chiral morpholine-based precatalysts is shown in Figure 29. This catalyst generation is derived from commercially available enantiopure amino acids which are converted to the resulting *N*-protected methyl esters. Using different Grignard reagents for the synthesis of the tertiary alcohol intermediates, the steric effect of the residues next the stereogenic center can be investigated. The lactam adduct can be synthesized in a one-pot two step procedure of Glorius starting from the deprotected amino alcohol.[111] In the last step, the triazolium salt intermediate can be formed using the one-pot three-step procedure of Rovis.[112] In this one-pot synthetic strategy, different *N*-aryl hydrazines can be employed which allow the modification at the *N*-aryl position of the precatalyst.

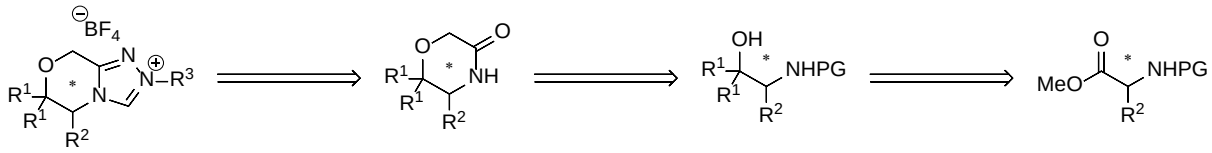
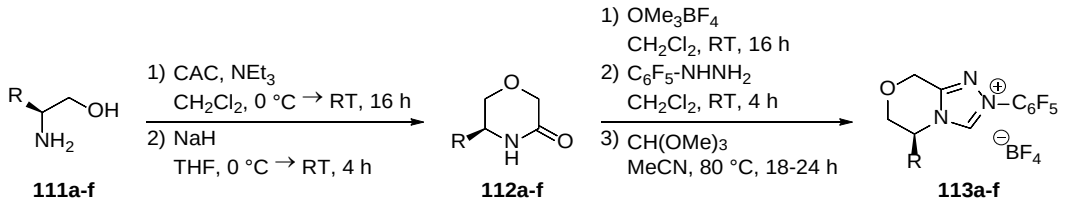
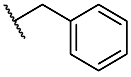


Figure 29: Retrosynthetic analysis of morpholine-based precatalysts.

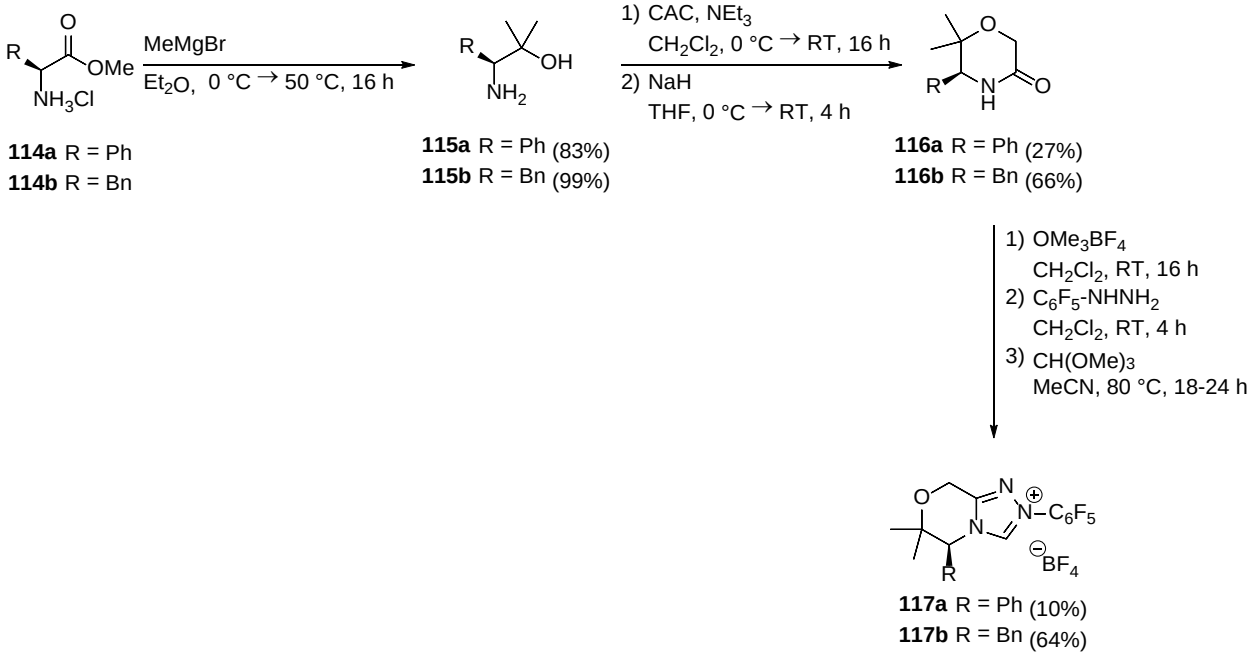
First, commercially available amino alcohols **111a-f** were converted to the resulting lactams **112a-f** by treating the starting material with chloroacetyl chloride (CAC) to form the chloro acetamide intermediate. Afterwards, sodium hydride was added to the crude chloro acetamide and after cyclization the corresponding lactams **112a-f** were isolated in low to moderate yield. In the last step, the triazolium salts **113a-f** were synthesized using the one-pot three-step synthetic protocol developed by the Rovis group.[112] First an imidate intermediate was formed by treatment of the lactam with Meerwein's salt followed by amidrazone adduct formation. In the last step, the precatalyst was formed by refluxing the crude amidrazone intermediate in trimethyl orthoformate. After purification of the crude product all triazolium salts **113a-f** were isolated in low yield. In each case the crude reaction mixture after the cyclization step with orthoformate was analyzed by ESI-MS analysis and indicated predominantly product formation. However, because of purification problems only low yield were achieved (Table 28).

Table 28: Synthesis of triazolium salts derived from commercially available amino alcohols **113a-f**.



entry	R	lactam 112 (yield in %)	triazolium salt 113 (yield in %)
1		**112a** (64)	**113a** (10)
2		**112b** (64)	**113b** (34)
3		**112c** (52)	**113c** (4)
4		**112d** (85)	**113e** (19)
5		**112e** (47)	**113f** (35)

To study the effect of residues next to the stereogenic center, catalysts such as **117a** or **117b** were synthesized in a six-step synthesis. Tertiary alcohols **115a-b** were formed by treating the corresponding amino acid hydrochloride salts **114a-b** with an excess of methyl magnesium bromide reagent and after lactam formation intermediates **116a-b** were isolated in good to moderate yield over two steps. Again, the challenging step was the isolation of the precatalyst. After the one-pot, three-step synthesis the triazolium salts **117a-b** were only obtained in low to moderate yield (Scheme 47).



114a R = Ph
114b R = Bn

115a R = Ph (83%)
115b R = Bn (99%)

116a R = Ph (27%)
116b R = Bn (66%)

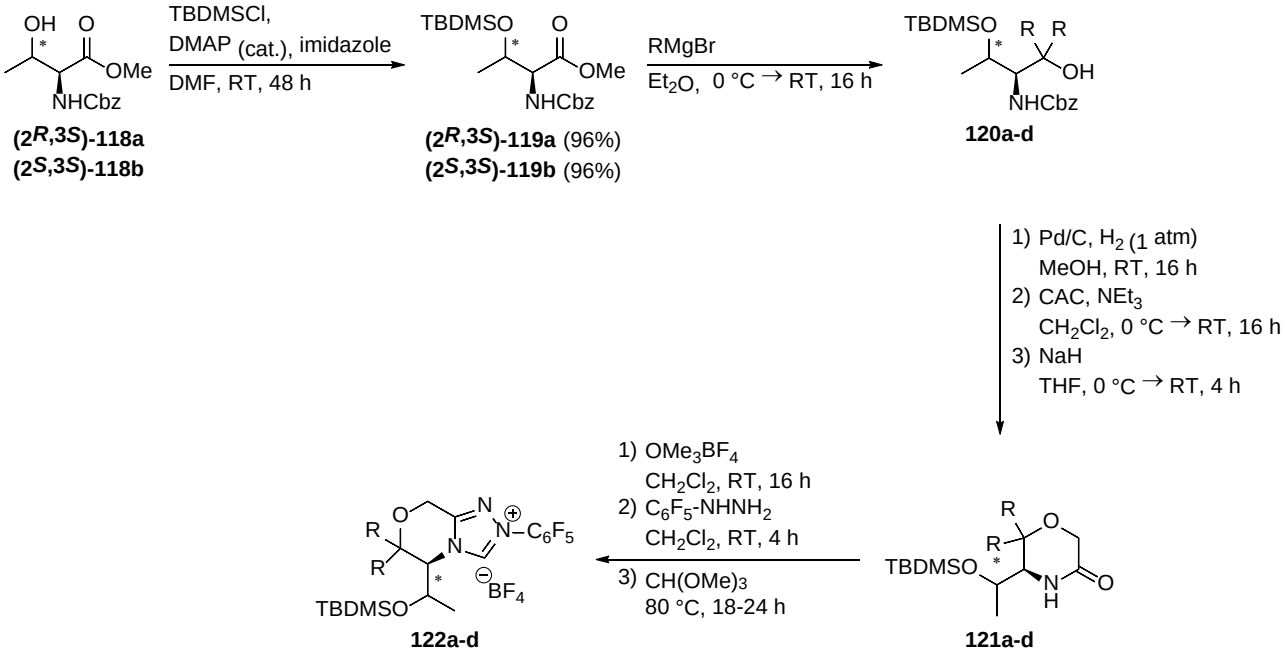
117a R = Ph (10%)
117b R = Bn (64%)

Scheme 47: Synthesis of triazolium salts **117a-b**.

To obtain a more modular lead structure, the amino acid was changed to threonine, thereby increasing the possible positions which could be optimized. For threonine-derived triazolium salts both diastereomers of the precatalyst were prepared following an eight-step synthetic procedure. In the first step, the secondary alcohol was protected with TBDMS chloride followed by addition of different Grignard reagents to afford the resulting tertiary alcohol intermediates **120a-d**. After palladium catalyzed carboxybenzyl (Cbz) deprotection of the amino group under hydrogen atmosphere, the resulting crude amines were directly used for the one-pot lactam synthesis. Afterwards the crude reaction mixture was purified by column chromatography to give the lactams **121a-d** in low to good yield. Only in the case of the diethyl substituted lactam the yield was low. This could be explained by the steric hindrance of the ethyl substituents, which might disfavor the cyclization of the chloro acetamide intermediate. For lactam **121a** and **121b** the final precatalysts **122a** respectively **122b** were isolated in low yield after using the one-pot standard procedure (Table 29, entries 1-2). Moreover, for diethyl substituted lactam **121c** the desired precatalyst **122c** was isolated in moderate yield (entry 3). No pure product was obtained in the synthesis of triazolium salt derived from the diphenyl substituted lactam **121d** due to the low solubility of the lactam precursor in dichloromethane. Moreover, problems in the purification step which resulted

from low conversion to the desired product and byproduct formation further lowered the yield of triazolium salt formation (entry 4).

Table 29: Synthesis of threonine-derived triazolium salts **122a-d**.



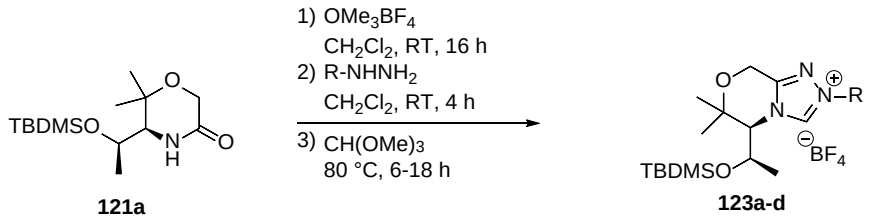
entry	start material	R	alcohol 120 (yield in %)	lactam 121 (yield in %)	triazolium salt 122 (yield in %)
1	(2*R*,3*S*)-**115a**	Me	**120a** (91)	**121a** (73)	**122a** (18)
2	(2*S*,3*S*)-**115b**	Me	**120b** (99)	**121b** (73)	**122b** (19)
3	(2*R*,3*S*)-**115a**	Et	**120c** (80)	**121c** (29)	**122c** (40)
4	(2*R*,3*S*)-**115a**	Ph	**120d** (84)	**121d** (84)	**122d** (-[a])

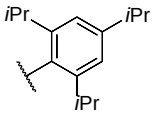
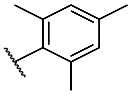
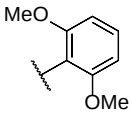
[a]: No pure product was isolated.

To investigate the effect of the *N*-aryl residue on the triazolium ring on the asymmetric cross-benzoin reaction, threonine-derived precatalysts with different *N*-substituents were synthesized (Table 30). The aromatic hydrazines used were either commercially available (phenyl hydrazine) or freshly prepared by basic aqueous extraction (saturated sodium carbonate solution in ether) of

the corresponding hydrochloride salt. 2,4,6-Trimethylphenylhydrazine hydrochloride was commercially available and the other hydrazine precursors were prepared by a of Bolm.[113] In this process, di-*tert*-butyl azodicarboxylate was treated with the corresponding Grignard reagent to form the resulting Boc protected hydrazine which was converted to the final hydrazine hydrochloride salt after Boc deprotection. Finally, all hydrazines were successfully applied for the synthesis of four different triazolium salts derived from lactam **121a** and in all cases the resulting precatalysts **123a-d** were isolated in moderate yield.

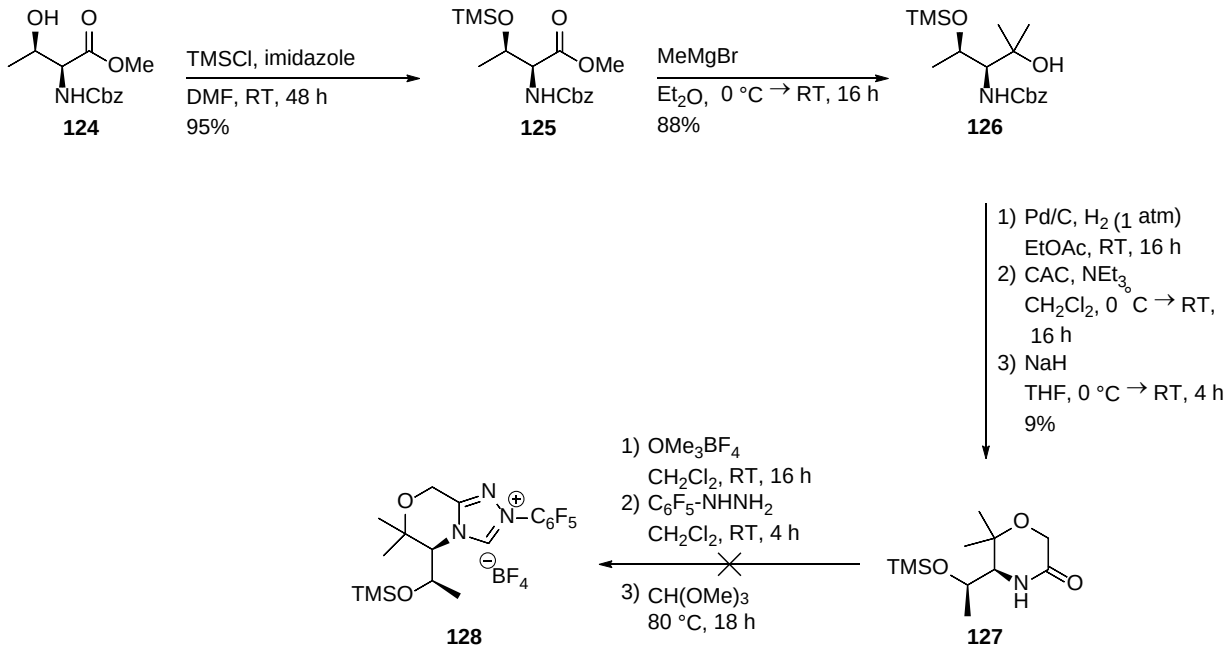
Table 30: Synthesis of different *N*-aryl substituted precatalysts **123a-d** derived from lactam **121a**.



entry	R	triazolium salt 123 (yield in %)	entry	R	triazolium salt 123 (yield in %)
1		**123a** (58)	1		**123c** (36)
2		**123b** (55)	2		**123d** (53)

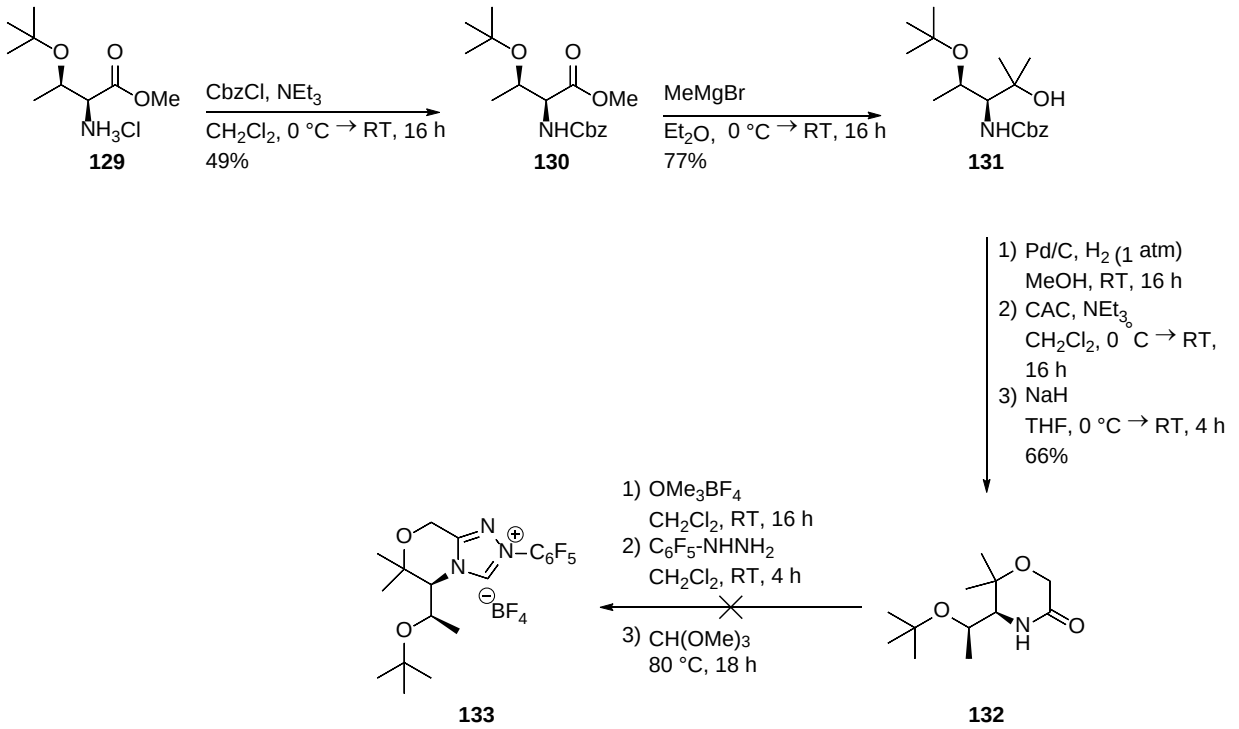
Precatalyst **128** was designed in order to investigate the steric effect of the silyl group on the stereo- and chemoselectivity of the cross-benzoin reaction. TMS protected threonine intermediate **125** was prepared in very good yield by silylation of the hydroxyl group with TMS chloride. After methyl Grignard addition, the purified alcohol adduct **126** was subjected to palladium catalyzed Cbz deprotection under hydrogen atmosphere. The crude amine was then directly converted into the lactam adduct to give lactam **127** in only 9% yield. A possible explanation for the low yield might be the low stability of the TMS group towards hydrolysis so that under the applied reaction conditions the TMS group might have been cleaved. Unfortunately, ESI-MS analysis of the crude reaction mixture of the triazolium salt synthesis showed no conversion to the desired precatalyst **128** (Scheme 48). Again, due to the low stability of the TMS-ether group only the product without

a TMS-ether group and various unknown byproducts were detected by ESI-MS analysis.



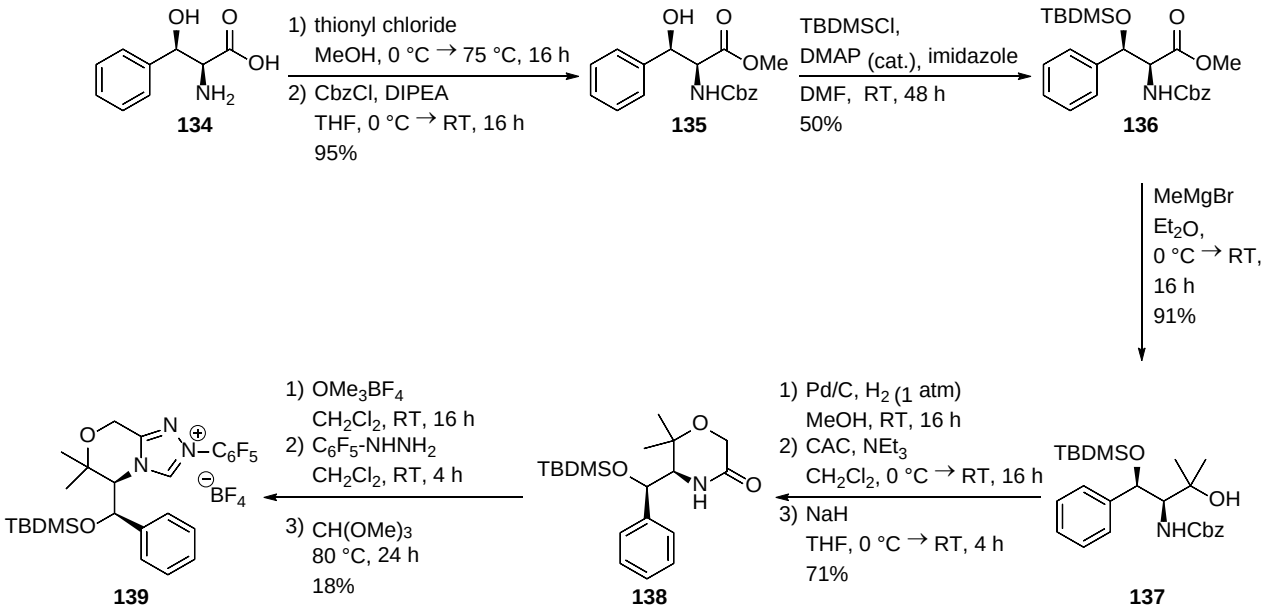
Scheme 48: Synthesis of TMS-protected threonine-derived triazolium salt **128**.

Because of the problems encountered in the synthesis of the TMS protected threonine-derived precatalyst and the failed isolation of the triazolium salt **128**, a different approach which began from the commercially available *O-tert*-butyl-L-threonine methyl ester hydrochloride **129** was investigated. Herein, a smaller group was installed at the hydroxyl position to study the effect of steric interaction on the chemoselectivity of the cross-benzoin reaction. Cbz protected amine **130** was obtained in moderate yield and after Grignard addition the resulting tertiary alcohol adduct **131** was isolated in good yield. In the next synthetic sequence, the alcohol intermediate was converted to the lactam **132** according to the three step procedure for the previous lactam synthesis. Following a standard protocol for the synthesis of a triazolium salt, the final precatalyst **133** was not isolated after purification by column chromatography (Scheme 49). ESI-MS analysis of the crude reaction mixture after hydrazine addition showed clearly the formation of the amidrazone intermediate, but after refluxing in trimethyl orthoformate only one by-product without the *tert*-butyl group was detected which indicated that the alcohol was deprotected under condensation reaction conditions.



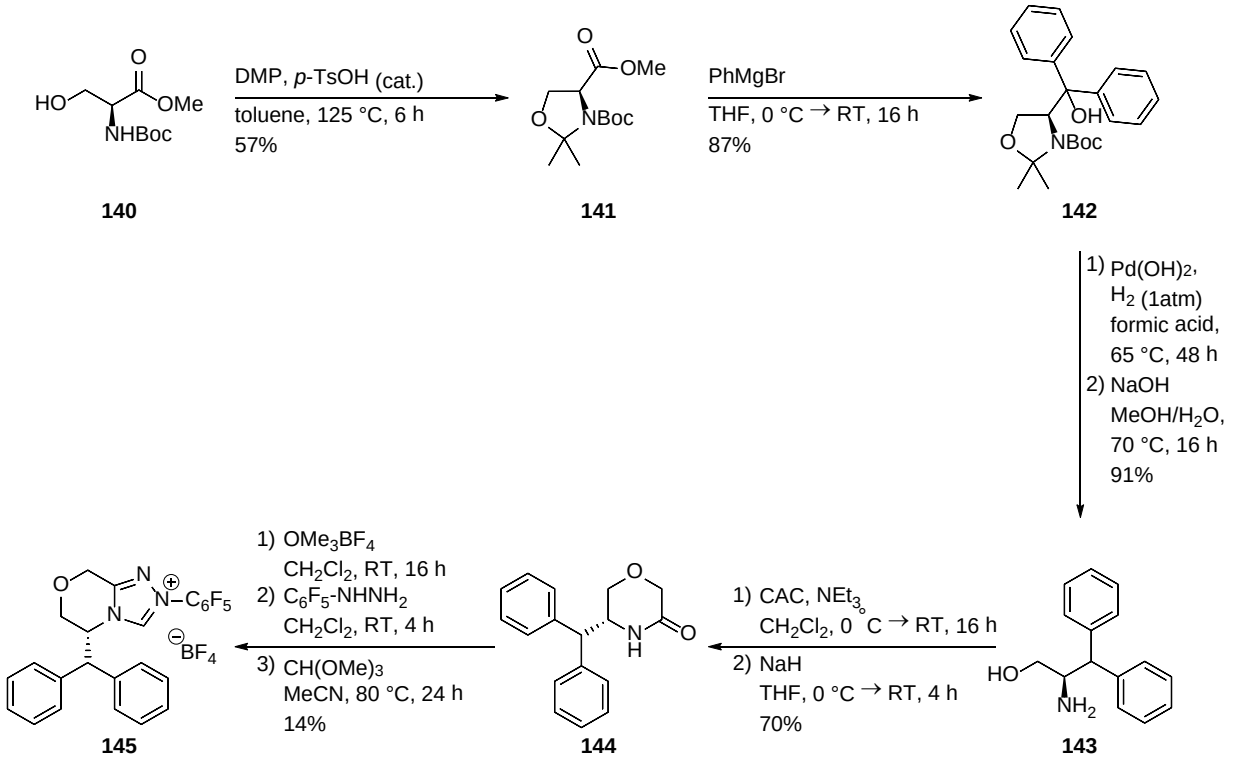
Scheme 49: Synthesis of *O-tert*-butyl threonine-derived triazolium salt **133**.

The synthetic approach to the phenyl serine-derived triazolium salt is presented in Scheme 50. Starting from *L*-phenyl serine **134**, the *N*-Cbz protected methyl ester intermediate **135** was isolated in 95% yield after treatment of amino acid **134** with thionyl chloride in methanol followed by amino group protection with benzyl chloroformate. The *O*-TBDMS protected adduct **136** was isolated in moderate yield using the standard synthetic protocol with TBDMS chloride, catalytic amount of DMAP and imidazole. The reason for the lower yield obtained in this case compared to the threonine derivative could be due to the steric hindrance at the benzylic alcohol position which disfavors the TBDMS silylation of the hydroxyl group. This is reinforced by the observation, that after column chromatography 50% of the starting material **135** was recovered. After Grignard addition to the ester adduct **136**, Cbz deprotection and one-pot lactam formation, intermediate **138** was isolated in good yield over all steps. Lastly, the phenyl serine-derived triazolium salt **139** was formed in 18% yield using the previous standard methodology for the precatalyst synthesis.



Scheme 50: Synthesis of phenyl serine-derived triazolium salt **139**.

The last type of morpholine-based precatalyst contains a chiral diphenylmethane group. Triazolium salt **144** was synthesized following an eight step sequence which began from Boc-*L*-serine methyl ester **140** (Scheme 51). First, dimethyl oxazolidine **141** was obtained by refluxing compound **140** with 2,2-dimethoxypropane and a catalytic amount of *p*-TsOH. Alcohol intermediate **141** was isolated in good yield after treating ester **142** with an excess of phenyl magnesium bromide. In the following step amino alcohol **143** was synthesized according to a procedure of Avenoza.[114] In this synthetic approach, catalytic dehydroxylation occurred *via* formation of a carbamate intermediate which was then cleaved by palladium hydroxide in hydrogen atmosphere. Subsequent hydrolysis in sodium hydroxide water/methanol solution gave amino alcohol **143** in good yield. The crude amino alcohol **139** was directly converted to the lactam **144** and the final precatalyst **145** was isolated in 14% yield following the modified Rovis procedure.[112]



Scheme 51: Synthesis of triazolium salt **145** derived from diphenylmethane lactam **144**.

3.2.2 Synthesis of Piperidine-Based Triazolium Salts

For the synthesis of piperidine-based precatalysts two different synthetic approaches were developed (Figure 30). In strategy **A**, the ester lactam precursor was synthesized following a multi-step sequence which began with the commercially available lysine methyl ester hydrochloride. The resulting lactam intermediate is a useful synthetic precursor because the ester group can be converted to different functional groups easily, which permits the preparation of structurally diverse precatalysts. In the last step, the triazolium salt can be formed using the standard cyclization protocol from the previously described syntheses. Because the cyclization of the fully protected lysine intermediate under harsh reaction conditions proved to be problematic and therefore an alternative approach was developed. For the strategy **B**, the synthetic precursor was the commercially available *N*-Boc protected pipecolic acid. After alpha oxidation and Boc deprotection the ester lactam adduct could be formed and then converted to different functionalized lactams. The synthesis of the triazolium salt synthesis proceeded in the same manner as in strategy **A**.

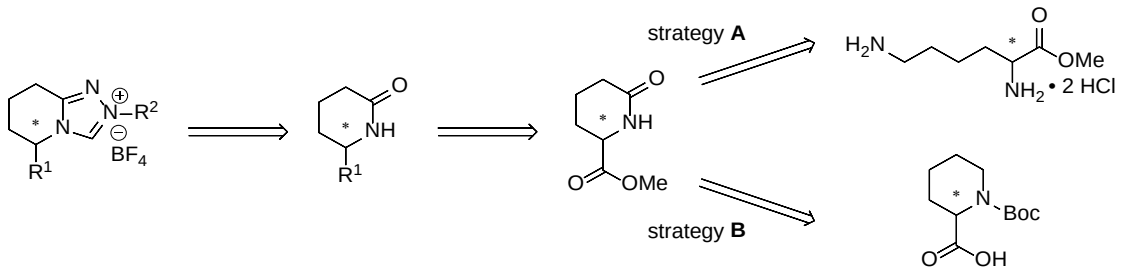
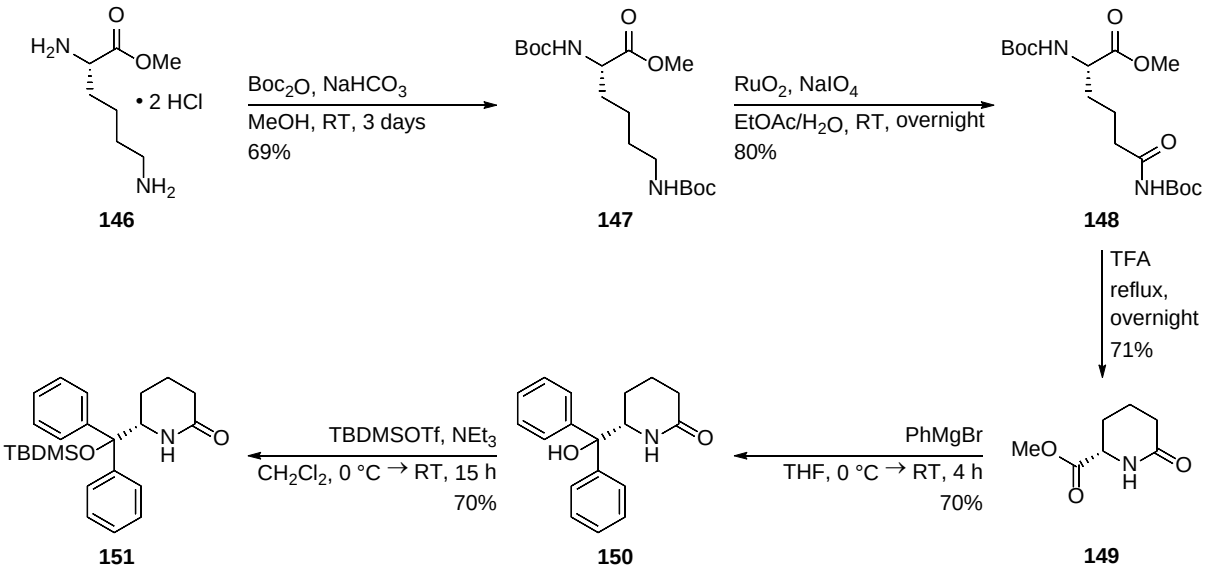


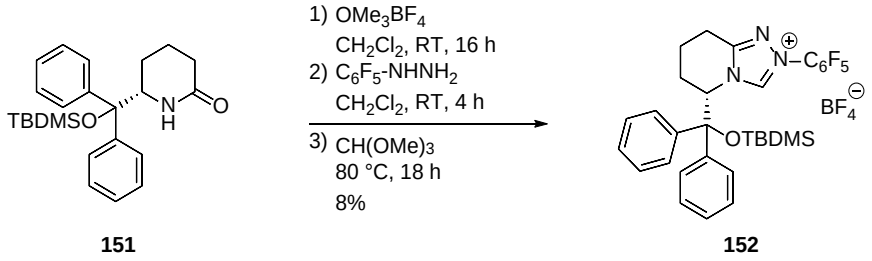
Figure 30: Retrosynthetic analysis of piperidine-based triazolium salts.

The first strategy was investigated by Mirjam Schreier during her Wahlpraktikum. In this approach, lysine methylester hydrochloride **146** was converted to the double Boc protected amino acids **147** using Boc anhydride and sodium hydrogen carbonate as a base. Afterwards, the amide **148** was obtained in high yield by oxidation of the alpha position to the primary *N*-Boc amino group using ruthenium oxide and sodium periodate in an ethyl acetate/water mixture. Lactam ester **149** was isolated in 71% yield after trifluoroacetic acid induced cyclization of the amide intermediate **148**. In the following steps, the ester group was converted to the tertiary alcohol adduct **150** by adding the Grignard reagent. After silylation with TBDMS triflate the final *O*-TBDMS-protected lactam **151** was isolated in good yield over the last two steps (Scheme 52).



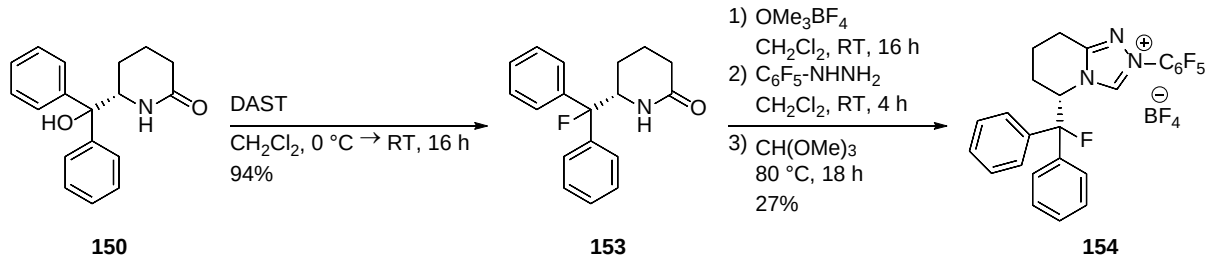
Scheme 52: Synthesis of TBDMS-protected diphenylmethane-derived lactam **141**.

In the last step of the precatalyst synthesis, lactam **151** was subjected to the one-pot three step protocol of Rovis[112] and after column chromatography the resulting triazolium salt **152** was isolated in low yield (Scheme 53).



Scheme 53: Synthesis of triazolium salt **152** starting from *O*-TBDMS protected diphenylmethane lactam **151**.

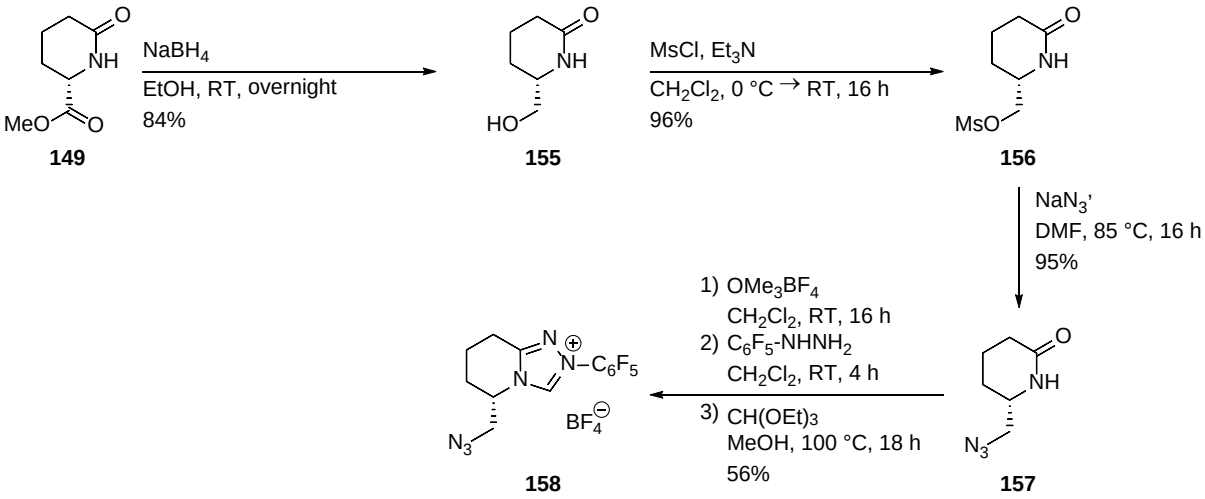
For investigations of the effect of the benzylic substituent on the stereoselectivity and chemoselectivity of the cross benzoin reaction, fluoro substituted diphenyl lactam-derived triazolium salt **154** was synthesized in a two-step procedure (Scheme 54). Fluorine atoms exert a conformational effect (Gauche effect) which restricts the free rotation of the fluoro diphenyl group and favors the gauche conformation between the F- and N atoms.[115,116] Fluoro lactam **153** was isolated in excellent yield after deoxyfluorination of alcohol adduct **150** with diethylaminosulfur trifluoride (DAST). The corresponding triazolium salt **154** was obtained in 27% yield after using the previously established one-pot three-step synthetic protocol.



150 **153** **154**

Scheme 54: Synthesis of fluorodiphenyl substituted triazolium salt **154**.

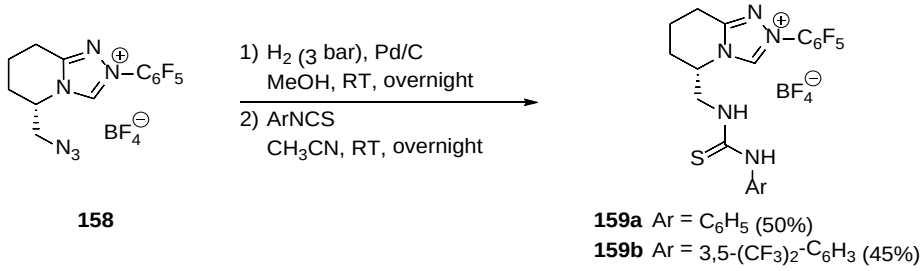
For studies concerning the effect of hydrogen-bonding subunits on the chemo- and enantioselectivity of the cross-benzoin reaction, bifunctional precatalysts were synthesized by Mirjam Schreier during her Master practical course (Scheme 55). First, the azide lactam-derived triazolium salt **158** was synthesized following a modified procedure by Waser.[91] In this multi-step synthesis the ester group of lactam **149** was reduced to the resulting alcohol intermediate **155** using sodium borohydride. After mesylation of the alcohol group followed by nucleophilic substitution with sodium azide, the azide lactam **157** was isolated in excellent yield over two steps. In the last part of the triazolium salt synthesis, the lactam was converted to the resulting precatalyst **158** using Meerwein's salt for imidate formation (step 1). Pentafluorophenylhydrazine was used for amidrazone formation (step 2) and finally the amidrazone adduct was cyclized to give the corresponding triazolium salt **158** by refluxing in triethyl orthoformate (step 3).



149 **155** **156** **157** **158**

Scheme 55: Synthesis of azide lactam-derived triazolium salt **158**.

In the last step of the synthesis, the azide group was reduced by palladium catalyzed hydrogenation and the resulting crude amine was directly used for the coupling reaction with the corresponding aryl isothiocyanate to yield the resulting bifunctional triazolium salts **159a** and **159b** in moderate yield (Scheme 56).

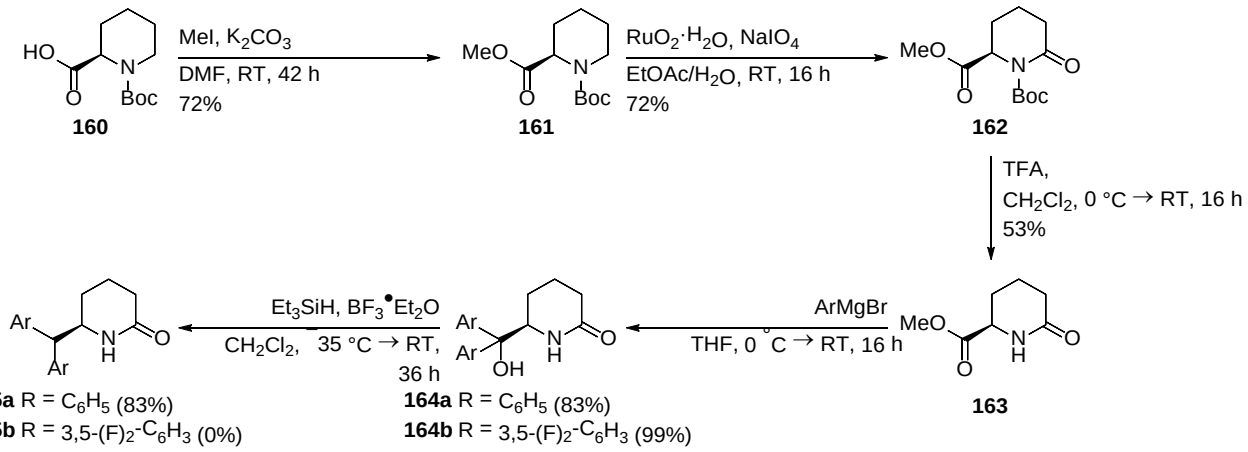


158

159a Ar = C_6H_5 (50%)
159b Ar = 3,5-$(CF_3)_2$-C_6H_3 (45%)

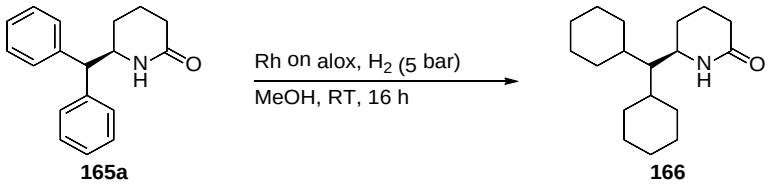
Scheme 56: Synthesis of bifunctional triazolium salts **159a/b**.

For the synthesis of the chiral diaryl piperidine-2-one derivatives strategy 2 was applied. In this synthetic approach the lactam **165a-b** was formed following a multi-step synthesis starting from commercially available (*R*)-1-Boc piperidine-2-carboxylic acid **160** (Scheme 57). Methyl ester **161** was isolated after methylation of the carboxylic acid with methyl. In the following step, the α position of the *N*-Boc group was oxidized with ruthenium oxide and sodium periodate as a co-oxidant to yield ester lactam intermediate **162** in good yield. After Boc deprotection with TFA and aryl Grignard addition to the ester moiety the resulting alcohol lactam intermediates **164a-b** were isolated in 83 to 99% yield. In the last step, the hydroxyl group was removed by BF_3 induced deoxygenation with triethylsilane. For phenyl systems the resulting deoxygenated product **165a** was isolated in excellent yield. Unfortunately, starting from the difluoro phenyl substituted derivative **164b**, no conversion to the desired product was observed by ^{1}H-NMR analysis of the crude mixture and the starting material was fully recovered.



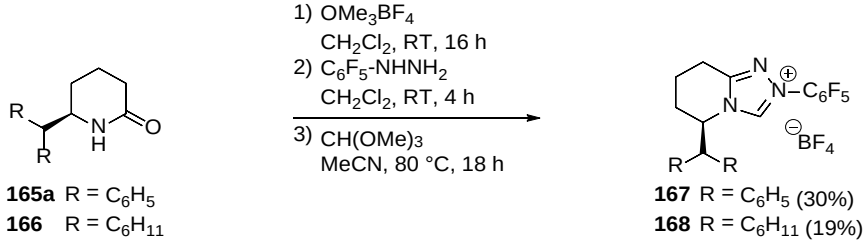
Scheme 57: Synthesis of chiral diaryl piperidin-2-ones **165a-b**.

To investigate the impact of steric hindrance on the asymmetric cross-benzoin reaction the phenyl rings of lactam **165a** were reduced to give the resulting cyclohexyl residue by rhodium on alumina catalyzed hydrogenation, giving lactam **166** in quantitative yield (Scheme 58).



Scheme 58: Synthesis of chiral dicylcohexyl piperidin-2-one **166**.

Lastly, lactams **165a** and **166** were subjected to the synthesis of the corresponding triazolium salts using the one-pot three-step synthetic procedure of Rovis. This procedure gave precatalysts **167** and **168** in low yield (Scheme 59).



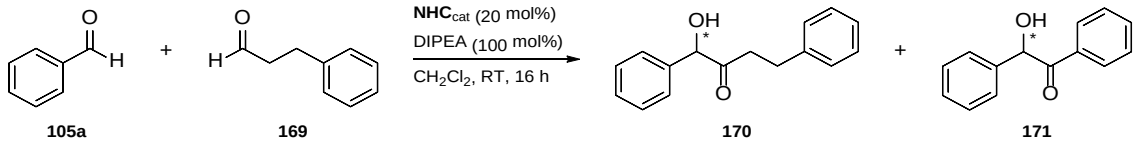
Scheme 59: Synthesis of triazolium salt **167/168** derived from chrial disubstituted piperdine-2-ones **155a/166**.

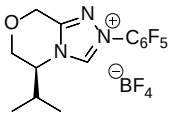
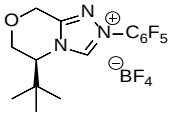
3.3 Catalyst Screening for the Asymmetric Cross-Benzoin Reaction

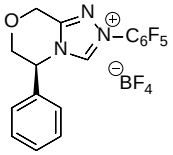
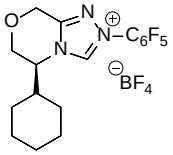
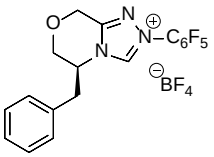
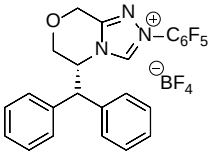
3.3.1 Screening of Morpholine-Based Triazolium Salts

First, the effect of the chiral backbone of morpholine-based precatalysts on the chemo- and enantioselectivity of the cross-benzoin condensation between benzaldehyde **105a** and hydrocinnamaldehyde **169** was investigated. Chiral catalyst **109a** developed by the Gravel group[103] was used as a reference system (Table 31, entry 1). With this catalyst, the cross-benzoin product was obtained with excellent chemoselectivity, moderate enantioselectivity and good conversion. Similar conversion and slightly lower enantioselectivity was observed when the steric hindrance at the α-position was increased by replacing the *iso*-propyl group with a *tert*-butyl group, but the chemoselectivity was eroded from 20:1 to 2:1 (entry 2). The chemo- and stereoselectivity was further improved by using precatalyst **113c** with a planar phenyl substituent in the chiral backbone (entry 3). Again, increasing steric hindrance in triazolium salt **113d** with an cyclohexyl moiety resulted in inferior results (entry 4). Moreover, the cross-benzoin product **170** was obtained with low enantiomeric excess and poor chemoselectivity, using either benzyl- or diphenylmethane substituted carbenes (entries 5-6).

Table 31: Screening of morpholine-based precatalysts with different chiral backbones.



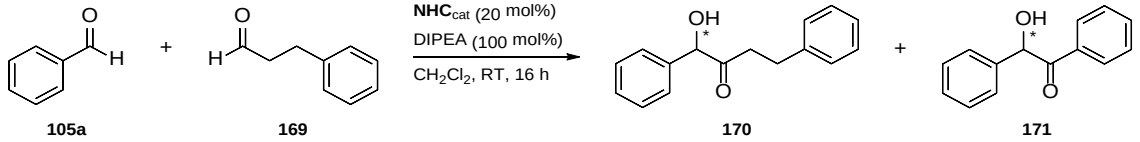
entry	NHC_{cat}		conversion [%][a]	ratio 170/171[a]	*ee* [%][b] 170
1		**113a**	94	20:1	40 (*R*)
2		**113b**	95	2:1	36 (*R*)

3		**113c**	90	5:1	50 (*R*)
4		**113d**	97	4:1	26 (*R*)
5		**113e**	98	3:1	10 (*S*)
6		**145**	76	4:1	4 (*S*)

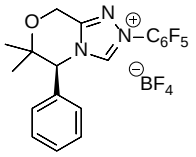
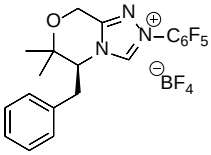
[a]: Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b]: Determined by HPLC on a chiral stationary phase.

Next, the effect of the steric hindrance at the β-position on the chemo- and enantioselectivity was investigated. Better chemo- and slightly higher enantioselectivity was observed, however reactivity decreased when NHC catalyst **117a** was used (Table 32, entry 1). Compared to catalyst **113c** (Table 31, entry 3), carbene **117a** (Table 32, entry 1) contains a dimethyl group at the β-position which may block the free rotation of the phenyl group. This higher rigidity of the catalyst structure could have a positive impact on the selectivity. A more drastic increase of chemo- and enantioselectivity was achieved when the β-position of the catalyst **117b** was substituted with two methyl groups (entry 2). With identical reactivity, the ratio was increased towards the cross-benzoin product **170** from 3:1 to 5:1 and the enantiomeric excess improved by 40%.

Table 32: Screening of β-dimethylated morpholine-based precatalysts.



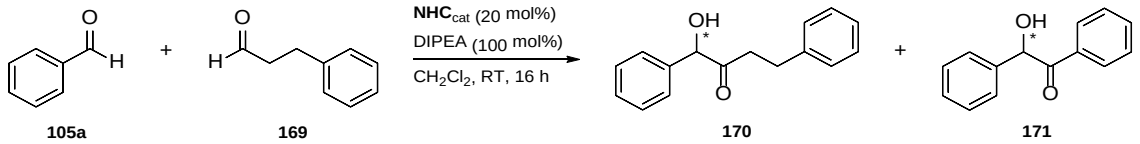
105a **169** **170** **171**

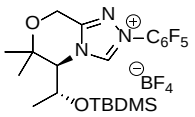
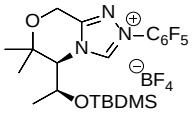
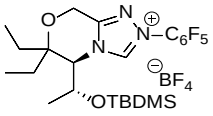
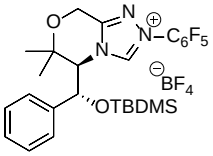
entry	NHC_{cat}		conversion [%][a]	ratio 170/171[a]	*ee* [%][b] 170
1		**117a**	68	7:1	52 (*R*)
2		**117b**	97	5:1	50 (*S*)

[a]: Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b]: Determined by HPLC on a chiral stationary phase.

Next, threonine-derived NHCs were investigated. First, the (*S*,*R*)-diastereomer of the threonine-derived precatalyst was tested in the asymmetric cross-benzoin reaction and the cross-benzoin product **170** was obtained with good chemo- and enantioselectivity (Table 33, entry 1). The other diastereomer of the catalyst gave lower selectivities but had similar reactivity (entry 2), indicating that the (*S*,*R*)-configuration of the catalyst is optimal. The stereoselectivity was further improved by installing sterically more demanding ethyl groups at the β-position but unfortunately the reactivity and the cross-selectivity was reduced (entry 3). With the phenyl serine-derived triazolium salt **139** the steric effect of the chiral backbone on the asymmetric cross-benzoin reaction was investigated. With this catalyst, lower reactivity and slightly lower selectivities were obtained (entry 4).

Table 33: Screening of threonine- and phenyl serine-derived precatalysts.

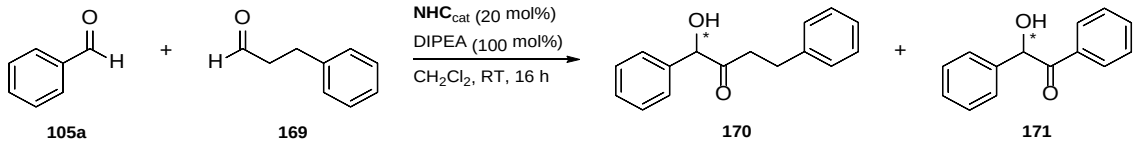


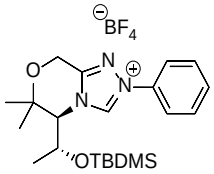
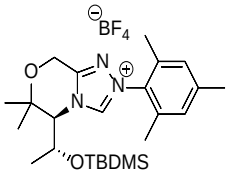
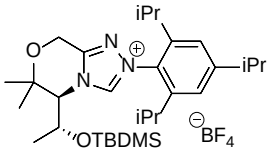
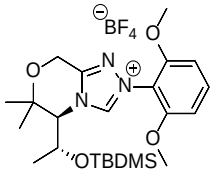
entry	NHC_{cat}		conversion [%][a]	ratio 170/171[a]	*ee* [%][b] 170
1		**122a**	86	10:1	60 (*S*)
2		**122b**	85	5:1	38 (*S*)
3		**122c**	72	8:1	66 (*S*)
4		**139**	70	9:1	56 (*S*)

[a]: Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b]: Determined by HPLC on a chiral stationary phase.

Last, the effect of the *N*-residue on the chemo- and enantioselectivity was studied using different *N*-substituted threonine-derived precatalysts. NHC **123a** with an *N*-phenyl substituent gave the desired cross-benzoin product **170** with moderate enantioselectivity but low chemoselectivity. Furthermore, the reactivity observed was quite low (Table 34, entry 1). An additional improvement of the enantioselectivity was achieved after installing an *N*-mesitylene group. However, only low conversion to the products was observed (entry 2). To investigate the effect of steric hindrance at the *N*-phenyl residue, triazolium salt **123c** with an *iso*-propyl substituted *N*-phenyl ring was tested. Unfortunately, this catalyst showed essentially no chemo- and enantioselectivity (entry 3). The reactivity of the precatalyst was slightly increased compared to *N*-phenyl catalyst **123a** by installing an *N*-(2,6-dimethoxy)phenyl residue on the triazolium moiety. Moreover, excellent chemo- and improved stereoselectivity was detected for NHC **123d** (entry 4).

Table 34: Screening of threonine-derived precatalysts with different *N*-aryl residues.



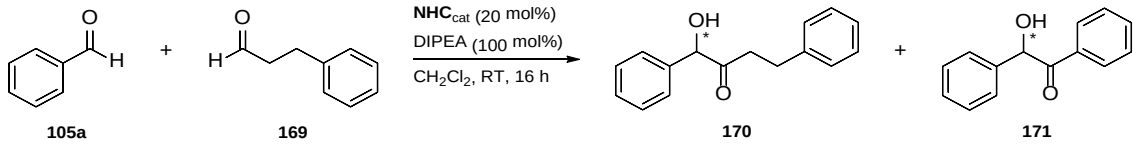
entry	NHC$_{cat}$		conversion [%][a]	ratio 170/171[a]	*ee* [%][b] 170
1		**123a**	12	3:1	58 (*S*)
2		**123b**	7	20:1	85 (*S*)
3		**123c**	94	1:1	4 (*R*)
4		**123d**	27	30:1	66 (*S*)

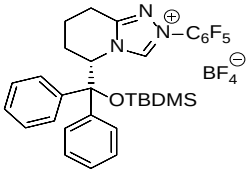
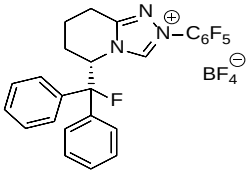
[a]: Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b]: Determined by HPLC on a chiral stationary phase.

3.3.2 Screening of Piperidine-Based Triazolium Salts

In further studies, piperidine-based triazolium salts were evaluated for the asymmetric cross-benzoin reaction between benzaldehyde **105a** and hydrocinnamaldehyde **169**. First, precatalysts containing a diphenylmethylene group in the chiral backbone were investigated. NHC **152**, synthesized and evaluated by Mirjam Schreier, gave the desired cross-benzoin product in good chemo- and moderate enantioselectivity.[117] However, the reactivity observed was low. It may be argued that this result could arise from the steric hindrance of the TBDMS-protected alcohol group which blocks the nucleophilic center (Table 35, entry 1). In the carbene structure **154**, the silyl group was replaced by a fluoride atom, to see if the fluorine-gauche effect could influence the outcome of the cross-benzoin reaction. Compared to TBDMS-NHC **152**, higher reactivity, but lower chemo- and enantioselectivities were observed (entry 2).

Table 35: Screening of diphenyl substituted piperidine-based precatalysts.

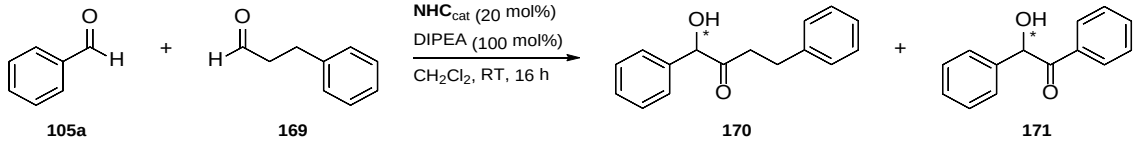


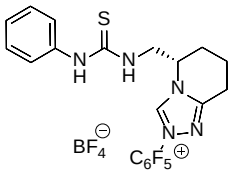
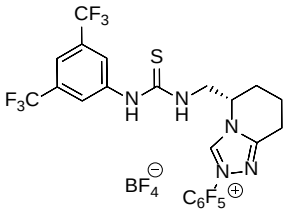
entry	NHC$_{cat}$		conversion [%][a]	ratio 170/171[a]	*ee* [%][b] 170
1		**152**	17	10:1	30 (*S*)
2		**154**	66	5:1	8 (*S*)

[a]: Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b]: Determined by HPLC on a chiral stationary phase.

A different approach to the selective cross-product formation was investigated by Mirjam Schreier during her Master practicum using piperidine derived bifunctional NHCs.[117] Herein, the effect of possible H-bonding interactions with the substrates to achieve higher selectivities was studied. However, in both cases insufficient selectivities were observed (Table 36, entries 1-2). Moreover, using THF as reaction solvent and cesium carbonate as a base, the benzoin product **171** was formed preferably when NHC **159b** was used as catalyst (entry 2).

Table 36: Screening of bifunctional precatalysts.

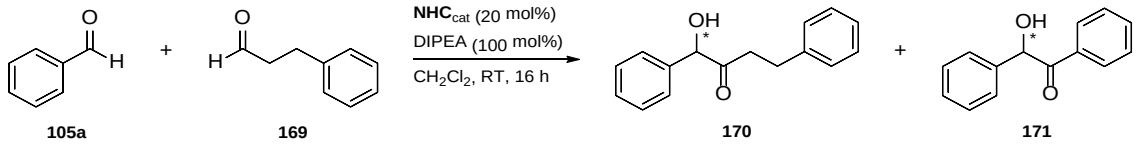


entry	NHC$_{cat}$		conversion [%][a]	ratio 170/171[a]	*ee* [%][b] 170
1		**159a**	60	2:1	12 (*S*)
2[c]		**159b**	64	1:2	22 (*S*)

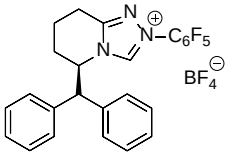
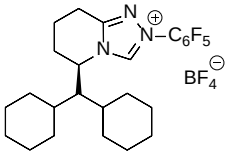
[a]: Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b]: Determined by HPLC on a chiral stationary phase. [c]: THF was used as solvent and Cs_2CO_3 as a base.

Finally, precatalysts derived from chrial disubstituted piperdine-2-ones were investigated. For NHC **167**, with contained a diphenyl residue in the chiral backbone good reactivity was detected. However, only very low chemo- and enantioselecitivty towards the cross-product **170** were achieved (Table 37, entry 1). Moreover, installing more sterically demanding dicyclcohexyl residues such as in catalyst **168** in the chiral backbone resulted in lower reactivity and enantioselecitivty in the cross-benzoin reaction. Neverthless, the chemoselectivity was slightliy improved from 2:1 to 5:1 compared to NHC **167** (entry 1 vs. entry 2).

Table 37: Screening of chiral precatalysts with an disubstituted group.



105a **169** **170** **171**

entry	NHC_{cat}		conversion [%][a]	ratio 170/171[a]	*ee* [%][b] 170
1		**167**	88	2:1	6 (*S*)
2		**168**	53	5:1	2 (*R*)

[a]: Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b]: Determined by HPLC on a chiral stationary phase.

3.4 Conclusion and Outlook

In conclusion, the synthesis of two different catalyst classes is described in chapter three (Figure 31). For morpholine-based precatalysts, the effects of the chiral backbone, the *N*-residue on the triazolium ring and the substituents next to the stereogenic center on the chemo- and enantioselectivity of the cross-benzoin reaction were investigated. Moreover, for piperidine-based triazolium salts the effect of the chiral backbone and the impact of an additional hydrogen-bonding subunit on the outcome of the cross-coupling of aldehydes was studied.

Figure 31: Catalyst classes for the asymmetric cross-benzoin reaction.

Only threonine-derived morpholine-based precatalysts gave good results in terms of chemo- and enantioselectivity. For NHC-catalyst **122a** (R = Me) and **122c** (R = Et) good chemo selectivities and reactivities were obtained, indicating the importance of the *N*-pentafluoro phenyl residue on the triazolium unit. Moreover, for catalyst **122c** higher enantioselectivity was achieved by installing a *N*-mesyl group such as in catalyst **123b**.

Future work on this project might be directed towards the optimization of the reaction conditions for catalyst **122a/c** and **123b**. A new catalyst is presented in Figure 32 which combines the important structural units of both NHCs. A new *N*-residue was designed containing *ortho*-substituents for steric interactions to improve enantioselectivity. In addition, fluorine residues are present to promote π-stacking interaction which could potentially impact the chemoselectivity.

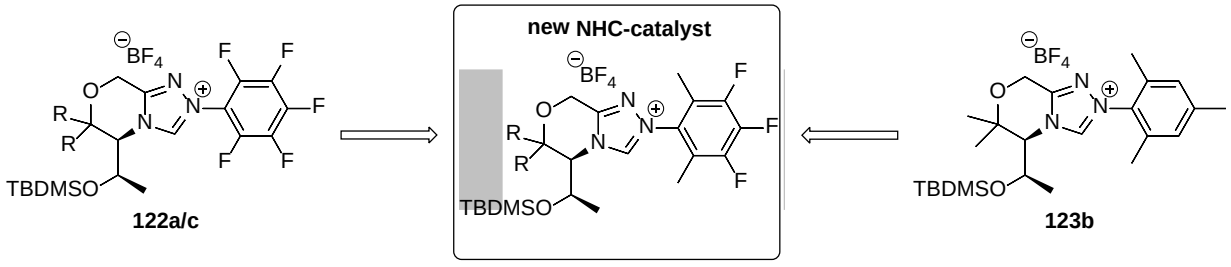


Figure 32: New possible NHC-precatalyst for the asymmetric cross-benzoin reaction.

Chapter 4

Bidentate *N*-Heterocyclic Carbene-Phosphine Ligands for the Asymmetric Hydrogenation

4.1 Introduction

4.1.1 Carbenes as Ligands for Metal-Complexes

In 1964, the first isolated and characterized transition-metal carbene complex was reported by Fischer and Maasböl.[118] In their approach, a tungsten carbonyl carbene complex was isolated after nucleophilic addition of phenyllithium to a carbonyl of tungsten hexacarbonyl followed by acidic work-up and *O*-methylation with diazomethane (Figure 33). Since then, complexes with singlet carbene ligands which are electrophilic at the carbene carbon are referred to as Fischer carbenes.[119]

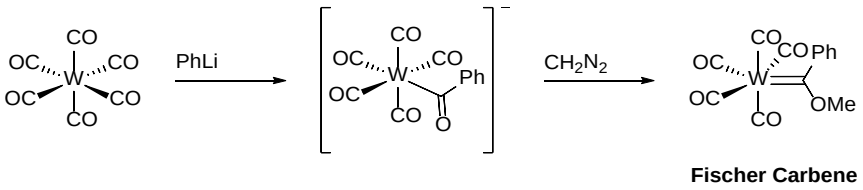


Figure 33: Synthesis of the first transition-metal carbene complex by Fischer.[118]

Four years later, the first imidazole-2-ylidene-based NHC-transition metal complexes were independently synthesized and characterized by Wanzlick[120] and Öfele.[121] In the approach of Wanzlick, the preligand was mixed with mercury(II) acetate and afterwards the resulting mercury carbene complex was isolated. In the example of Öfele, a chromium(0) NHC complex was generated by refluxing the ligand precursor which contained the chromium metal as anion (Figure 34).

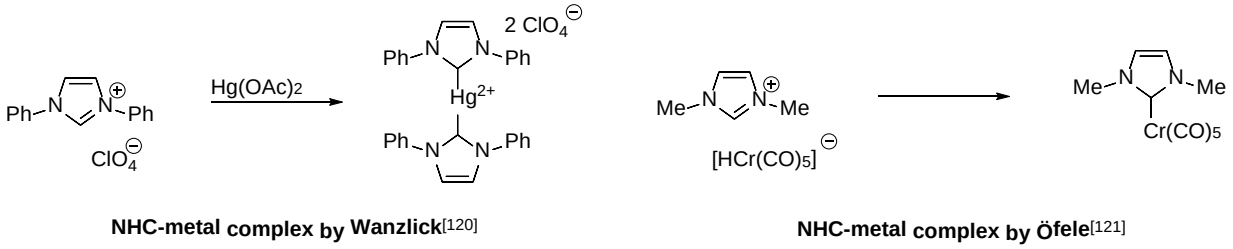


Figure 34: Synthesis of first NHC-metal complexes by Wanzlick[120] and Öfele.[121]

Ten years after the seminal reports of Fischer carbenes, a different class of metal-carbene complexes was developed by Schrock.[122] The typical characteristics of the so-called Schrock carbenes are that the carbene carbon has a nucleophilic character. (Figure 35).

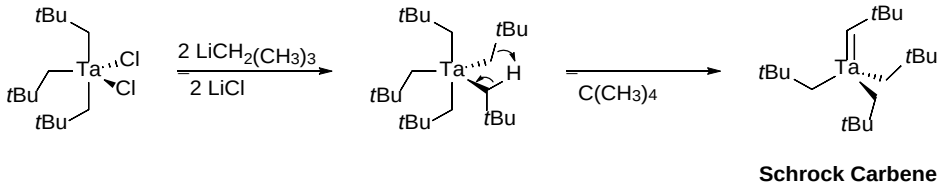


Figure 35: Synthesis of the first Schrock carbene by Schrock.[122]

In Figure 36, the three possible orbital interaction between a carbene and a metal center are presented. Because of the relatively weak π-acceptor properties of NHC-ligands, σ-donation is the most important interaction involved in ligand bonding. Moreover, NHC π-donation to the *d*-orbital of the metal only plays a role in electron poor complexes with empty *d*-orbitals.[123]

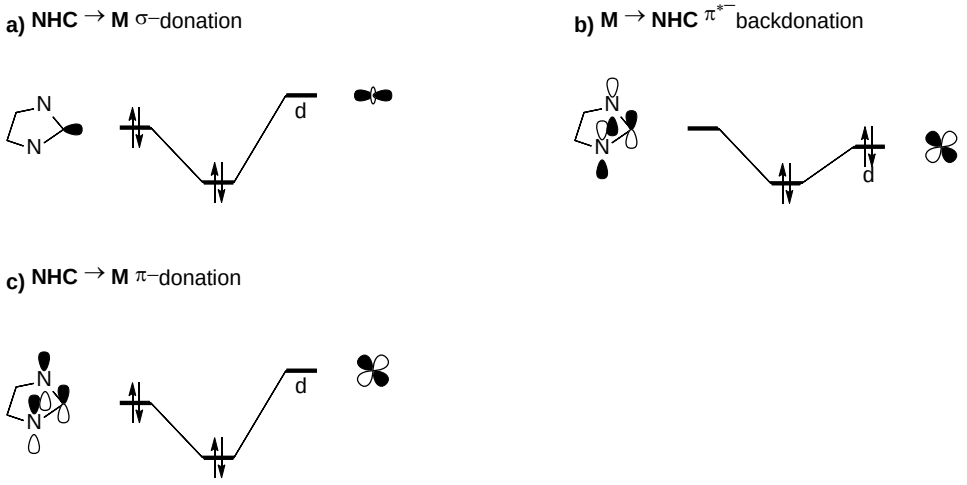
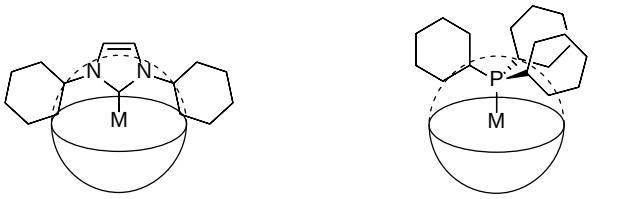


Figure 36: Three orbital contributions to the metal-NHC bond.

Because of the strong σ-donating and weak π-acceptor properties of NHCs, this ligand class is comparable with phosphine-type ligands.[124] However, NHCs are stronger electron-donating compared to phosphines and therefore the corresponding metal-carbene bond is stronger and shorter. This leads to thermally and oxidatively more stable metal-complexes compared to complexes with phosphine ligands.[125] Furthermore, carbene-type ligands are sterically more

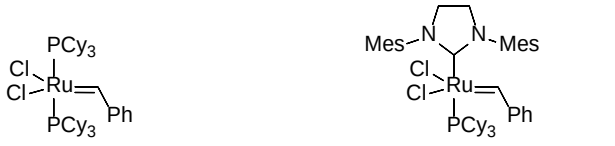
demanding due to the concave structure of the carbene unit (Figure 37). Moreover, the phosphine center is sp^3-hybridizied which results in a cone-shaped spatial arrangement of the ligand.[126]



NHC-metal complex **phosphine-metal complex**

Figure 37: Comparison of steric hindrance in a metal-complex by a NHC- or phosphine-type ligand.

Because of these unique features and the beneficial properties of the resulting metal-complexes many NHC-based catalyst systems were developed for a wide variety of transition-metal catalyzed transformations. For examples, NHC-ruthenium complexes are used for the olefin metathesis reaction. In the Grubbs first generation catalyst the metal center was coordinated with two phosphine ligands and the activity was further improved in cross- and ring-closing metathesis by replacing one phosphine-ligand by a NHC-ligand. The second generation Grubbs catalysts are thermally more stable, can be applied with lower catalyst loadings and have a broader substrate scope (Figure 38).[127]



Grubbs Catalyst 1st Generation **Grubbs Catalyst 2nd Generation**

Figure 38: Grubbs catalysts for the olefin metathesis reaction.[125]

A different application range of NHC-ligands are palladium-catalyzed cross-coupling reactions. Because of the electronic and steric properties of the carbene ligand, the Pd(0) intermediate in the catalytic cycle is stabilized and due to the electron-donating properties of the NHC the oxidative addition is facilitated. Moreover, due to the steric-hindrance of the carbene-ligand the reductive elimination step is promoted. In 2006, Organ and coworkers reported a Pd-PEPPSI-NHC (**P**yridine-**E**nhanced **P**recatalyst **P**reparation **S**tabilization and **I**nitiation) precatalyst as a robust and reactive catalyst for the Suzuki–Miyaura Reaction (Figure 39).[128] Moreover, in the last

years this ligand class was successfully applied for a wide variety of different coupling reaction such as Negishi, Suzuki-Miyaura, Buchwald-Hartwig and Kumada reaction.[129,130]

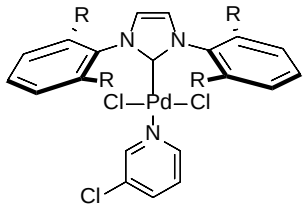
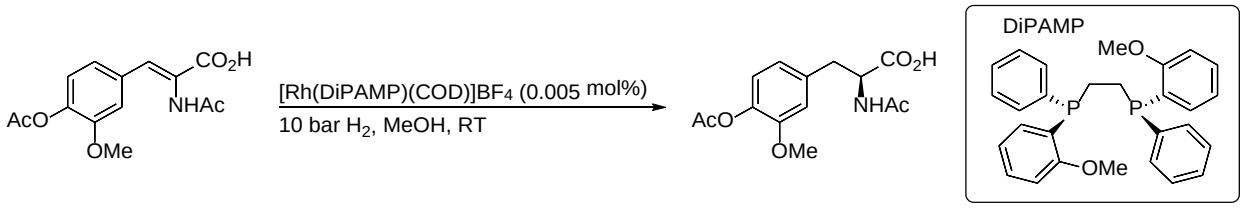


Figure 39: General structure of PEPPSI-NHC precatalyst.

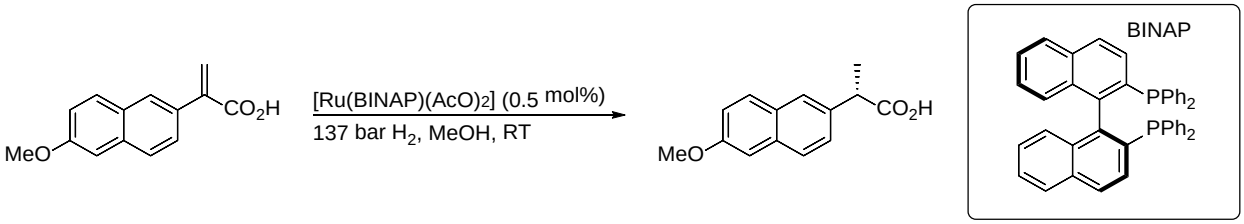
4.1.2 Asymmetric Hydrogenation

Asymmetric hydrogenation is a powerful methodology for the transformation of an unsaturated and prochiral substrate to a chiral product. This type of reaction has several advantages such as perfect atom economy, mild reaction conditions, low catalyst loading, often high enantiomeric excess and high conversions.[131] In 2001, the importance of asymmetric hydrogenation was rewarded with the Nobel prize in chemistry towards Knowles and Noyori together with Sharpless for his contribution in the asymmetric oxidation of organic molecules. Knowles developed rhodium complexes with *P*-chiral diphosphine ligands for the hydrogenation of α,β-dehydroamino acids (Scheme 60),[132] which were successfully applied for the asymmetric synthesis of L-DOPA, a medicament for the treatment of Parkinson.[133]



Scheme 60: Rhodium-catalyzed asymmetric hydrogenation step towards the L-DOPA synthesis.[133]

Noyori introduced Ru catalysts based on BINAP as chiral ligand for the asymmetric reduction of ketones or functionalized alkenes.[134] For example, the unsaturated carboxylic acid was reduced by the ruthenium-complex and the resulting product (*S*)-naproxen, an anti-inflammatory agent, was isolated in high yield and excellent enantioselectivity (Scheme 61).[135]



Scheme 61: Ruthenium-catalyzed asymmetric hydrogenation of unsaturated carboxylic acid.[135]

Since these seminal reports by Knowles and Noyori many catalyst systems were developed and applied to different substrates classes. However, high enantioselectivity was only achieved when a coordinating group was attached next the carbon-carbon double bond.[125,126]

In 1979, Crabtree and coworkers reported an iridium complex (the so called Crabtree catalyst) with a monodentate phosphine and pyridine ligand for the hydrogenation of nonfunctionalized mono-, di-, tri-, and tetra-substituted alkenes.[138] Years later, our group developed a chiral derivative of Crabtree's system, which in contrast to rhodium and ruthenium catalysts allowed the hydrogenation of alkenes lacking coordinating groups with high enantiomeric excess and conversions.[139] In this approach, a chiral bidentate *P*,*N*-based phosphinooxazoline (PHOX) ligand was used, which was originally developed for the asymmetric palladium-catalyzed allylic substitution by Helmchen, Williams and Pfaltz (Figure 40).[140]

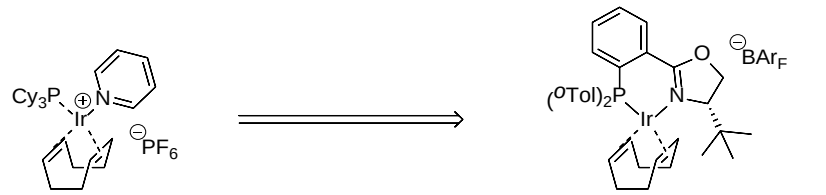


Figure 40: Iridium complexes for the hydrogenation of unfunctionalized alkenes.

Since the first discoveries, many variation of *P*,*N* ligands were developed by our laboratory and other research groups around the world for the iridium-catalyzed asymmetric hydrogenation of a wide variety of different functionalized and nonfunctionalized substrates (see Figure 41 for representative ligand examples).[141]

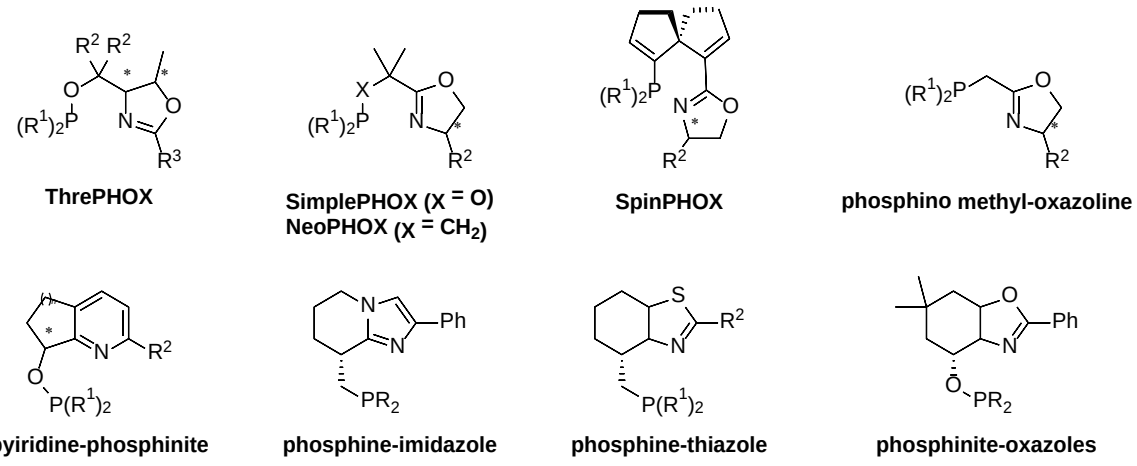


Figure 41: Representative examples of *P*,*N*-type ligands for the asymmetric iridium-catalyzed hydrogenation.

Since the seminal report of Herrmann about the use of rhodium-NHC complexes for asymmetric catalysis,[142] many catalyst systems with either monodentate, bidentate or even tridentate NHC ligands in combination with different transition-metals were developed for the asymmetric hydrogenation of different substrate classes.[143] A powerful iridium-catalyst for the asymmetric hydrogenation of nonfunctionalized alkenes was introduced by Burgess in 2001 (Figure 42).[144] High selectivities and conversions were achieved by using a chiral imidazolylidene ligand. Five years later, the Pfaltz group developed an oxazoline-NHC ligand which formed six-membered iridacycles. These catalysts showed good reactivity but lower selectivities compared to the Burgess type catalyst.[145] More recently, our group reported iridium complexes with chiral NHC/pyridine ligands as hydrogenation catalysts, which gave enantioselectivities comparable to the best *P*,*N*-ligand complexes. In addition, also acid-sensitive substrates containing groups such as OTMS or Boc were reduced due to the lower acidity of the iridium hydride intermediates formed in the catalytic cycle.[146]

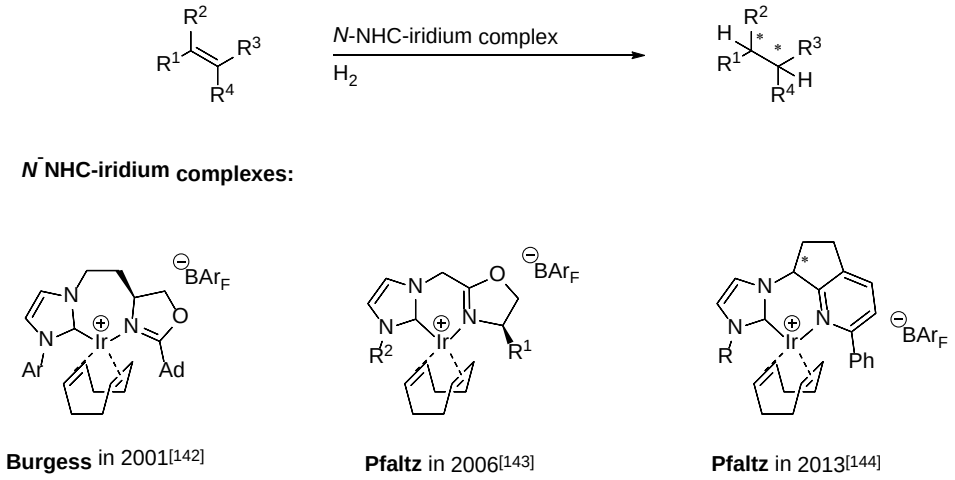
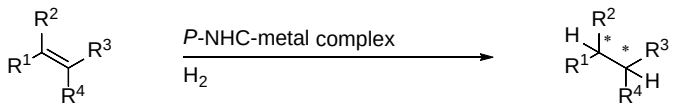


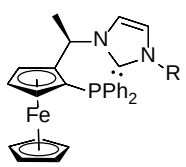
Figure 42: Overview of *N*-NHC-iridium complexes for the asymmetric hydrogenation of alkenes.

Most ligands for transition-metal catalyzed asymmetric hydrogenation contain a chiral phosphine moiety as an important structural motif for selectivity and reactivity issues. Therefore, the design of chiral phosphine-NHC ligands would combine advantages of both phosphine and NHC-systems. The first achiral phosphine-carbene ligand was reported by Herrmann in 1996 which was used for metal-complex formation with ruthenium.[147] However, for hydrogenation reactions only few bidentate *P*-NHC ligands have been studied until now. Inspired from the Josiphos ligand, the Chung group developed the first chiral bidentate phosphine-NHC ligand for rhodium-catalyzed hydrogenation of alkenes. Unfortunately, the product after reduction of the terminal double-bond

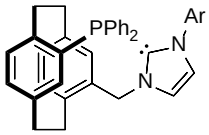
in dimethyl itaconate was obtained in low enantiomeric excess.[148] One year later, Bolm and coworkers introduced a planar chiral phosphinyl-imidazolylidene ligand for the iridium-catalyzed hydrogenation of different olefins, but only moderate selectivities were achieved and long reaction time was needed to get reasonable conversions.[149] In 2006, an iridium-catalyst with a phosphine-NHC ligand was investigated for the asymmetric reduction of functionalized and unfunctionalized alkenes by our research group.[150] However, only moderate enantioselectivities were observed for the tested substrates. More recently, the Shi group reported a bidentate ligand with a chiral 1,1'-binaphthyl framework for the reduction of alkenes but also herein only moderate selectivities were obtained.[151]



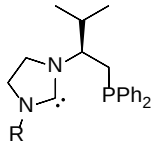
Phosphine-NHC ligands:



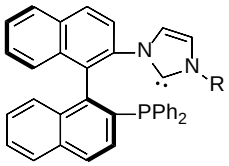
Chung in 2003[148]



Bolm in 2004[149]



Nanchen & Pfaltz in 2006[150]



Shi in 2013[151]

Figure 43: Overview of phosphine-NHC ligands for the asymmetric hydrogenation of alkenes.

4.2 Synthesis of Iridium Complexes derived from Chiral Bidentate NHC-Phosphine Ligands

In the synthesis of chiral bifunctional triazolium salts (see Chapter 3.2.2) a mesyl lactam intermediate was used as a synthetic precursor. Inspried by the work of Nannchen, who developed different NHC-phosphine ligands (see Figure 43), it was thought that this mesylate intermediate could be an ideal precursor for the synthesis of bidentate NHC-phosphine-based preligands with conformationally more rigid structures.

The retrosynthetic analysis of the iridium complexes derived from chiral bidentate NHC-phosphine type ligands is presented in Figure 44. For the synthesis of the ligand two different synthetic approaches were investigated. In strategy **A**, the phosphine residue was introduced in a late-stage of the synthesis to avoid problems of phosphine alkylation during the triazolium salt synthesis. The mesyl group of the triazolium salt was displaced by the phosphine source in a substitution reaction. Alternatively, in strategy **B** the phosphine is introduced in an early-stage of the synthesis. In this synthetic design, the mesyl lactam is converted to the resulting phosphine lactam which could then be subjected to the triazolium salt synthesis. The key-intermediate for both strategies is the mesyl lactam precursor-derived from the corresponding five or six-membered hydroxyl lactam.

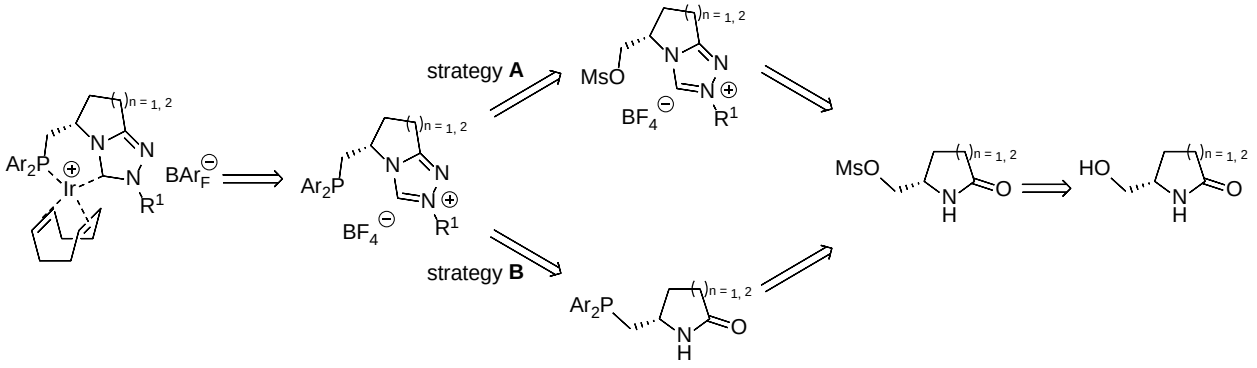
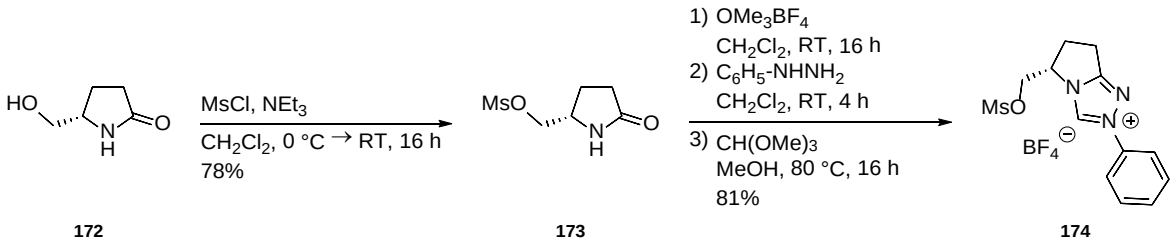


Figure 44: Retrosynthetic analysis of iridium complexes derived from chiral bidentate phosphine-NHC ligand.

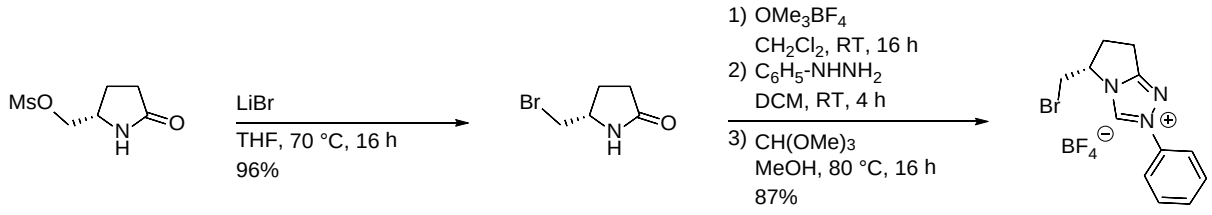
First, synthetic strategy **A** was investigated. The mesyl triazolium salt **174** was synthesized *via* a four-step sequence which began with commercially available (*S*)-pyroglutaminol **172**. First, mesyl lactam **173** was isolated in good yield after treating hydroxy lactam **172** with mesyl chloride and triethylamine. In the last step, triazolium salt **174** was synthesized according a one-pot three-step procedure by Rovis[112] to yield the final mesyl intermediate **174** in 81% yield (Scheme 62).



172 **173** **174**

Scheme 62: Synthesis of mesyl triazolium salt **174**.

As an alternative precursor for the phosphine triazolium salt synthesis, bromo triazolium salt **176** was formed in a four-step sequence. Mesyl lactam **173** was converted to bromo lactam **175** by refluxing in THF with lithium bromide. Next, precursor **176** was obtained in very good yield after using the standard synthetic procedure for the triazolium salt synthesis.



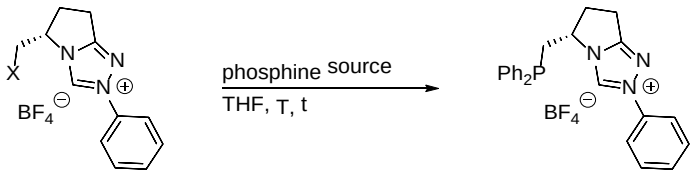
173 **175** **176**

Scheme 63: Synthesis of bromo triazolium salt **176**.

In the next step, the late-stage introduction of the phosphine residue was investigated using either from the mesyl- or bromo-triazolium salt. In initial studies, mesyl precursor **174** was used for the nucleophilic displacement by potassium or lithium diphenylphosphide. Unfortunately, for both phosphine sources conversion to the substituted product **177** (Table 38, entries 1-2,) was not detected by ESI-MS analysis of the crude reaction mixture. These analyses showed, that the starting material was decomposed to unknown by-products. A likely problem is the acidity of the carbene C-H proton, which could be deprotonated by the metal diphenylphosphide. In an attempt to alleviate this potential problem an excess of potassium diphenylphosphide (two equivalents)

was tested, however, no phosphine product **177** was formed. To avoid problems related to deprotonation of the triazolium salt, a less basic but nucleophilic diphenylphosphine in combination with a higher reaction temperature was applied for the nucleophilic substitution. Unfortunately, in this case as well product formation was not observed by ESI-MS analysis (entry 3). When the leaving group was changed from a mesylate to a bromide such as in triazolium salt **176**, the formation of the desired phosphine product **177** was also not detected (entries 4-5).

Table 38: Studies for the synthesis of phosphine-triazolium salt **177**.



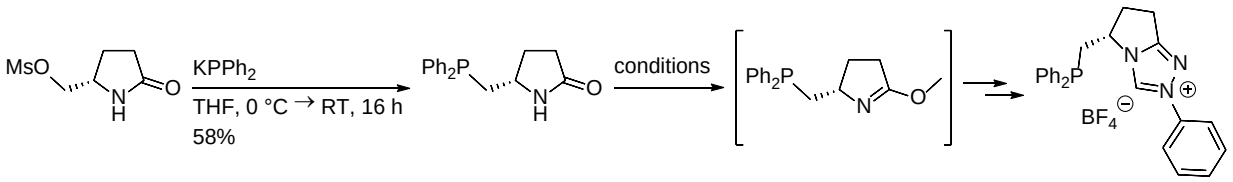
174/176 **177**

entry	X	phosphine source	T [°C]	t [h]	conversion[a]
1	OMs (**174**)	$KPPh_2$	0	4	no
2	OMs (**174**)	$LiPPh_2$	0	4	no
3	OMs (**174**)	$HPPh_2$	75	16	no
4	Br (**177**)	$KPPh_2$	0	4	no
5	Br (**177**)	$HPPh_2$	75	16	no

[a]: Determined by ESI-MS analysis of the crude reaction mixture.

Because the late-stage phosphine introduction was not successful, synthetic strategy **B** was applied. In the first step, phosphine lactam **178** was obtained after nucleophilic substitution of the mesylate group of lactam **173** by potassium diphenylphosphide. Afterwards, the triazolium salt synthesis which began with phosphine lactam **178** was investigated. In the precatalyst synthesis the imidate formation might be the problematic step because of the possible alkylation of the phosphine residue by the alkylation reagent. Using standard reaction conditions with trimethyloxonium tetrafluoroborate (Meerwein's salt) as an *O*-alkylation reagent, imidate intermediate **179** was not detected by ESI-MS analysis of the crude reaction mixture. Instead, the

P-methylated by-product was observed exclusively by ^{31}P-NMR and ESI-MS analysis. Therefore, dimethyl sulfate was tested as an alternative alkylation reagent. Unfortunately, in this case the phosphorus atom was also alkylated. In a last attempt, phosphoryl chloride was used for the *in situ* formation of a Vilsmeier-type chloro iminiumion intermediate which then could be used for the nucleophilic displacement with phenyl hydrazine. Unfortunately, also herein no formation of the desired adduct was observed (Scheme 64).

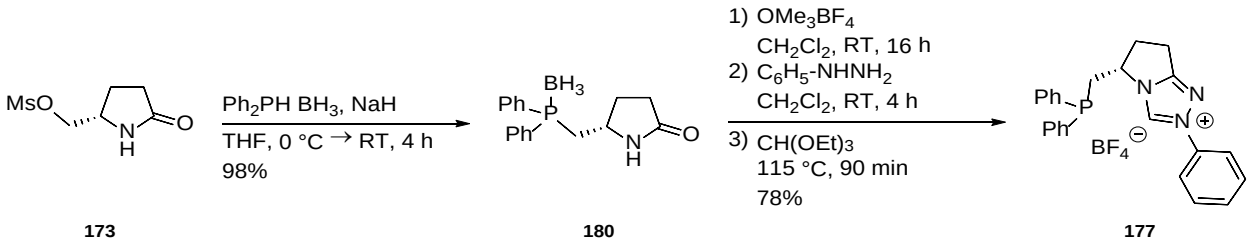


173 **178** **179** **177**

tested conditions for amidate formation:
1) OMe_3BF_4 in CH_2Cl_2 (no amidate formation)
2) $C_2H_6O_4S$ in MeCN (no amidate formation)
3) $POCl_3$ in CH_2Cl_2 (no chloro iminiumion formation)

Scheme 64: Synthesis of phosphine triazolium salt **177** by strategy **B**.

To avoid alkylation of the phosphorus atom, strategy **B** was slightly modified. In the new approach, a borane-protected phosphine intermediate was used as the lactam precursor for the triazolium salt synthesis. The requisite phosphine-borane lactam **177** was isolated in excellent yield after treating mesyl lactam **173** with sodium diphenylphosphide borane adduct (Scheme 65). When the borane adduct **180** was subjected to the procedure for triazolium salt synthesis, no alkylation or borane-deprotection of the phosphine residue was observed using Meerwein's salt for the imidate formation. Also treatment of the imidate intermediate with phenyl hydrazine did not deprotect the phosphorus atom. The synthetic procedure for the cyclization of the amidrazone intermediate was slightly optimized for the phosphine containing triazolium salt, in order to achieve borane-deprotection in the same step. The desired deprotected product **177** was obtained in 9% yield after 16 hours in refluxing trimethyl orthoformate. ESI-MS analysis of the crude reaction mixture revealed that the main problem was the alkylation of the phosphine center after *in situ* borane deprotection. To prevent alkylation of the phosphorus atom, the condensation reagent was changed to the sterically bulkier triethyl orthoformate and the reaction time was reduced from 16 hours to 90 minutes. With the optimized reaction conditions known, ligand precursor **177** was isolated in good yield after purification by column chromatography.

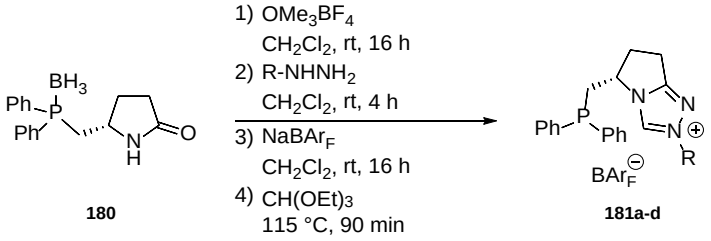


173 **180** **177**

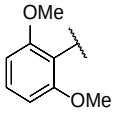
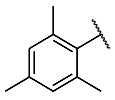
Scheme 65: Synthesis of phosphine triazolium salt **177** by a modified strategy **B**.

Because the preferred anion of the hydrogenation-catalyst is BAr_F, an alternative ligand precursor with the BAr_F counterion was synthesized. Thus different *N*-substituted triazolium BAr_F salts were synthesized starting from the borane-protected diphenylphosphine lactam **180**. After imidate formation, a range of hydrazines were used in the *in situ* formation of the resulting amidrazone intermediate. Compared to the synthesis of BF_4 triazolium salts, an additional anion-exchange step was introduced by adding sodium BAr_F to the crude reaction mixture. An initial trial to exchange the counterion of the triazolium salt **177** failed, because of separation problems of the BF_4 and BAr_F salts. After filtration of the crude amidrazone BAr_F salt followed by condensation with triethyl orthoformate all triazolium salts **181a-d** were isolated in low to good yield (Table 39).

Table 39: Synthesis of triazolium BAr_F salts with different *N*-residues.

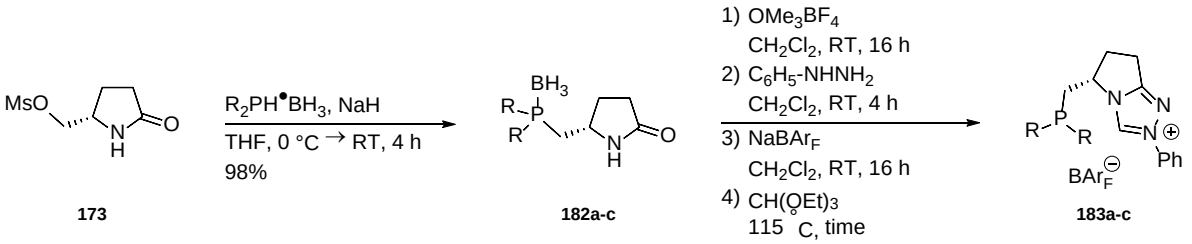


180 **181a-d**

entry	R	triazolium salt 181 (yield in %)	entry	R	triazolium salt 181 (yield in %)
1		**181a** (75)	3		**181c** (16)
2		**181b** (86)	4		**181d** (67)

With the optimized conditions for the triazolium BAr_F salts synthesis in hand, three different phosphine substituted triazolium salts were synthesized. In the first step, phosphine lactam intermediates **182a-c** were isolated in low to good yield after treating mesyl lactam **173** with the corresponding sodium phosphide borane adduct. All phosphine lactams were then subjected to the synthetic procedure for the triazolium salt synthesis and for all phosphine adducts the corresponding deprotected ligand precursors **183a-c** were isolated in good to moderate yield (Table 40). Because of the stronger stability of the borane-dialkylphosphine adduct **182b** and **182c**, the reaction time was increased from 90 to 120 minutes to get full deprotection of the phosphorus center.

Table 40: Synthesis of triazolium BAr_F salts with different phosphine residues.



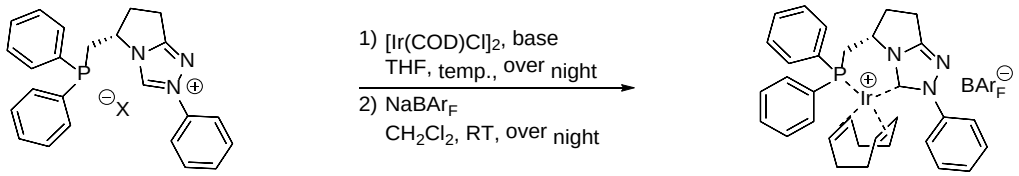
173 **182a-c** **183a-c**

entry	R	phosphine lactam 182 (yield in %)	time [min] (cyclisation step)	triazolium salt 183 (yield in %)
1		**182a** (84)	90	**183a** (75)
2		**182b** (18)	120	**183b** (66)
3		**182c** (59)	120	**183c** (27)

In the next step, the complexation of ligand precursor **177** with iridium was investigated. First, a two-step sequence with the BF_4 salt of the ligand precursor was studied. The precatalyst could be deprotonated by a base to form the bidentate ligand which then could coordinate with iridium to generate a complex with a BF_4 counter ion. After counterion exchange with sodium BAr_F, the final iridium catalyst **184** should be obtained. Unfortunately, no conversion to the desired iridium complex **184** was detected by ESI-MS analysis of the crude reaction mixture when lithium *tert*-butoxide was used as a base (Table 41, entry 1). Also, higher temperature or a change of the

base to potassium *tert*-butoxide did not result in product formation (entries 2-3). After the first test with the BAr_F precursor **181a** and lithium *tert*-butoxide as base, no complex formation was detected by ESI-MS analysis. In the second trial, the carbene C-H proton was deprotonated by potassium *tert*-butoxide to form the free carbene and after addition of $[Ir(cod)Cl]_2$ the desired iridium complex was observed by ESI-MS analysis. After purification of the crude mixture, the resulting iridium catalyst **184** was isolated in good yield as a red solid.

Table 41: Studies for the complexdation with iridium.



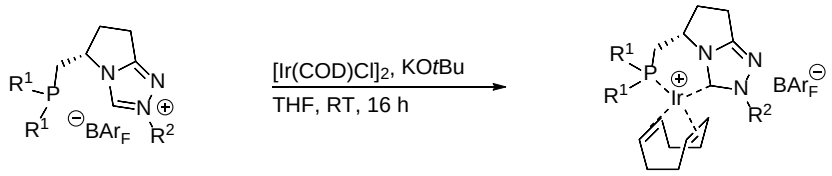
177/181a **184**

entry	X	base	T [°C]	conversion[a]	yield [%][b]
1	BF_4 (**177**)	LiO*t*Bu	rt	no	-
2	BF_4 (**177**)	LiO*t*Bu	40	no	-
3	BF_4 (**177**)	KO*t*Bu	rt	no	-
4[c]	BAr_F (**181a**)	LiO*t*Bu	rt	no	-
5[c]	BAr_F (**181a**)	KO*t*Bu	rt	yes	78

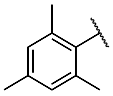
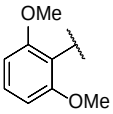
[a]: Determined by ESI-MS analysis of the crude reaction mixture. [b] Isolated yield. [c]: No BAr_F addition step.

With the complexation conditions optimized, the formation of different iridium complexes derived from the corresponding ligand precursors **181/183a-c** was investigated. The iridium complex **185a** derived from the triazolium salt with a *N*-mesitylene group was obtained in lower yield compared to the *N*-phenyl substituted ligand such as in complex **184** (Table 42, entry 1) due to the steric hindrance. Moreover, also iridium catalyst **185b** derived from a triazolium salt with a *N*-2,6-dimethoxy phenyl residue gave only moderate yield (entry 2). Catalyst **185c** derived from a *N-tert* butyl substituted precatalyst **181d** was formed in 74% yield (entry 3). The introduction of sterically demanding *ortho*-tolyl, cyclohexyl or *tert*-butyl phosphine substituents lowered the yield of the desired iridium complex **185d**, **185e** and **185f** (entry 4-6).

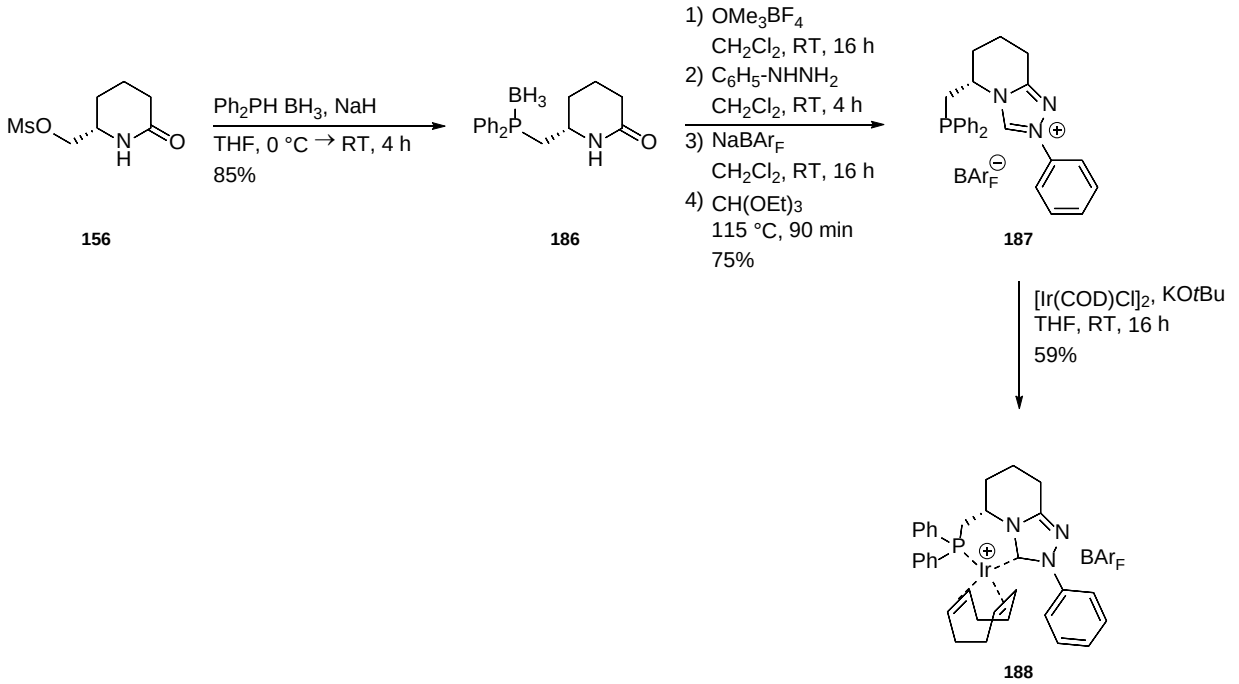
Table 42: Synthesis of iridium complexes **185a-f**.



181a-c/183a-c **185a-f**

entry	R^1	R^2	**iridium complex 185** (yield in %)
1			**185a** (46)
2			**185b** (46)
3			**185c** (74)
4[c]			**185d** (32)
5[c]			**185e** (30)
6			**185f** (36)

For studies concerning the effect of the fused-ring system, a phosphine-NHC precursor with a six-membered fused-ring was synthesized in a six-step synthetic sequence. In the first step, the borane protected phosphine intermediate **186** was isolated in 85% yield after nucleophilic displacement of the mesylate group in adduct **156** by sodium borane diphenylphosphide. Next, triazolium salt **187** was formed by using the four-step one-pot procedure to generate the ligand precursor **187** in good yield. Finally, the iridium complex **189** was formed in good yield after complexation with the deprotonated BAr_F salt **187** (Scheme 66).

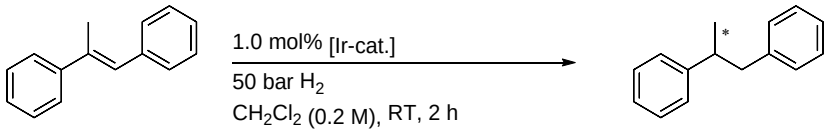


Scheme 66: Synthesis of iridium complex **182** derived from six-membered fused-ring phosphine-NHC precursor **181**.

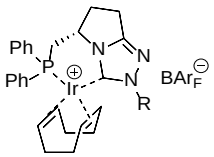
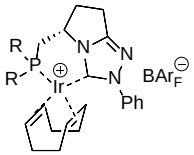
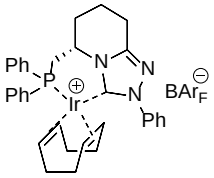
4.3 Hydrogenation Results of Model Substrates

In an initial study the new ligand class was tested in the iridium-catalyzed asymmetric hydrogenation of unfunctionalized olefins, namely the model substrate **189** (Table 43). Unfortunately, the majority of the iridium-catalysts showed almost no reactivity (entries 1-3, 5-6 and 8). Interestingly, when the *N*-residue on the triazolium ring was changed from an aromatic to an aliphatic group a drastic increase in reactivity was observed (entry 4 vs. entry 1). For example, by using catalyst **185c** the chiral product **190** was obtained with complete conversion and moderate enantiomeric excess (entry 4). A further improvement of the enantioselectivity was observed with complex **185f** (entry 7), however, low conversion to the desired product was observed.

Table 43: Iridium-catalyzed asymmetric hydrogenation of (*E*)-1,2-diphenyl-1-propene **189**.



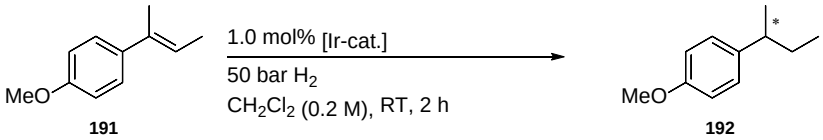
189 **190**

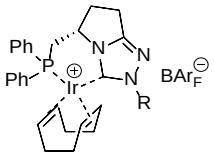
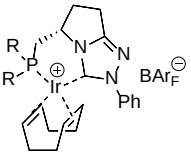
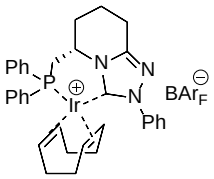
entry	Ir-catalyst		R	conv. [%][a]	*ee* [%][b]
1		**184**	Ph	3	n.d.
2		**185a**	Mes	1	n.d.
3		**185b**	1,3-(OMe_2)-Ph	1	n.d.
4		**185c**	*t*Bu	99	50 (*R*)
5		**185d**	*o*Tol	1	n.d.
6		**185e**	Cy	2	n.d.
7		**185f**	*t*Bu	14	58 (*R*)
8		**188**		7	n.d.

[a]: Determined by GC analysis of the reaction mixture after removal of the catalyst. [b]: Determined by HPLC analysis on a chiral stationary phase.

The results of the iridium-catalyzed hydrogenation of the (*E*)-double bond in substrate **191** using NHC-phosphine ligands are presented in Table 44. Moderate conversions and low *ee*'s (20%) of product **185** were obtained for ligands with a diphenylphosphine unit and an *N*-aryl residue (entries 1-3). Replacing the *N*-aryl unit to an *N*-alkyl unit resulted again in a drastic increase in reactivity and selectivity to give the reduced substrate **192** (entry 4). The steric hindrance at the phosphorus center was increased, but this gave only inferior results (entries 5-7). The ligand with a six-membered fused ring system showed a slightly higher reactivity compared to the five-membered derivative (entry 8 vs. entry 1). However, the enantiomeric excess was reduced from 20% to 7%.

Table 44: Iridium-catalyzed asymmetric hydrogenation of (*E*)-2-(4-methoxyphenyl)-2-butene **191**.

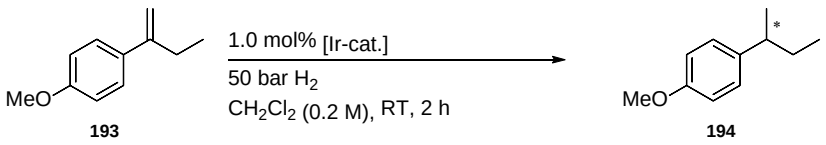


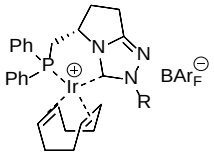
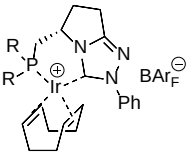
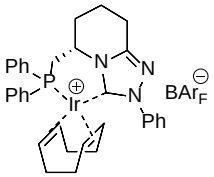
entry	Ir-catalyst		R	conv. [%][a]	*ee* [%][b]
1		**184**	Ph	48	20 (*R*)
2		**185a**	Mes	37	20 (*R*)
3		**185b**	1,3-(OMe_2)-Ph	46	20 (*R*)
4		**185c**	*t*Bu	>99	38 (*R*)
5		**185d**	*o*Tol	20	6 (*S*)
6		**185e**	Cy	33	8 (*R*)
7		**185f**	*t*Bu	27	6 (*R*)
8		**188**		58	7 (*R*)

[a]: Determined by GC analysis of the reaction mixture after removal of the catalyst. [b]: Determined by HPLC analysis on a chiral stationary phase.

Next, the reduction of the terminal double bond in substrate **193** was investigated. In general, all iridium catalysts showed higher reactivity towards the hydrogenation of the terminal double bond compared to an internal one, as in substrate **191** (Table 45 vs. Table 44). Nevertheless, only poor enantioselectivities were achieved.

Table 45: Iridium-catalyzed asymmetric hydrogenation of 1-(but-1-en-2-yl)-4-methoxybenzene **193**.

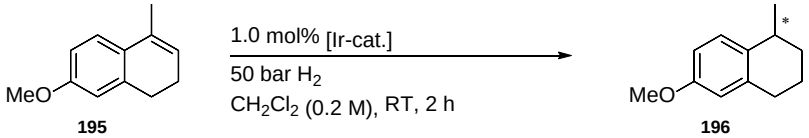


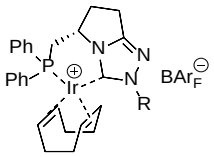
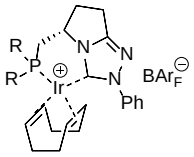
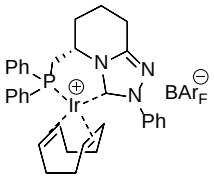
entry	Ir-catalyst		R	conv. [%][a]	*ee* [%][a]
1		**184**	Ph	73	6 (*S*)
2		**185a**	Mes	80	4 (*S*)
3		**185b**	1,3-(OMe_2)-Ph	98	8 (*S*)
4		**185c**	*t*Bu	>99	4 (*S*)
5		**185d**	*o*Tol	81	2 (*S*)
6		**185e**	Cy	75	5 (*R*)
7		**185f**	*t*Bu	>99	6 (*R*)
8		**188**		>99	2 (*S*)

[a]: Determined by GC analysis of the reaction mixture after removal of the catalyst. [b]: Determined by HPLC analysis on a chiral stationary phase.

Next, the asymmetric hydrogenation of the cyclic unfunctionalized olefin **195** was studied (Table 46). For all catalysts containing an *N*-aryl group at the triazolium ring conversion to the desired chiral product **196** was observed. However, only low enantioselectivities were achieved (entries 1-3 and 6). The reactivity of the catalyst was further increased when iridium complexes were used that contained either an *N*-alkyl residue (entry 4), *P*-alkyl substituents (entries 6-7) or a six-membered fused ring system on the ligand (entry 8). For this substrate class the best lead was identified to be complex **185c** which gave the desired product **196** with high conversion but low enantiomeric excess (entry 4).

Table 46: Iridium-catalyzed asymmetric hydrogenation of 6-methoxy-1-methyl-3,4-dihydronaphthalene **195**.

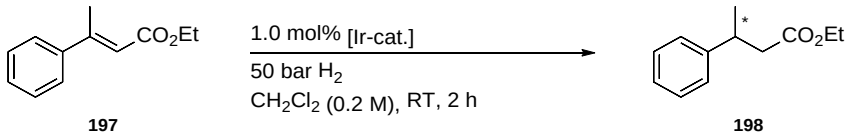


entry	Ir-catalyst		R	conv. [%][a]	*ee* [%][b]
1		**184**	Ph	47	4 (*S*)
2		**185a**	Mes	65	8 (*S*)
3		**185b**	1,3-(OMe_2)-Ph	53	rac.
4		**185c**	*t*Bu	>99	24 (*S*)
5		**185d**	*o*Tol	21	14 (*R*)
6		**185e**	Cy	47	14 (*R*)
7		**185f**	*t*Bu	90	16 (*R*)
8		**188**		80	rac.

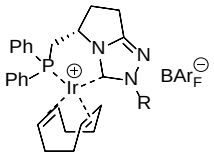
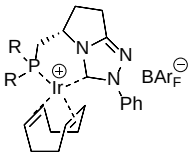
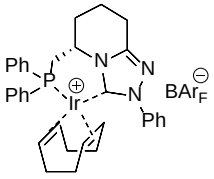
[a]: Determined by GC analysis of the reaction mixture after removal of the catalyst. [b]: Determined by HPLC analysis on a chiral stationary phase.

The trisubstituted α,β-unsaturated ester **197** proved to be more reactive than unfunctionalized alkenes (Table 44 or 46), and the reduced product **198** was obtained in almost every case with complete conversion (Table 47). Only in the case of catalyst **185a**, which contained a sterically demanding *N*-mesitylene group, only moderate reactivity was detected (entry 3). However, for each of the iridium complexes only low to moderate enantioselectivities were observed. The best catalyst was iridium complex **185e** which gave the chiral ester **198** with an enantiomeric excess of 32% (entry 6).

Table 47: Iridium-catalyzed asymmetric hydrogenation of (*E*)-ethyl 3-phenylbut-2-enoate **197**.



197 **198**

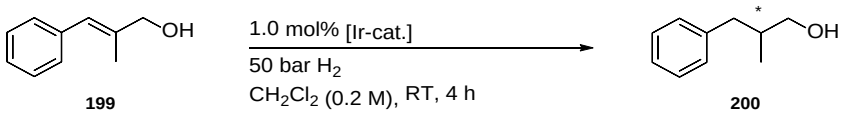
entry	Ir-catalyst		R	conv. [%][a]	*ee* [%][b]
1		**184**	Ph	>99	10 (*S*)
2		**185a**	Mes	56	22 *(R)*
3		**185b**	1,3-(OMe_2)-Ph	>99	24 (*R*)
4		**185c**	*t*Bu	>99	8 (*S*)
5		**185d**	*o*Tol	>99	10 (*R*)
6		**185e**	Cy	>99	32 (*R*)
7		**185f**	*t*Bu	>99	30 (*R*)
8		**188**		>99	12 (*S*)

[a]: Determined by GC analysis of the reaction mixture after removal of the catalyst. [b]: Determined by HPLC analysis on a chiral stationary phase.

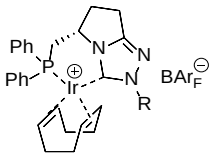
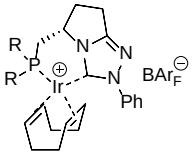
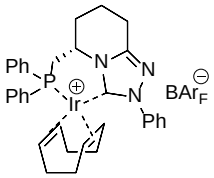
In the hydrogenation of allylic alcohol **199** the iridium complexes showed, in general, high reactivities (Table 48). For ligands with a diphenylphosphine moiety only low enantioselectivities were achieved (entries 1-4 and 8). The selectivity could not be improved by installing *ortho*-tolyl

or *di-tert*-butyl substituents at the phosphorus center (entry 5 and 7). The catalyst with a dicyclohexylphosphine unit in the ligand system showed high reactivity and moderate enantioselectivity (entry 6).

Table 48: Iridium-catalyzed asymmetric hydrogenation of (*E*)-2-methyl-3-phenylprop-2-en-1-ol **199**.



199 **200**

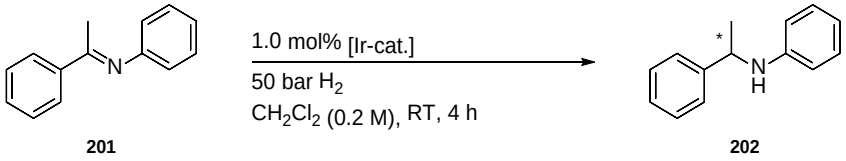
entry	Ir-catalyst		R	conv. [%][a]	*ee* [%][b]
1		**184**	Ph	>99	34 (*S*)
2		**185a**	Mes	74	18 (*S*)
3		**185b**	1,3-(OMe_2)-Ph	84	24 (*S*)
4		**185c**	*t*Bu	>99	26 (*S*)
5		**185d**	*o*Tol	>99	24 (*S*)
6		**185e**	Cy	>99	50 (*S*)
7		**185f**	*t*Bu	>99	32 (*S*)
8		**188**		>99	32 (*S*)

[a]: Determined by GC analysis of the reaction mixture after removal of the catalyst. [b]: Determined by HPLC analysis on a chiral stationary phase.

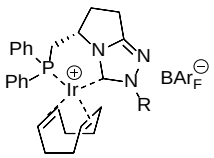
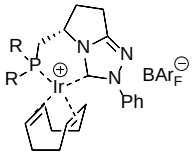
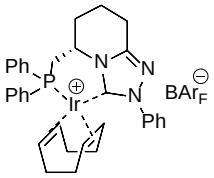
As a final test substrate, *N*-phenyl ketimine **201** was investigated (Table 49). First, the effect of the *N*-residue on the selectivity and reactivity was studied. Only catalyst **184** which contained an *N*-phenyl residue, gave full conversion to the chiral amine **202**, albeit with low enantiomeric excess (entry 1). Although the selectivity was improved by installing more sterically hindered *N*-residues such as in *N*-mesitylene (entry 2) or *N*-di-*ortho*-methoxyphenyl (entry 3) groups, the reactivity observed was low. Moreover, for iridium catalyst **185c** with a *N-tert*-butyl residue only inferior results were obtained (entry 4). Next the effect of different *P*-residues was investigated. Increasing the steric hindrance at the phosphorus center such as in catalyst **185d** resulted in high reactivity

but almost no selectivity was observed (entry 5). Alkyl substituted phosphine ligands gave as well high conversions. In addition, higher enantioselectivities were achieved when compared to the diphenylphosphine-based ligands (entries 6-7 vs entries 1-5). Promising results were observed especially for dicyclohexylphosphine-NHC iridium complex **185e**. Finally, for iridium complex **188**, which contained a six-membered fused-ring system better enantioselectivity was obtained when compared to the five-membered system (entry 8 vs entry 1).

Table 49: Iridium-catalyzed asymmetric hydrogenation of *N*-(1-phenylethylidene)-aniline **201**.



201 **202**

entry	Ir-catalyst		R	conv. [%][a]	*ee* [%][b]
1		**184**	Ph	>99	28 (*R*)
2		**185a**	Mes	68	44 (*R*)
3		**185b**	1,3-(OMe_2)-Ph	76	44 (*R*)
4		**185c**	*t*Bu	17	8 (*S*)
5		**185d**	*o*Tol	>99	4 (*S*)
6		**185e**	Cy	>99	64 (*R*)
7		**185f**	*t*Bu	>99	48 (*R*)
8		**188**		95	58 (*R*)

[a]: Determined by GC analysis of the reaction mixture after removal of the catalyst. [b]: Determined by HPLC analysis on a chiral stationary phase.

4.4 Conclusion and Outlook

In conclusion, the synthesis of eight new chiral bidentate NHC-phosphine ligands and the formation of the corresponding iridium complexes is described in chapter four (Figure 45). The influence of each structural unit (*N*-residue on the triazolium ring, *P*-residues, size of fused-ring system) on the asymmetric hydrogenation of model substrates was investigated. Unfortunately, with unfunctionalized olefins only low conversions and low enantioselectivities were achieved for most ligands. Only catalyst **185c**, with an *N*-alkyl group at the triazolium unit showed high reactivity towards unfunctionalized alkenes. On the other hand, alkenes with functional groups such as a hydroxy or ester group and an imine were suitable substrates for the hydrogenation reaction but only low to moderate enantioselectivities were observed. The best rests were obtained with catalyst **185e**, which gave high conversion and moderate enantioselectivities in the reduction of allylic alcohol **199** (>99% conversion, 50% *ee*) and of imine **201** (>99% conversion, 64% *ee*).

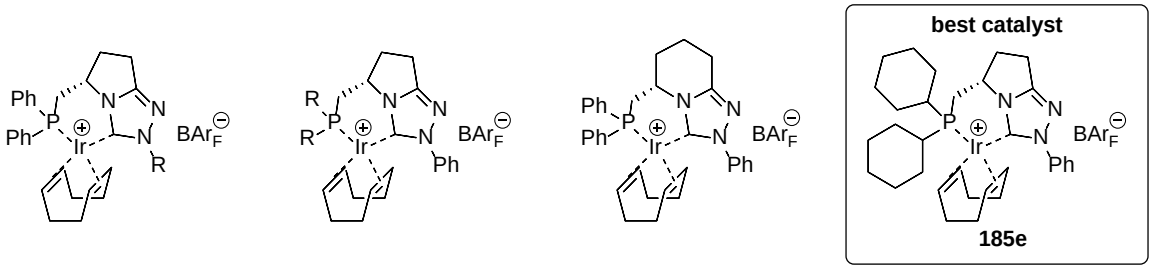


Figure 45: Iridium complexes derived from chiral bidentate NHC-phosphine ligands.

Future work on this project should be dedicated to the optimization of the catalyst lead structure to design a selective catalyst for the asymmetric hydrogenation of imines. Based on the screening results, a possible new iridium complex is oposed in Figure 46.

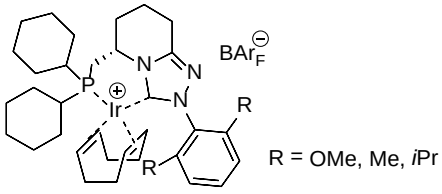


Figure 46: New possible iridium-complex for the asymmetric hydrogenation of imines.

Chapter 5

Experimental Part

5.1 General Informations

5.1.1 Working Techniques

Commercially available reagents were purchased from Acros, Aldrich, Alfa or Fluka and used as received. All preparative reactions, involving a phosphine compound were carried out in heat-gun dried glassware under inert atmosphere using Schlenk techniques. All reactions were carried out in dry solvents. The solvents were purchased from Aldrich in sure/sealed™ bottles. Column chromatographic purifications were performed on Fluka silica gel 60 (Buchs, particle size 40-63 nm). The eluents for column chromatography were prepared from technical solvents.

5.1.2 Analytical Methods

Melting Points (M.P.): Melting points were determined on a Büchi 535 apparatus and are uncorrected.

Thin Layer Chromatography (TLC): TLC plates were obtained from Machrey-Nagel (Polygram SIL/UV254, 0.2 mm silica with fluorescence indicator). UV light (254 nm), CER or basic permanganate solution were used to visualize the respective compounds.

NMR-Spectroscopy (NMR): NMR spectra were measured either on a Bruker Avance 400 (400 MHz) or a Bruker Avance 500 (500 MHz) spectrometer. The chemical shifts (δ) are given in ppm. The chemical shift δ values were corrected to the signal of the deuterated solvents: 7.26 ppm (^{1}H NMR) and 77.16 ppm (^{13}C NMR) for $CDCl_3$; 5.32 ppm (^{1}H NMR) and 54.00 ppm (^{13}C NMR) for CD_2Cl_2 and 39.52 ppm (^{13}C NMR) for $(CD_3)_2SO$. The assignment of ^{1}H and ^{13}C signals was accomplished, when needed by two-dimensional correlation experiments (HSQC (heteronuclear single quantum coherence) and HMBC (heteronuclear multiple quantum coherence)). Multiplets are assigned as: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet) and m (multiplet). Broad signals are assigned with: br (broad).

Infrared Spectroscopy (IR): Infrared spectra were collected on a Shimadzu FTIR-8400S spectrometer. The compounds were measured as pure substance via Specac ATR attachment. Absorption bands are given in wave numbers ([cm^{-1}]). The peak intensity is describedby: s (strong), m (medium), w (weak).

High Resolution Mass Spectrometry (HRMS-ESI): Mass spectra were measured by Dr. H. Nadig (Department of Chemistry, University of Basel) on a bruker maXis 4G.

Electrospray Ionization Mass Spectrometry (ESI-MS): ESI-MS spectra were measured on a Varian 1200L Quadrupol MS/MS spectrometer using mild desolvation conditions (39 psi nebulising gas, 4.9 kV spray voltage, 19 psi drying gas at 125 °C, 100 eV capillary voltage, 1300 V detector voltage). The samples were diluted immediately prior to their analysis and measured using direct injection. The signals are given in mass-to-charge ratios (m/z) with the relative intensity in brackets.

Optical Rotations: Optical rotations were measured on a Perkin Elmer Polarimeter 341 (in a cuvette (l = 1 dm)) at 20 °C at 589 nm. The concentration (c) is given in g/100 mL.

Elemental Analysis (EA): Elemental analyses were measured by Sylvie Mittelheisser (Department of Chemistry, University of Basel) on a Leco CHN-900 (C-, H-, N-detection). The data are indicated in mass percent.

Gas Chromatography (GC): Gas chromatographs were collected on Shimadzu GC 2010-Plus instrument. Achiral separations were performed on a Restek Rtx®-1701 column (30 m x 0.25 mm x 0.25 µm) or on a Optima 5-Amine (30 m x 0.25 mm x 0.25 µm) using He as carrier gas.

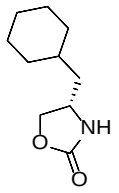
High Performance Liquid Chromatography (HPLC): HPLC analyses were performed on Shimadzu systems with SLC-10A system controller, CTO-10AC column oven, LC10-AD pump system, DGU-14A degasser and SPD-M10A diode array- or UV/VIS detector. Chiral columns Chiracel OD-H or IC (4.6 x 250 mm) from Daicel Chemical Industries were used.

Semipreparative High Performance Liquid Chromatography (Semipreparative HPLC): Separations by semipreparative HPLC were performed on Shimadzu systems with SIL 10 Advp autosampler, CTO 10 ASVP column oven, LC 10 Atvp pump system, FCV 10 Alvp degasser and SPD M10 Acp diode array detector. As column with chiral stationary phase Chiracel IC (2 x 25 cm) from Daicel Chemical Industries was used.

5.2 Asymmetric Morita-Baylis-Hillman Reaction

5.2.1 Synthesis of 1st Generation Catalysts

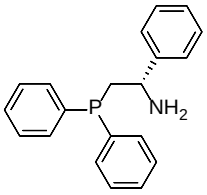
(*S*)-4-(Cyclohexylmethyl)oxazolidin-2-one (17e)



Under argon atmosphere a heat-gun dried round-bottomed flask was charged with *N-Boc*-(1-cyclohexyl-3-hydroxypropan-2-yl) (**16e**) (160 mg, 620 µmol) and THF (4 mL). At 0 °C, thionyl chloride (592 mg, 0.36 mL, 4.97 mmol) was added dropwise over 5 min. After complete addition the reaction mixture was stirred for additional three hours at 0 °C and for further 16 hours at room temperature. Afterwards the reaction mixture was concentrated under vacuum and the crude was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (5:2), d x h: 2.5 x 15 cm) to afford the product **17e** (69.0 mg, 380 µmol, 61%) as a white solid.

$C_{10}H_{17}NO_2$ (183.25 g/mol):
MP: 84-85 °C.
TLC: R_f = 0.44 (SiO_2, CH_2Cl_2:ethyl acetate (10:4)).
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 5.88 (br s, 1H, N*H*), 4.52-4.44 (m, 1H, NC*H*), 4.01-3.92 (m, 2H, OCH_2), 1.74-1.62 (m, 6H, cy-CH_2, NCHCH_2), 1.58-1.51 (m, 1H, cy-C*H*), 1.44-1.38 (m, 1H, cy-CH_2), 1.34-1.09 (m, 3H, cy-CH_2), 1.00-0.86 (m, 2H, cy-CH_2).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm: 159.9, 70.9, 50.6, 43.3, 34.7, 33.7, 33.1, 26.4, 26.2, 26.1.
IR (ATR) $\tilde{\nu}$/cm^{-1} = 3251 (m), 2910 (s), 2844 (s), 1742 (s), 1709 (s), 1397 (m), 1243 (s), 1200 (w), 1126 (w), 1079 (w), 1057 (s), 999 (m), 962 (w), 927 (s), 681 (m), 527 (w).
EA ($C_{10}H_{17}NO_2$) calc.: C 65.54, H 9.35, N 7.64; found: C 65.51, H 9.01, N 7.86.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −28.6 (*c* = 1.07, MeOH).

(*S*)-2-(Diphenylphosphanyl)-1-phenylethan-1-amine (18a)



Under argon atmosphere a heat-gun dried two-necked flask was charged with (*S*)-4-phenyloxazolidin-2-one (**17a**) (702 mg, 4. 30 mmol) and toluene (15 mL). Then the reaction mixture was degassed three-times by freeze-pump-thaw method. Afterwards diphenylphosphine (1.69 g, 1.58 mL, 8.60 mmol) and trifluoromethanesulfonic acid (1.94 g, 1.15 mL, 12.9 mmol) were added to the reaction mixture. After complete addition, the mixture was refluxed for 24 hours. At room temperature, the reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed aqueous saturated K_2CO_3 and then the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (3:7) + 1% NEt_3, d x h: 3.5 x 16 cm) to afford the product **18a** (900 mg, 2.95 mmol, 69%) as a pale yellow oil.

$C_{20}H_{20}NP$ (305.36 g/mol):

TLC: R_f = 0.30 (SiO_2, cyclohexane:ethyl acetate (3:7) + 1% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.53-7.42 (m, 4H, ar-*H*), 7.40-7.31 (m, 10H, ar-*H*), 7.30-7.21 (m, 1H, ar-*H*), 4.03 (ddd, $^3J_{HP}$ = 9.3 Hz, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, C*H*), 2.57 (ddd, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 2.4 Hz, 1H, CH_2), 2.45 (ddd, $^2J_{HP}$ = 13.6 Hz, $^3J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 2.3 Hz, 1H, CH_2), 1.78 (s, 2H, NH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm: 146.7 (d, J_{CP} = 6.3 Hz), 138.9 (d, J_{CP} = 12.1 Hz), 138.2 (d, J_{CP} = 12.8 Hz), 133.2 (d, J_{CP} = 19.4 Hz), 132.7 (d, J_{CP} = 18.4 Hz), 129.0, 128.7, 128.6, 128.6, 128.5, 127.3, 126.3, 53.8 (d, J_{CP} = 16.0 Hz), 40.2 (d, J_{CP} = 14.1 Hz).

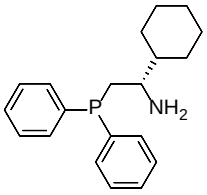
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm: −21.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2913 (w), 2844 (w), 1652 (m), 1429 (w), 1308 (w), 880 (w), 767 (s), 739 (m), 690 (s), 529 (m), 497 (s), 477 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{20}H_{20}NP^+$: 306.1406 $[M+H]^+$; found: 306.1408.

$[\alpha]_D^{20}$ = +0.9 (*c* = 1.11, MeOH).

(*S*)-1-Cyclohexyl-2-(diphenylphosphanyl)ethan-1-amine (18b)



Under argon atmosphere a heat-gun dried two-necked flask was charged with (*S*)-4-cyclohexyloxazolidin-2-one (**17b**) (500 mg, 2.95 mmol) and toluene (9 mL). Then the reaction mixture was degassed three-times by freeze-pump-thaw method. Afterwards diphenylphosphine (1.16 g, 1.10 mL, 5.91 mmol) and trifluoromethanesulfonic acid (1.33 g, 0.78 mL, 8.86 mmol) were added to the reaction mixture. After complete addition, the mixture was refluxed for 24 hours. At room temperature, the reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed aqueous saturated K_2CO_3 and then the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1 to 2:5) + 5% NEt_3, d x h: 4.5 x 15 cm) to afford the product **18b** (496 mg, 1.59 mmol, 54%) as a colorless oil.

$C_{20}H_{26}NP$ (311.41 g/mol):

TLC: R_f = 0.55 (SiO_2, cyclohexane:ethyl acetate (2:5) + 5% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.50-7.27 (m, 10H, ar-*H*), 2.69-2.57 (m, 1H, C*H*), 2.38 (dt, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, CH_2), 1.95 (ddd, $^2J_{HP}$ = 13.4 Hz, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, CH_2), 1.78-1.61 (m, 5H, NH_2, cy-CH_2, cy-C*H*), 1.39-0.94 (m, 8H, cy-CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm: 139.6 (d, J_{CP} = 12.1 Hz), 138.2 (d, J_{CP} = 13.0 Hz), 133.3 (d, J_{CP} = 19.4 Hz), 132.5 (d, J_{CP} = 18.3 Hz), 128.9, 128.6, 128.5, 128.5, 128.4, 128.4, 53.7 (d, J_{CP} = 13.2 Hz), 45.0 (d, J_{CP} = 7.1 Hz), 35.2 (d, J_{CP} = 11.7 Hz), 29.5, 27.9, 26.7, 26.5, 26.4.

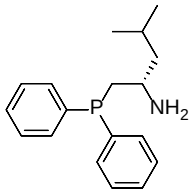
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm: −21.6.

IR (ATR): $\tilde{\nu}$/cm^{-1}: 3069 (w), 2919 (s), 2848 (m), 1571 (w), 1479 (w), 1432 (m), 1093 (w), 831 (w), 735 (s), 693 (s), 504 (m), 479 (m), 420 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{20}H_{26}NP^+$: 312.1876 $[M+H]^+$; found: 312.1878.

$[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = +40.1 (*c* = 1.02, MeOH).

(*S*)-1-(Diphenylphosphanyl)-4-methylpentan-2-amine (18c)



Under argon atmosphere a heat-gun dried two-necked flask was charged with (*S*)-4-isobutyloxazolidin-2-one (**17c**) (450 mg, 3.14 mmol) and toluene (12 mL). Then the reaction mixture was degassed three-times by freeze-pump-thaw method. Afterwards diphenylphosphine (1.24 g, 1.15 mL, 6.29 mmol) and trifluoromethanesulfonic acid (1.42 g, 0.84 mL, 9.43 mmol) were added to the reaction mixture. After complete addition, the mixture was refluxed for 24 hours. At room temperature, the reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed aqueous saturated K_2CO_3 and then the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (2:5) + 1% NEt_3, d x h: 3 x 16 cm) to afford the product **18c** (451 mg, 1.58 mmol, 50%) as a pale yellow oil.

$C_{18}H_{24}NP$ (285.37 g/mol):

TLC: R_f = 0.22 (SiO_2, cyclohexane:ethyl acetate (2:5) + 1% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.40-7.32 (m, 4H, ar-*H*), 7.29-7.18 (m, 6H, ar-*H*), 2.85-2.75 (m, 1H, NC*H*), 2.21 (ddd, $^2J_{HP}$ = 13.6 Hz, $^3J_{HH}$ = 4.5 Hz, $^3J_{HH}$ = 2.5 Hz, 1H, PCH_2), 1.94 (ddd, $^2J_{HP}$ = 13.6 Hz, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 1.5 Hz, 1H, PCH_2), 1.67-1.55 (m, 1H, C*H*$CH_2(CH_3)_2$), 1.36 (br s, 2H, NH_2), 1.36-1.16 (m, 2H, C*H*$(CH_3)_2$), 0.75 (d, $^3J_{HH}$ = 3.2 Hz, 3H, CHCH_3), 0.74 (d, $^3J_{HH}$ = 3.1 Hz, 3H, CHCH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm: 139.2 (d, J_{CP} = 11.9 Hz), 138.5 (d, J_{CP} = 12.3 Hz), 133.1 (d, J_{CP} = 19.0 Hz), 132.7 (d, J_{CP} = 18.5 Hz), 128.8, 128.6, 128.6, 128.5, 49.1 (d, J_{CP} = 7.7 Hz), 47.0 (d, J_{CP} = 14.3 Hz), 38.9 (d, J_{CP} = 12.4 Hz), 25.0, 23.3, 22.2.

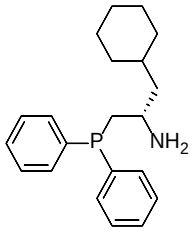
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ/ppm: −22.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3069 (w), 3052 (w), 2952 (m), 2907 (w), 1756 (w), 1466 (w), 1432 (m), 1365 (w), 1094 (w), 1026 (w), 836 (w), 816 (w), 737 (s), 693 (s), 503 (m), 478 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{18}H_{24}NP^+$: 286.1719 $[M+H]^+$; found: 286.1721.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +21.7 (*c* = 1.00, MeOH).

(*S*)-1-Cyclohexyl-3-(diphenylphosphanyl)propan-2-amine (18e)



Under argon atmosphere a heat-gun dried two-necked flask was charged with (S)-4-(cyclohexylmethyl)oxazolidin-2-one (**17e**) (800 mg, 4.37 mmol) and toluene (20 mL). Then the reaction mixture was degassed three-times by freeze-pump-thaw method. Afterwards diphenylphosphine (1.71 g, 1.60 mL, 8.74 mmol) and trifluoromethanesulfonic acid (1.97 g, 1.16 mL, 13.1 mmol) were added to the reaction mixture. After complete addition, the mixture was refluxed for 24 hours. At room temperature, the reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed aqueous saturated K_2CO_3 and then the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (2:3) + 2% NEt_3, d x h: 3.5 x 22 cm) to afford the product **18e** (874 mg, 2.69 mmol, 62%) as a pale yellow oil.

$C_{21}H_{28}NP$ (325.44 g/mol):

TLC: R_f = 0.32 (SiO_2, cyclohexane:ethyl acetate (2:3) + 2% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: δ 7.50-7.37 (m, 4H, ar-*H*), 7.36-7.28 (m, 6H, ar-*H*), 2.98-2.84 (m, 1H, NC*H*), 2.28 (ddd, $^2J_{HP}$ = 13.6 Hz, $^3J_{HH}$ = 4.5 Hz, $^2J_{HH}$ = 2.5 Hz, 1H, PCH_2), 2.01 (ddd, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 8.5 Hz, $^2J_{HH}$ = 1.6 Hz, 1H, PCH_2), 1.71-1.58 (m, 4H, cy-CH_2), 1.58-1.48 (m, 1H, cy-C*H*), 1.45-1.05 (m, 8H, cy-CH_2*, CHCH_2*), 0.93-0.74 (m, 2H, cy-CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm: 139.3 (d, J_{CP} = 12.1 Hz), 138.6 (d, J_{CP} = 12.3 Hz), 133.1 (d, J_{CP} = 19.1 Hz), 132.7 (d, J_{CP} = 18.5 Hz), 128.8, 128.6 (d, J_{CP} = 4.7 Hz), 128.5, 128.5, 47.7 (d, J_{CP} = 7.7 Hz), 46.3 (d, J_{CP} = 14.3 Hz), 39.0 (d, J_{CP} = 12.4 Hz), 34.6, 34.1, 33.0, 26.7, 26.4, 26.3.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ/ppm: −22.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3069 (w), 3051 (w), 2918 (m), 2847 (w), 1756 (w), 1584 (w), 1480 (w), 1432 (m), 1094 (w), 968 (w), 841 (w), 737 (s), 693 (s), 504 (m), 478 (m), 422 (w).

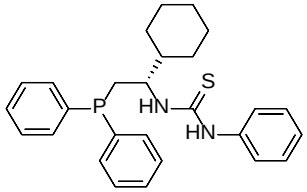
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{21}H_{28}NP^+$: 326.2032 $[M+H]^+$; found: 326.2034.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +10.2 (*c* = 0.94, MeOH).

General Procedure (GP1): Amino phosphine coupling with isothiocyanate precursor

Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with the amino phosphine (1.0 eq.), the isothiocyanate precursor (1.1 eq.) and CH_2Cl_2 (3 mL per mmol). Then the reaction mixture was stirred for 16 hours at room temperature. Afterwards the mixture was concentrated under vacuum and the crude product was purified by column chromatography.

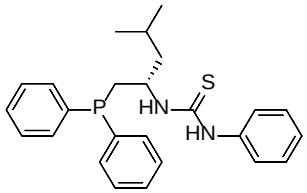
(*S*)-1-(1-Cyclohexyl-2-(diphenylphosphanyl)ethyl)-3-phenylthiourea (19b)



According to general procedure **GP1**, (*S*)-1-cyclohexyl-2-(diphenylphosphanyl)ethan-1-amine (**18b**) (105 mg, 337 µmol), phenyl isothiocyanate (51.2 mg, 45.2 µL, 371 µmol) and CH_2Cl_2 (1.1 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 3.5 x 20 cm) to afford the product **19b** (150 mg, 336 µmol, 99%) as a white solid.

$C_{27}H_{31}N_2PS$ (446.60 g/mol):
TLC: R_f = 0.30 (SiO_2, cyclohexane:ethyl acetate (5:1)).
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.66 (br s, 1H, N*H*), 7.43-7.35 (m, 4H, ar-*H*), 7.34-7.14 (m, 9H, ar-*H*), 7.00 (d, $^3J_{HH}$ = 7.8 Hz, 2H, ar-*H*), 6.01 (br s, 1H, N*H*), 4.57 (br s, 1H, NC*H*), 2.41 (ddd, $^2J_{HP}$ = 14.3 Hz, $^3J_{HH}$ = 5.5 Hz, $^2J_{HH}$ = 2.4 Hz, 1H, PCH_2), 2.23 (dd, $^2J_{HP}$ = 14.3 Hz, $^3J_{HH}$ = 7.6 Hz, 1H, PCH_2), 1.67-1.50 (m, 6H, cy-CH_2), 1.13-0.88 (m, 4H, cy-CH_2), 0.85-0.71 (m, 1H, cy-C*H*).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 180.2, 136.1, 133.1 (d, J_{CP} = 4.3 Hz), 133.0 (d, J_{CP} = 4.4 Hz), 130.2, 129.0, 128.7 (d, J_{CP} = 2.9 Hz), 128.6 (d, J_{CP} = 3.1 Hz), 127.2, 125.3, 58.2 (d, J_{CP} = 14.1 Hz), 41.8 (d, J_{CP} = 8.1 Hz), 31.4 (d, J_{CP} = 13.3 Hz), 29.7, 28.7, 26.5, 26.1, 26.1.
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −24.9.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3219 (w), 2919 (w), 2848 (w), 1522 (s), 1495 (s), 1305 (m), 1235 (m), 1166 (w), 1094 (w), 1026 (w), 736 (s), 693 (s), 502 (m).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{27}H_{31}N_2PS^+$: 447.2018 $[M+H]^+$; found: 447.2018.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +16.1 (*c* = 0.65, MeOH).

(*S*)-1-(1-(Diphenylphosphanyl)-4-methylpentan-2-yl)-3-phenylthiourea (19c)



According to general procedure **GP1**, (*S*)-1-(diphenylphosphanyl)-4-methylpentan-2-amine (**18c**) (40 mg, 140 µmol), phenyl isothiocyanate (22.7 mg, 20.0 µL, 168 µmol) and CH_2Cl_2 (0.8 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (6:1), d x h: 1.5 x 14 cm) to afford the product **19c** (54 mg, 128 µmol, 92%) as a colorless gum.

$C_{25}H_{29}N_2PS$ (420.55 g/mol):

TLC: R_f = 0.25 (SiO_2, cyclohexane:ethyl acetate (6:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.77 (br s, 1H, N*H*), 7.53-7.41 (m, 3H, ar-*H*), 7.39-7.23 (m, 7H, ar-H), 7.05 (d, $^3J_{HH}$ = 7.7 Hz, 2H, ar-*H*), 6.05 (s, 1H, N*H*), 4.81 (s, 1H, C*H*), 2.56 (dd, $^2J_{HP}$ = 14.5 Hz, $^3J_{HH}$ = 6.3 Hz, 1H), 2.45-2.37 (m, 1H, CH_2), 1.59-1.42 (m, 3H, CH_2CH$(CH_3)_2$*, CH_2C*H*$(CH_3)_2$*), 0.85 (d, $^3J_{HH}$ = 2.5 Hz, 3H, CH(CH_3)$_2$), 0.83 (d, $^3J_{HH}$ = 2.6 Hz, 3H, CH(CH_3)$_2$).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 179.8, 133.3, 133.1, 132.9, 132.7, 130.2, 129.2, 129.0, 128.7 (d, J_{CP} = 3.3 Hz), 128.7 (d, J_{CP} = 3.4 Hz), 127.2, 125.2, 52.3, 44.7 (d, J_{CP} = 9.4 Hz), 34.4, 25.3, 22.9, 22.6.

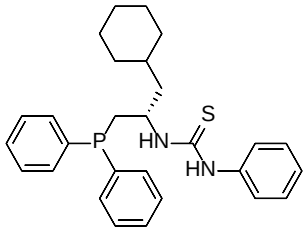
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −25.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3370 (w), 3187 (w), 1595 (m), 1525 (s), 1496 (s), 1496 (m), 1433 (w), 1303 (w), 1237 (m), 999 (w), 754 (s), 696 (s), 504 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{25}H_{29}N_2PS^+$: 421.1862 $[M+H]^+$; found: 421.1866.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +25.8 (*c* = 0.85, $CHCl_3$).

(*S*)-1-(1-Cyclohexyl-3-(diphenylphosphanyl)propan-2-yl)-3-phenylthiourea (19e)



According to general procedure **GP1**, (*S*)-1-cyclohexyl-3-(diphenylphosphanyl)propan-2-amine (**18e**) (60.0 mg, 184 µmol), phenyl isothiocyanate (27.9 mg, 24.7 µL, 202 µmol) and CH_2Cl_2 (0.6 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 2.5 x 15 cm) to afford the product **19e** (84.2 mg, 155 µmol, 71%) as a white solid.

$C_{28}H_{33}N_2PS$ (460.62 g/mol):

MP: 60-61 °C.

TLC: R_f = 0.38 (SiO_2, cyclohexane:ethyl acetate (5:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = (br s, 1H, N*H*), 7.54-7.26 (m, 13H, ar-*H*), 7.06 (d, $^3J_{HH}$ = 7.5 Hz, 2H, ar-*H*), 5.97 (d, $^3J_{HH}$ = 8.6 Hz, 1H, N*H*), 4.82 (br s, 1H, NC*H*), 2.55 (dd, $^2J_{HP}$ = 14.1 Hz, $^3J_{HH}$ = 6.4 Hz, 1H, PCH_2), 2.42 (ddd, $^2J_{HP}$ = 14.1 Hz, $^3J_{HH}$ = 5.4 Hz, $^4J_{HH}$ =1.7 Hz, 1H, PCH_2), 1.73-1.42 (m, 7H, cy-CH_2*, cy-C*H*, NCHCH_2), 1.24-1.06 (m, 4H, cy-CH_2), 0.96-0.75 (m, 2H, cy-CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 179.6, 138.1 (d, J_{CP} = 11.7 Hz), 135.9, 133.1 (d, J_{CP} = 19.5 Hz), 132.7 (d, J_{CP} = 19.1 Hz), 130.1, 128.8, 128.7, 128.5 (d, J_{CP} = 3.7 Hz), 128.5 (d, J_{CP} = 3.5 Hz), 127.1, 125.2, 51.7 (d, J_{CP} = 15.5 Hz), 43.0 (d, J_{CP} = 9.6 Hz), 34.5, 34.4, 33.3, 33.0, 26.4, 26.2, 26.1.

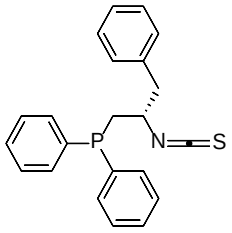
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −25.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3176 (w), 2914 (m), 2846 (m), 1650 (s), 1441 (m), 1403 (m), 1310 (w), 1089 (w), 959 (w), 834 (m), 675 (w), 518 (w), 458 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. $C_{28}H_{33}N_2PS^+$: 983.3495 $[2M+Cu]^+$; found: 983.3473.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −12.3 (*c* = 0.62, MeOH).

(*S*)-(2-Isothiocyanato-3-phenylpropyl)diphenylphosphane (21)



Under argon atmosphere, a heat-gun dried round two-necked flask was charged with (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (520 mg, 1.63 mmol), *N,N'*-dicyclohexyl-carbodiimide (336 mg, 1.63 mmol) and THF (15 mL). Then, the reaction mixture was cooled in an ice-bath and at 0 °C carbon disulfide (1.64 g, 1.30 mL, 21.5 mmol) was added dropwise over 10 minutes to the reaction solution. After addition, the reaction mixture was stirred for 16 hours at room temperature and then the crude product was concentrated under vacuum and was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1), d x h: 3.5 x 15 cm) to afford the product **21** (489 mg, 1.35 mmol, 83%) as a pale yellow oil.

$C_{22}H_{20}NPS$ (361.44 g/mol):

TLC: R_f = 0.30 (SiO_2, cyclohexane:ethyl acetate (10:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.50-7.30 (m, 13H, ar-*H*), 7.25-7.19 (m, 2H, ar-*H*), 3.15 (dd, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 5.1 Hz, 1H, PCH_2), 3.09-3.01 (m, 1H, PCH_2), 2.54-2.41 (m, 2H, Ph- CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 136.4, 133.1, 132.9, 132.7, 129.6, 129.2, 129.2, 128.9, 128.8, 128.8, 127.3, 57.7 (d, J_{CP} = 18.9 Hz), 43.2 (d, J_{CP} = 7.7 Hz), 35.1 (d, J_{CP} = 16.8 Hz).

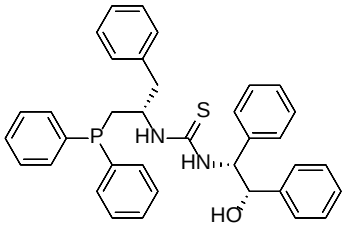
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −22.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3052 (w), 3026 (w), 2919 (w), 2048 (s), 1480 (w), 1432 (m), 1339 (m), 1069 (w), 1026 (w), 927 (w), 736 (s), 693 (s), 500 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{22}H_{20}NPS^+$: 362.1127 $[M+H]^+$; found: 362.1124.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +52.6 (*c* = 0.64, MeOH).

1-((*S*)-1-(Diphenylphosphanyl)-3-phenylpropan-2-yl)-3-((1*R*,2*S*)-2-hydroxy-1,2-diphenyl-ethyl)thiourea (20e)



Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with (*S*)-(2-isothiocyanato-3-phenylpropyl)diphenylphosphane (**21**) (40 mg, 111 µmol) and CH_2Cl_2 (0.4 mL). Then, (1*S*,2*R*)-2-amino-1,2-diphenylethanol (30.7 mg, 144 µmol) was added in one portion to the corresponding reaction mixture and was stirred for 16 hours at room temperature. Afterwards the crude product was concentrated under vacuum and was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (3:1), d x h: 2 x 20 cm) to afford the product **20e** (61 mg, 106 µmol, 96%) as a white solid.

$C_{36}H_{35}N_2OPS$ (574.73 g/mol):

MP: 79-80 °C.

TLC: R_f = 0.38 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 8.02 (br s, 1H, N*H*), 7.44 (d, $^3J_{HH}$ = 8.3 Hz, 2H, ar-*H*), 7.41-7.32 (m, 2H, ar-*H*), 7.32-7.12 (m, 11H, ar-*H*), 7.08-7.04 (m, 2H, ar-*H*), 6.92 (d, $^3J_{HH}$ = 8.3 Hz, 2H, ar-*H*), 6.03 (br s, 1H, N*H*), 4.83 (br s, 1H, C*H*), 3.04 (dd, $^2J_{HP}$ = 13.9 Hz, $^3J_{HH}$ = 6.3 Hz, 1H, PCH_2), 2.96 (dd, $^2J_{HP}$ = 13.9 Hz, $^3J_{HH}$ = 7.0 Hz, 1H, PCH_2), 2.44-2.29 (m, 2H, Ph-CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 181.1, 139.3, 137.9 (d, J_{CP} = 11.5 Hz), 137.6, 136.0, 133.1 (d, J_{CP} = 19.4 Hz), 132.9 (d, J_{CP} = 19.0 Hz), 129.8, 129.0, 128.8, 128.7, 128.7, 128.6, 128.3 (d, J_{CP} = 11.8 Hz), 128.1, 126.8, 126.7, 76.6, 63.8, 53.9 (d, J_{CP} = 15.6 Hz), 40.8, 33.4.

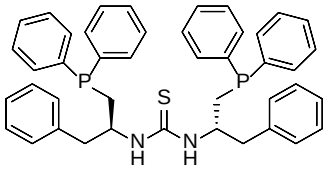
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −24.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3247 (w), 3027 (w), 1525 (m), 1492 (m), 1289 (w), 1212 (w), 1190 (w), 1083 (m), 1050 (m), 1026 (w), 927 (w), 737 (m), 695 (s), 581 (w), 499 (m), 418 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{36}H_{35}N_2OPS^+$: 575.2280 $[M+H]^+$; found: 575.2277.

$[\alpha]_D^{20}$ = +60.5 (*c* = 0.52, MeOH).

1,3-bis((*S*)-1-(Diphenylphosphanyl)-3-phenylpropan-2-yl)thiourea (20f)



Under argon atmosphere, a heat-gun dried round-bottomeded flask was charged with (*S*)-(2-isothiocyanato-3-phenylpropyl)diphenylphosphane (**21**) (27.0 mg, 74.7 µmol) and CH_2Cl_2 (0.5 mL). Then, (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (28.6 mg, 89.6 µmol) was added to the corresponding reaction mixture in one portion and was stirred for 16 hours at room temperature. Afterwards the crude product was concentrated under vacuum and was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1), d x h: 2.5 x 14 cm) to afford the product **20f** (48.0 mg, 71.0 µmol, 94%) as a white solid.

$C_{43}H_{42}N_2P_2S$ (680.83 g/mol):

MP: 157-158 °C.

TLC: R_f = 0.38 (SiO_2, cyclohexane:ethyl acetate (10:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.35-7.11 (m, 26H, ar-*H*), 6.99 (d, $^3J_{HH}$ = 7.0 Hz, 4H, ar-*H*), 5.28 (br s, 2H, N*H*), 4.21 (br s, 2H, NC*H*), 2.79 (br s, 4H, Ph-CH_2), 2.22-2.07 (m, 4H, PCH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 180.2, 138.0, 137.9, 137.8, 137.4, 133.1 (d, J_{CP} = 19.6 Hz), 132.9 (d, J_{CP} = 19.3 Hz), 129.6, 129.1, 129.0, 128.8, 128.8, 128.7, 126.8, 53.4 (d, J_{CP} = 15.5 Hz), 41.0 (d, J_{CP} = 8.1 Hz), 33.4 (d, J_{CP} = 15.4 Hz).

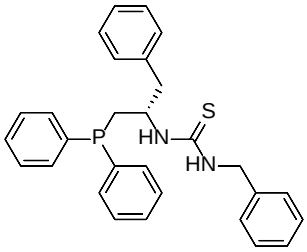
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −24.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2839 (w), 2890 (w), 2856 (w), 1529 (m), 1355 (w), 1318 (w), 1234 (w), 1079 (m), 814 (m), 736 (s), 692 (s), 534 (m), 493 (m), 469 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{43}H_{42}N_2P_2S^+$: 681.2617 $[M+H]^+$; found: 681.2615.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +23.5 (*c* = 0.77, MeOH).

(*S*)-1-Benzyl-3-(1-(diphenylphosphanyl)-3-phenylpropan-2-yl)thiourea (20g)



Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with (*S*)-(2-isothiocyanato-3-phenylpropyl)diphenylphosphane (**21**) (50.0 mg, 138 µmol) and CH_2Cl_2 (0.8 mL). Then, benzylamine (19.4 mg, 19.8 µL, 179 µmol) was added in one portion to the reaction mixture and was stirred for 16 hours at room temperature. Afterwards the crude product was concentrated under vacuum and was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 2.5 x 13 cm) to afford the product **20g** (60.0 mg, 128 µmol, 93%) as a white solid.

$C_{29}H_{29}N_2PS$ (468.60 g/mol):

MP: 54-55 °C.

TLC: R_f = 0.46 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = δ 7.36-7.03 (m, 20H, ar-*H*), 5.86-5.42 (br m, 2H, N*H*), 4.53 (s, 1H, C*H*), 4.14 (s, 2H, benz-CH_2), 2.97 (dd, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, PCH_2), 2.88 (dd, $^2J_{HP}$ = 13.9, $^3J_{HH}$ = 6.8 Hz, 1H, PCH_2), 2.30 (dd, $^4J_{HP}$ = 14.1, $^3J_{HH}$ = 6.2 Hz, 1H, Ph-CH_2), 2.19 (dd, $^4J_{HP}$ = 14.1, $^3J_{HH}$ = 6.8 Hz, 1H, Ph-CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 181.2, 137.4, 133.1 (d, J_{CP} = 16.5 Hz), 132.9 (d, J_{CP} = 16.2 Hz), 129.6, 129.1, 129.0, 128.8 (d, J_{CP} = 5.1 Hz), 128.8, 128.7, 128.1, 127.7, 126.8, 54.1 (d, J_{CP} = 14.3 Hz), 47.9, 41.1, 33.2.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −24.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3238 (m), 3051 (w), 3025 (w), 1532 (s), 1432 (m), 1342 (w), 1269 (w), 1226 (w), 1025 (w), 732 (s), 691 (s), 500 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{29}H_{29}N_2PS^+$: 469.1862 $[M+H]^+$; found: 469.1858.

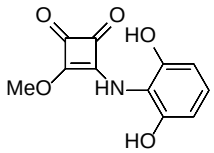
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +18.8 (*c* = 0.90, MeOH).

5.2.2 Synthesis of 2nd Generation Catalysts

General Procedure (GP2): Amine coupling with dimethylsquarate

Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with 3,4-dimethoxy-3-cyclobutene-1,2-dione (1.1 eq.) and methanol (3 mL per mmol dimethylsquarate). Then the primary amine (1.0 eq.) was added dropwise to the reaction mixture. The corresponding mixture was stirred for 48 hours at room temperature. The precipitated product was filtered off and the corresponding crystals were washed with ice-cold methanol to yield the desired squaramide precursor after high-vacuum drying.

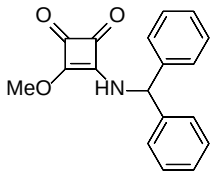
3-((2,6-Dihydroxyphenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (24d)



According to general procedure **GP2**, 3,4-dimethoxy-3-cyclobutene-1,2-dione (**22**) (100 mg, 704 µmol), methanol (2.2 mL) and 2-aminobenzene-1,3-diol (**23d**) (80.0 mg, 604 µmol) were stirred for 48 hours to give the product **24d** (113 mg, 480 µmol, 75%) as a white solid.

$C_{11}H_9NO_5$ (235.20 g/mol):
MP: 216-217 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.65 (br s, 3H, N*H**, O*H**), 6.87 (t, $^3J_{HH}$ = 8.1 Hz, 1H, ar-H), 6.33 (d, $^3J_{HH}$ = 8.1 Hz, 2H, ar-H), 4.19 (s, 3H, OCH_3).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 183.9, 173.1, 153.8, 127.6, 112.4, 106.5, 59.9.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3435 (w), 3273 (m), 1807 (w), 1689 (m), 1606 (s), 1525 (m), 1503 (s), 1478 (s), 1450 (m), 1370 (s), 1329 (m), 1260 (w), 1161 (s), 1064 (w), 1016 (s), 935 (m), 784 (w), 732 (m), 631 (m), 588 (m).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{11}H_9NO_5^+$: 258.0373 $[M+Na]^+$; found: 258.0375.

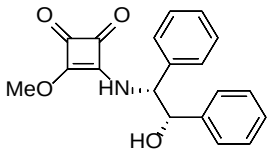
3-(Benzhydrylamino)-4-methoxycyclobut-3-ene-1,2-dione (24f)



According to general procedure **GP2**, 3,4-dimethoxy-3-cyclobutene-1,2-dione (**22**) (110 mg, 774 µmol), methanol (2.3 mL) and benzhydrylamine (**23f**) (133 mg, 125 µL, 704 µmol) were stirred for 48 hours to give the product **24f** (130 mg, 440 µmol, 63%) as a white solid.

$C_{18}H_{15}NO_3$ (293.32 g/mol):
MP: 175-176 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.83/9.62* (d, $^3J_{HH}$ = 9.5 Hz, 1H, N*H*), 7.40-7.26 (m, 10H, ar-*H*), 6.47/5.94* (d, $^3J_{HH}$ = 9.3 Hz, 1H, C*H*Ph$_2$), 4.30 (s, 3H, OC*H*$_3$). [* refers to signal of rotamers]
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 189.3/188.8*, 182.8/182.5*, 178.0/177.4*, 171.7/171.0*, 141.3/140.9*, 128.6, 127.5, 127.2, 61.8/60.6*, 60.4/60.0*.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3239 (m), 1805 (m), 1699 (s), 1605 (s), 1468 (s), 1389 (s), 1120 (w), 1046 (w), 918 (w), 805 (w), 742 (m), 696 (s), 603 (s), 514 (m), 473 (m).
EA ($C_{18}H_{15}NO_3$) calc.: C 73.71, H 5.15, N 4.78; found: C 73.61, H 5.24, N 4.94.

3-(((1*R*,2*S*)-2-Hydroxy-1,2-diphenylethyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (24h)



According to general procedure **GP2**, 3,4-dimethoxy-3-cyclobutene-1,2-dione (**22**) (183 mg, 1.29 mmol), methanol (3.9 mL) and (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**23h**) (250 mg, 1.17 mmol) were stirred for 48 hours to give the product **24h** (188 mg, 581 µmol, 50%) as a white solid.

$C_{19}H_{17}NO_4$ (293.32 g/mol):
MP: 208-209 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.18/9.01* (d, $^3J_{HH}$ = 9.9 Hz, 1H, N*H*), 7.48-7.21 (m, 10H, ar-*H*), 5.61 (br s, 1H, O*H*), 5.24/4.63* (t, $^3J_{HH}$ = 9.2 Hz, 1H, NC*H*), 4.86 (t, $^3J_{HH}$ = 9.7 Hz, 1H, OC*H*), 4.21/4.19* (s, 3H, OCH_3). [* refers to signal of rotamers]

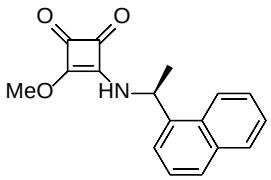
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 189.1/188.8*, 182.2/182.1*, 177.3/176.8, 171.4/171.0*, 142.6, 139.8/139.4*, 128.0, 128.0, 127.8, 127.7, 127.4, 127.4, 127.3, 127.1, 127.0, 74.9, 64.7, 63.2, 60.2/59.9*.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3251 (w), 1680 (m), 1578 (s), 1492 (s), 1390 (s), 1114 (m), 1052 (w), 923 (w), 828 (m), 761 (m), 698 (s), 608 (m), 553 (m), 527 (m), 411 (w).

EA ($C_{19}H_{17}NO_4$) calc.: C 70.58, H 5.30, N 4.33; found: C 70.64, H 5.36, N 4.52.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +98.3 (*c* = 0.95, DMSO).

(*S*)-3-Methoxy-4-((1-(naphthalen-1-yl)ethyl)amino)cyclobut-3-ene-1,2-dione (24i)



According to general procedure **GP2**, 3,4-dimethoxy-3-cyclobutene-1,2-dione (**22**) (110 mg, 774 µmol), methanol (2.3 mL) and (*R*)-(+)-alpha-(1-napthyl)ethylamine (**23i**) (121 mg, 704 µmol) were stirred for 48 hours to give product **24i** (117 mg, 380 µmol, 54%) as a white solid.

$C_{17}H_{15}NO_3$ (281.31 g/mol):

MP: 168-169 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.42/9.19* (d, $^3J_{HH}$ = 8.2 Hz, 1H, N*H*), 7.96-7.87 (m, 3H, ar-*H*), 7.84-7.80 (m, 1H, ar-*H*), 7.59-7.47 (m, 3H, ar-*H*), 5.45 and 4.98 (t, $^3J_{HH}$ = 7.4 Hz, 1H, NC*H*), 4.30/4.28* (s, 3H, OCH_3), 1.61 (d, $^3J_{HH}$ = 5.8 Hz, 3H, CHCH_3). [* refers to signal of rotamers]

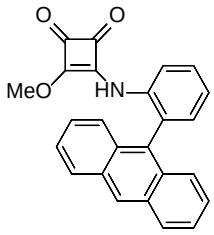
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 189.2, 182.5/182.2*, 177.7/177.2*, 171.4/171.2*, 140.9/140.6*, 132.8, 132.2, 128.3, 127.8, 127.5, 126.3, 126.0, 124.4, 124.4, 124.2, 60.2/59.9*, 54.0/53.1*, 22.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3214 (w), 3176 (w), 1797 (m), 1696 (s), 1586 (s), 1494 (s), 1466 (m), 1435 (m), 1394 (m), 1326 (w), 1295 (w), 1178 (w), 1142 (w), 1080 (w), 1035 (w), 867 (s), 821 (m), 764 (m), 718 (w), 612 (w), 482 (s).

EA ($C_{17}H_{15}NO_3$) calc.: C 72.58, H 5.37, N 4.98; found: C 72.80, H 5.46, N 5.22.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +216.5 (*c* = 0.95, DMSO).

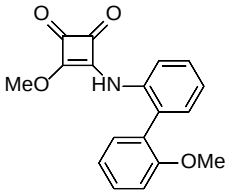
3-((2-(Anthracen-9-yl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (24j)



According to general procedure **GP2**, 3,4-dimethoxy-3-cyclobutene-1,2-dione (**22**) (85.4 mg, 601 µmol), methanol (1.8 mL) and 2-(anthracen-9-yl)aniline (**23j**) (147 mg, 546 µmol) were stirred for 48 hours to give the product **24j** (180 mg, 474 µmol, 87%) as a yellow solid.
$C_{17}H_{15}NO_3$ (281.31 g/mol):

MP: 155-156 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 10.05 (br s, 1H, N*H*), 8.70 (s, 1H, ar-*H*), 8.15 (d, $^3J_{HH}$ = 8.8 Hz, 2H, ar-*H*), 7.65-7.60 (m, 1H, ar-*H*), 7.54-7.47 (m, 5H, ar-*H*), 7.46-7.46 (m, 1H, ar-*H*), 7.42-7.32 (m, 3H, ar-*H*), 4.28/4.23* (s, 3H, OCH_3). [* refers to signal of rotamers]
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 189.1, 184.1/183.9*, 178.3, 170.7, 136.6, 132.3, 132.3, 132.2, 131.0, 129.7, 128.8, 128.5, 127.2, 126.7, 126.0, 125.9, 125.8, 125.3, 61.0/60.2*.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3170 (w), 3049 (w), 1799 (m), 1713 (m), 1577 (s), 1509 (m), 1473 (m), 1444 (m), 1350 (s), 1012 (w), 934 (w), 737 (s), 636 (w).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{17}H_{15}NO_3^+$: 402.1101 $[M+Na]^+$; found: 402.1105.

3-Methoxy-4-((2'-methoxy-[1,1'-biphenyl]-2-yl)amino)cyclobut-3-ene-1,2-dione (24k)



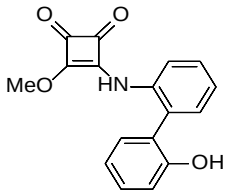
According to general procedure **GP2**, 3,4-dimethoxy-3-cyclobutene-1,2-dione (**22**) (78.5 mg, 552 µmol), methanol (1.7 mL) and 2'-methoxy-[1,1'-biphenyl]-2-amine (**23k**) (110 mg, 552 µmol) were stirred for 48 hours to give the product **24k** (125 mg, 404 µmol, 73%) as a white solid.

$C_{18}H_{15}NO_4$ (309.32 g/mol):

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.96 (br s, 1H, N*H*), 7.49-7.27 (m, 6H, ar-*H*), 7.18-7.06 (m, 2H, ar-*H*), 4.45 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 184.8, 155.5, 134.7, 132.2, 131.7, 130.2, 128.6, 126.7, 125.8, 122.0, 121.3, 111.7, 60.8, 56.1.

3-((2'-Hydroxy-[1,1'-biphenyl]-2-yl)amino)-4-methoxycyclobut-3-ene-1,2-dione (24l)



According to general procedure **GP2**, 3,4-dimethoxy-3-cyclobutene-1,2-dione (**22**) (75.2 mg, 529 µmol), methanol (1.6 mL) and 2'-amino-[1,1'-biphenyl]-2-ol (**23l**) (98 mg, 529 µmol) were stirred for 48 hours to give the product **24l** (92.0 mg, 312 µmol, 59%) as a white solid.

$C_{17}H_{13}NO_4$ (295.29 g/mol):

MP: 204-205 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.98 (br s, 1H, N*H*), 9.83 (br s, 1H, O*H*), 7.41-7.13 (m, 6H, ar-*H*), 6.98-6.86 (m, 2H, ar-*H*), 4.24 (s, 3H, OCH_3).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 183.9, 178.0, 170.2, 153.9, 135.1, 133.2, 131.7, 131.1, 129.2, 127.6, 126.1, 125.1, 124.3, 119.4, 115.6, 60.1.

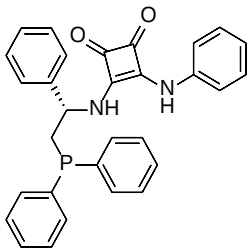
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3298 (w), 3252 (m), 1808 (m), 1712 (m), 1570 (s), 1507 (s), 1478 (m), 1439 (m), 1395 (m), 1287 (w), 1201 (w), 1162 (w), 1081 (w), 928 (w), 761 (s), 678 (m), 619 (m), 603 (m), 559 (m), 506 (w), 426 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{17}H_{13}NO_4^+$: 318.0737 $[M+Na]^+$; found: 318.0735.

General Procedure (GP3): Amino phosphine coupling with squaramide precursor

Under argon atmosphere, a round-bottomed flask was charged with the amino phosphine (1.0 eq.) and MeOH (20 mL per mmol). After addition of the squaramide precursor (1.0 eq.) the reaction mixture was stirred for two days at room temperature. The resulting precipitate was filtered off and washed with MeOH (2 x 10 mL per mmol) to afford the pure product after drying under vacuum.

(*S*)-3-((2-(Diphenylphosphanyl)-1-phenylethyl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione (25a)



According to general procedure **GP3**, (*S*)-2-(diphenylphosphanyl)-1-phenylethan-1-amine (**18a**) (30.0 mg, 98.2 µmol) in MeOH (2 mL) and 3-(methoxy)-4-(phenylamino)-3-cyclobutene-1,2-dione (**24a**) (18.1 mg, 89.3 µmol) were stirred for two days to give the product **25a** (33.0 mg, 69.0 µmol, 78%) as a white solid.

$C_{30}H_{25}N_2O_2P$ (476.51 g/mol):

MP: >250 °C.

^{1}H{^{1}H} NMR (400 MHz, DMSO-d_6): δ/ppm = 9.49 (s, 1H, N*H*), 8.14 (d, $^3J_{HH}$ = 9.0 Hz, 1H, ar-*H*), 7.51-7.26 (m, 19H, ar-*H*), 7.04 (t, $^3J_{HH}$ = 7.2 Hz, 1H, N*H*), 5.30-5.23 (m, 1H, C*H*), 2.95 (dd, $^2J_{HP}$ = 14.0 Hz, $^3J_{HH}$ = 9.2 Hz, 1H, CH_2), 2.82 (dd, $^2J_{HP}$ = 14.0, $^3J_{HH}$ = 6.0 Hz, 1H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 183.3, 180.3, 168.0, 163.5, 142.2 (d, J_{CP} = 5.9 Hz), 138.8, 137.7 (d, J_{CP} = 13.5 Hz), 137.5 (d, J_{CP} = 13.0 Hz), 132.7 (d, J_{CP} = 17.0 Hz), 132.5 (d, J_{CP} = 16.7 Hz), 129.3, 128.8 (d, J_{CP} = 3.5 Hz), 128.7, 128.6 (d, J_{CP} = 2.3 Hz), 128.5 (d, J_{CP} = 2.3 Hz), 127.7, 126.4, 122.7, 118.0, 55.8 (d, J_{CP} = 18.4 Hz), 35.7 (d, J_{CP} = 15.1 Hz).

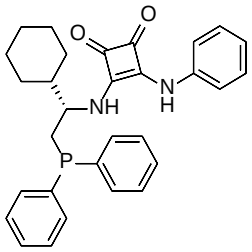
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −22.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3181 (w), 3119 (w), 3065 (w), 3036 (w), 1796 (w), 1652 (m), 1604 (m), 1563 (s), 1542 (s), 1476 (s), 1431 (s), 1251 (w), 1028 (w), 837 (w), 731 (m), 689 (s), 512 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{30}H_{25}N_2O_2P^+$: 477.1726 $[M+H]^+$; found: 477.1727.

$[\alpha]_D^{20}$ = +14.3 (*c* = 0.56, DMSO).

(*S*)-3-((1-Cyclohexyl-2-(diphenylphosphanyl)ethyl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione (25b)



According to general procedure **GP3**, (*S*)-1-cyclohexyl-2-(diphenylphosphanyl)ethan-1-amine (**18b**) (58.0 mg, 186 µmol) in MeOH (4 mL) and 3-(methoxy)-4-(phenylamino)-3-cyclobutene-1,2-dione (**24a**) (41.6 mg, 205 µmol) were stirred for two days to give the product **25b** (75.0 mg, 155 µmol, 84%) as a white solid.

$C_{30}H_{25}N_2O_2P$ (476.51 g/mol):

MP: 98-99 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.35 (s, 1H, N*H*), 7.56 (d, $^3J_{HH}$ = 9.7 Hz, 1H, ar-*H*), 7.47-7.22 (m, 14H, ar-*H*), 7.02 (t, $^3J_{HH}$ = 7.3 Hz, 1H, N*H*), 4.12 – 3.96 (m, 1H, NC*H*), 2.54 (d, $^2J_{HP}$ = 15.2 Hz, 1H, PCH_2), 2.36 (dd, $^2J_{HP}$ = 14.2 Hz, $^3J_{HH}$ = 10.1 Hz, 1H, PCH_2), 1.77-1.53 (m, 6H, cy-CH_2), 1.23-0.92 (m, 5H, cy-CH_2, cy-C*H*).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 183.4, 180.0, 168.9, 162.9, 139.0, 138.1 (d, J_{CP} = 12.6 Hz), 137.9 (d, J_{CP} = 13.5 Hz), 132.7 (d, J_{CP} = 2.1 Hz), 132.5 (d, J_{CP} = 2.3 Hz), 129.3, 128.8, 128.6, 128.5, 128.4, 122.5, 117.8, 57.1 (d, J_{CP} = 15.6 Hz), 43.3 (d, J_{CP} = 7.4 Hz), 32.0 (d, J_{CP} = 12.8 Hz), 29.2, 27.0, 25.8, 25.5 (d, J_{CP} = 3.7 Hz).

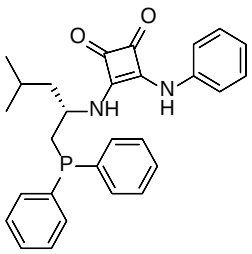
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −22.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3172 (w), 3055 (w), 2923 (w), 2850 (w), 1793 (w), 1655 (m), 1603 (m), 1562 (s), 1544 (s), 1446 (s), 1432 (s), 1250 (w), 1097 (w), 1029 (w), 831 (w), 748 (s), 730 (s), 685 (s), 505 (m), 463 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{30}H_{25}N_2O_2P^+$: 483.2196 $[M+H]^+$; found: 483.2200.

$[\alpha]_D^{20}$ = +28.9 (*c* = 0.48, DMSO).

(S)-3-((1-(Diphenylphosphanyl)-4-methylpentan-2-yl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione (25c)



According to general procedure **GP3**, (S)-1-(diphenylphosphanyl)-4-methylpentan-2-amine (**18c**) (60.0 mg, 0.21 mmol) in MeOH (4 mL) and 3-(methoxy)-4-(phenylamino)-3-cyclobutene-1,2-dione (**24a**) (42.7 mg, 0.21 mmol) were stirred for two days to give of the product **25c** (67.0 mg, 150 µmol, 70%) as a pale yellow solid.

$C_{28}H_{29}N_2O_2P$ (456.20 g/mol):

MP: >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.34 (s, 1H, N*H*), 7.62 (d, $^3J_{HH}$ = 8.9 Hz, 1H, N*H*), 7.49-7.25 (m, 14H, ar-*H*), 7.03 (t, $^3J_{HH}$ = 7.2 Hz, 1H, N*H*), 4.33-4.20 (m, 1H, C*H*), 2.57-2.42 (m, 2H, CH_2), 1.72-1.49 (m, 3H, CH_2, CH(CH_3)$_2$), 0.85 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH(CH_3)$_2$), 0.81 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH(CH_3)$_2$).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 183.3, 179.9, 168.6, 163.2, 139.0, 138.3 (d, J_{CP} = 13.0 Hz), 137.8 (d, J_{CP} = 12.6 Hz), 132.7 (d, J_{CP} = 19.7 Hz), 132.4 (d, J_{CP} = 19.1 Hz), 129.3, 128.6 (d, J_{CP} = 5.9 Hz), 128.5 (d, J_{CP} = 6.9 Hz), 122.5, 117.8, 51.1 (d, J_{CP} = 16.4 Hz), 45.8 (d, J_{CP} = 8.2 Hz), 35.7 (d, J_{CP} = 14.3 Hz), 24.4, 23.0, 21.3.

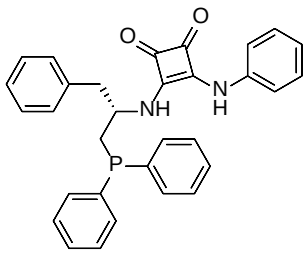
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −23.5.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3170 (w), 2955 (m), 1793 (m), 1651 (s), 1601 (s), 1563 (s), 1539 (s), 1430 (s), 1261 (m), 1025 (w), 728 (s), 684 (s), 496 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{28}H_{29}N_2O_2P^+$: 457.2039 $[M+H]^+$; found: 457.2042-

$[\alpha]_D^{20}$ = +46.7 (*c* = 0.82, DMSO).

(*S*)-3-((1-(Diphenylphosphino)-3-phenylpropan-2-yl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione (25d)



According to general procedure **GP3**, (*S*)-1-(diphenylphosphino)-3-phenylpropan-2-amine (**18d**) (110.0 mg, 340 µmol) in MeOH (7 mL) and 3-(methoxy)-4-(phenylamino)-3-cyclobutene-1,2-dione (**24a**) (69.9 mg, 340 µmol) were stirred for two days to give the product **25d** (142 mg, 290 µmol, 85%) as a white solid.

$C_{31}H_{27}N_2O_2P$ (490.54 g/mol):

MP: >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.35 (s, 1H, N*H*), 7.65 (d, $^3J_{HH}$ = 8.8 Hz, 1H, N*H*), 7.42-7.25 (m, 16H, ar-*H*), 7.23-7.15 (m, 3H, ar-*H*), 7.07-6.97 (m, 1H, ar-*H*), 4.41-4.29 (m, 1H, C*H*), 3.08 (dd, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, PCH_2), 2.97 (dd, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, Ph-CH_2), 2.63-2.56 (m, 1H, Ph-CH_2), 2.45 (dd, $^4J_{HP}$ = 14.3 Hz, $^3J_{HH}$ = 9.4 Hz, 1H, PCH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 183.3, 180.1, 168.6, 163.2, 138.9, 138.0, 137.9, 137.7, 137.6, 132.6, 132.4, 132.3, 129.3, 129.3, 128.7 (d, J_{CP} = 6.1 Hz), 128.6 (d, J_{CP} = 4.1 Hz), 128.5 (d, J_{CP} = 4.3 Hz), 128.3, 126.4, 122.5, 117.9, 54.2 (d, J_{CP} = 16.5 Hz), 43.0 (d, J_{CP} = 8.5 Hz), 34.1 (d, J_{CP} = 13.8 Hz).

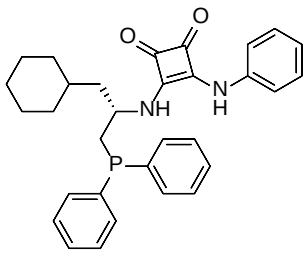
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −23.2.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3181 (w), 3031 (w), 1797 (m), 1653 (s), 1604 (s), 1539 (s), 1476 (s), 1431 (s), 1295 (w), 1172 (w), 1071 (w), 836 (w), 731 (s), 688 (s).

EA ($C_{31}H_{27}N_2O_2P$) calc.: C 75.90, H 5.55, N 5.71; found: C 75.90, H 5.59, N 5.73.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +50.9 (*c* = 0.92, DMSO).

(*S*)-3-((1-cyclohexyl-3-(diphenylphosphanyl)propan-2-yl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione (25e)



According to general procedure **GP3**, (*S*)-1-cyclohexyl-3-(diphenylphosphanyl)propan-2-amine (**18e**) (100 mg, 307 µmol) in MeOH (6 mL) and 3-(methoxy)-4-(phenylamino)-3-cyclobutene-1,2-dione (**24a**) (56.7 mg, 279 µmol) were stirred for two days to give the product **25e** (110 mg, 222 µmol, 79%) as a white solid.

$C_{31}H_{33}N_2O_2P$ (496.59 g/mol):

MP: >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.34 (br s, 1H, N*H*), 7.63 (d, $^3J_{HH}$ = 8.6 Hz, 1H, N*H*), 7.49-7.39 (m, 6H, ar-*H*), 7.39-7.24 (m, 8H, ar-*H*), 7.03 (t, $^3J_{HH}$ = 7.2 Hz, 1H, ar-*H*), 4.35-4.20 (m, 1H, NC*H*), 2.56-2.42 (m, 2H, PCH_2), 1.69 (d, $^3J_{HH}$ = 13.0 Hz, 1H, cy-C*H*), 1.64-1.49 (m, 6H, cy-CH_2), 1.38-1.26 (m, 1H, CH_2), 1.22-1.03 (m, 3H, cy-CH_2^*, CH_2*), 0.95-0.72 (m, 2H, cy-CH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 183.3, 179.9, 168.6, 163.2, 139.0, 138.3 (d, J_{CP} = 12.9 Hz), 137.8 (d, J_{CP} = 12.6 Hz), 132.7 (d, J_{CP} = 19.5 Hz), 132.4 (d, J_{CP} = 19.1 Hz), 129.3, 128.7 (d, J_{CP} = 2.9 Hz), 128.5 (d, J_{CP} = 6.9 Hz), 122.5, 117.8, 50.4 (d, J_{CP} = 16.2 Hz), 44.3 (d, J_{CP} = 8.5 Hz), 35.7 (d, J_{CP} = 13.9 Hz), 33.7, 33.2, 31.7, 26.0, 25.6, 25.4.

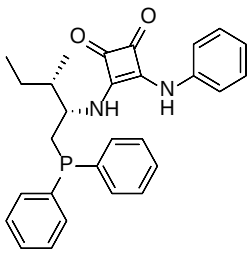
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −23.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3180 (w), 3064 (w), 3038 (w), 2920 (m), 2849 (w), 1793 (w), 1656 (m), 1605 (w), 1541 (s), 1480 (w), 1433 (s), 729 (s), 685 (s), 602 (w), 501 (m).

EA ($C_{31}H_{33}N_2O_2P$) calc.: C 74.98, H 6.70, N 5.64; found: C 74.68, H 6.69, N 5.86.

$[\alpha]_D^{20}$ = −3.3 (*c* = 0.80, DMSO).

3-(((2*S*,3*S*)-1-(Diphenylphosphanyl)-3-methylpentan-2-yl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione (25f)



According to general procedure **GP3**, (2*S*,3*S*)-1-(diphenylphosphanyl)-3-methylpentan-2-amine (**18f**) (100 mg, 351 µmol) in MeOH (7 mL) and 3-(methoxy)-4-(phenylamino)-3-cyclobutene-1,2-dione (**24a**) (64.8 mg, 319 µmol) were stirred for two days to give the product **25f** (96.0 mg, 210 µmol, 66%) as a white solid.

$C_{28}H_{29}N_2O_2P$ (456.53 g/mol):

MP: 227-228 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.34 (s, 1H, N*H*), 7.59 (d, $^3J_{HH}$ = 9.6 Hz, 1H, N*H*), 7.48-7.38 (m, 6H, ar-*H*), 7.38-7.22 (m, 8H, ar-*H*), 7.02 (t, $^3J_{HH}$ = 7.3 Hz, 1H, ar-*H*), 4.18-4.07 (m, 1H, NC*H*), 2.50-2.46 (m, 1H, PCH_2), 2.35-2.27 (m, 1H, PCH_2), 1.71-1.61 (m, 1H, C*H*CH_3), 1.54-1.40 (m, 1H, CH_2CH_3), 1.17-1.04 (m, 1H, CH_2CH_3), 0.89 (d, $^3J_{HH}$ = 6.7 Hz, 3H, CHCH_3), 0.80 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_2CH_3).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 183.4, 180.0, 168.8, 163.0, 139.0, 138.1 (d, J_{CP} = 12.6 Hz), 137.9 (d, J_{CP} = 13.7 Hz), 132.7 (d, J_{CP} = 14.8 Hz), 132.5 (d, J_{CP} = 14.7 Hz), 129.3, 128.9, 128.6, 128.5, 128.4, 122.5, 117.8, 56.6 (d, J_{CP} = 15.8 Hz), 40.4 (d, J_{CP} = 7.5 Hz), 31.1 (d, J_{CP} = 13.3 Hz), 23.9, 14.9, 11.3.

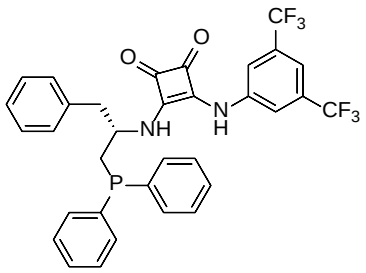
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −21.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3200 (w), 3137 (w), 3094 (w), 3066 (w), 2962 (w), 1794 (m), 1655 (m), 1561 (s), 1544 (s), 1480 (m), 1433 (m), 730 (s), 686 (s), 501 (m), 464 (m).

EA ($C_{28}H_{29}N_2O_2P$) calc.: C 73.67, H 6.40, N 6.14; found: C 73.54, H 6.36, N 6.48.

$[\alpha]_D^{20}$ = +40.4 (*c* = 0.76, DMSO).

(*S*)-3-((3,5-bis(Trifluoromethyl)phenyl)amino)-4-((1-(diphenylphosphanyl)-3-phenylpropan-2-yl)amino)cyclobut-3-ene-1,2-dione (26a)



According to general procedure **GP3**, (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (40.0 mg, 125 µmol) in MeOH (2.5 mL) and 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (**24b**) (38.6 mg, 113 µmol) were stirred for two days to give the product **26a** (17.5 mg, 28.0 µmol, 25%) as a pale yellow solid.

$C_{33}H_{25}F_6N_2O_2P$ (626.54 g/mol):

MP: 238-239 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.89 (s, 1H, N*H*), 7.97 (s, 2H, ar-*H*), 7.79 (d, $^3J_{HH}$ = 8.9 Hz, 1H, N*H*), 7.67 (s, 1H, ar-*H*), 7.43-7.16 (m, 15H, ar-*H*), 4.53-4.34 (m, 1H, C*H*), 3.15-3.09 (m, 1H, PCH_2), 3.03-2.95 (m, 1H, PCH_2), 2.65-2.51 (m, 2H, Ph-CH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 184.0, 180.2, 169.3, 162.0, 140.9, 140.8, 137.8, 137.6, 132.7, 132.6 (d, J_{CP} = 2.8 Hz), 132.5 (d, J_{CP} = 6.1 Hz), 132.4 (d, J_{CP} = 2.6 Hz), 132.3, 131.5, 129.3, 128.7, 128.7, 128.6 (d, J_{CP} = 2.8 Hz), 128.5 (d, J_{CP} = 2.9 Hz), 128.4, 128.3, 126.5, 124.5, 121.8, 117.9, 114.7, 54.5 (d, J_{CP} = 16.1 Hz), 43.0 (d, J_{CP} = 7.9 Hz), 34.1 (d, J_{CP} = 14.5 Hz).

^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −23.3.

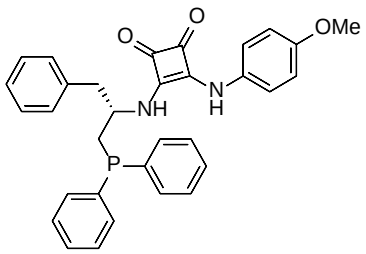
^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ/ppm = −61.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3139 (w), 3070 (w), 3027 (w), 2930 (w), 1659 (m), 1567 (s), 1495 (m), 1463 (m), 1375 (s), 1275 (s), 1180 (m), 1121 (s), 943 (w), 879 (w), 744 (m), 694 (s), 499 (m).

EA ($C_{33}H_{25}F_6N_2O_2P$) calc.: C 63.26, H 4.02, N 4.47; found: C 62.95, H 4.25, N 4.39.

$[\alpha]_D^{20}$ = −45.6 (*c* = 0.94, DMSO).

(*S*)-3-((1-(Diphenylphosphanyl)-3-phenylpropan-2-yl)amino)-4-((4-methoxyphenyl)amino)-cyclobut-3-ene-1,2-dione (26b)



According to general procedure **GP3**, (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (75.3 mg, 236 µmol) in MeOH (4.5 mL) and 3-methoxy-4-((4-methoxyphenyl)amino)cyclobut-3-ene-1,2-dione (**24c**) (50.0 mg, 214 µmol) were stirred for two days to give the product **26b** (110 mg, 211 µmol, 99%) as a white solid.

$C_{32}H_{29}N_2O_3P$ (520.57 g/mol):

MP: >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.26 (s, 1H, N*H*), 7.54 (d, $^3J_{HH}$ = 8.7 Hz, 1H, N*H*), 7.42-7.15 (m, 17H, ar-*H*), 6.91 (d, $^3J_{HH}$ = 9.0 Hz, 2H, ar-*H*), 4.34 (s, 1H, C*H*), 3.73 (s, 3H, OCH_3), 3.07 (dd, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, PCH_2), 2.97 (dd, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 8.0 Hz, 1H, PCH_2), 2.63-2.53 (m, 1H, Ph-CH_2), 2.44 (dd, $^4J_{HP}$ = 14.3 Hz, $^3J_{HH}$ =9.4 Hz, 1H, Ph-CH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 180.3, 168.1, 163.3, 155.1, 137.8, 132.5 (d, J_{CP} = 18.0 Hz), 132.3 (d, J_{CP} = 16.9 Hz), 132.0, 129.2, 128.7 (d, J_{CP} = 6.3 Hz), 128.6 (d, J_{CP} = 4.2 Hz), 128.5 (d, J_{CP} = 4.4 Hz), 128.3, 126.4, 119.5, 114.5, 55.2, 54.1 (d, J_{CP} = 16.9 Hz), 43.0 (d, J_{CP} = 7.0 Hz), 34.1 (d, J_{CP} = 14.4 Hz).

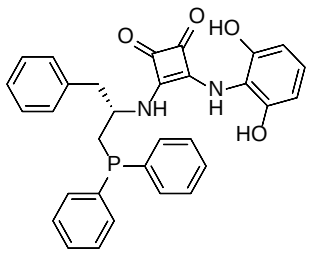
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −23.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3173 (w), 2999 (w), 1649 (m), 1610 (w), 1544 (s), 1515 (m), 1482 (m), 1445 (m), 1250 (s), 1184 (m), 1033 (m), 827 (s), 747 (s), 731 (s), 693 (s), 508 (s).

EA ($C_{32}H_{29}N_2O_3P$) calc.: C 73.83, H 5.62, N 5.38; found: C 73.47, H 5.71, N 5.57.

$[\alpha]_D^{20}$ = −42.7 (*c* = 0.56, DMSO).

(*S*)-3-((2,6-Dihydroxyphenyl)amino)-4-((1-(diphenylphosphanyl)-3-phenylpropan-2-yl)amino)cyclobut-3-ene-1,2-dione (26c)



According to general procedure **GP3**, (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (54.3 mg, 170 µmol) in MeOH (3.4 mL) and 3-((2,6-dihydroxyphenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (**24d**) (40.0 mg, 170 µmol) were stirred for two days to give the product **26c** (73.0 mg, 140 µmol, 82%) as a white solid.

$C_{31}H_{27}N_2O_4P$ (522.54 g/mol):

MP: >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.62 (br s, 2H, O*H*), 8.56 (br s, 1H, N*H*), 7.58-7.47 (m, 1H, ar-*H*), 7.41-7.14 (m, 15H, ar-*H*, N*H*), 6.82 (t, $^3J_{HH}$ = 8.2 Hz, 1H, ar-*H*), 6.35 (d, $^3J_{HH}$ = 8.1 Hz, 2H, ar-*H*), 4.25-4.13 (m, 1H, C*H*), 2.98 (d, $^3J_{HH}$ = 6.7 Hz, 2H, PCH_2), 2.59-2.50 (m, 1H, Ph-CH_2), 2.34-2.27 (m, 1H, Ph-CH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 183.9, 181.8, 168.1, 167.1, 152.7, 138.4 (d, J_{CP} = 12.5 Hz), 137.8, 137.4 (d, J_{CP} = 13.9 Hz), 132.5 (d, J_{CP} = 19.3 Hz), 132.3 (d, J_{CP} = 19.0 Hz), 129.3, 128.9, 128.7, 128.6, 128.3, 126.4, 126.2, 113.4, 106.6, 53.4 (d, J_{CP} = 16.3 Hz), 43.3, 33.9 (d, J_{CP} = 13.2 Hz).

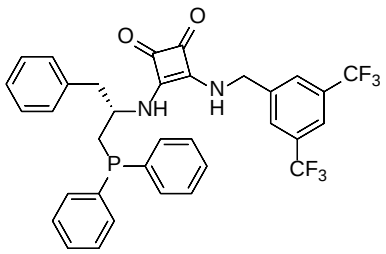
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −24.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3158 (m), 3024 (m), 1793 (w), 1675 (m), 1588 (s), 1533 (m), 1450 (s), 1359 (m), 1287 (w), 991 (s), 780 (m), 740 (m), 696 (s), 502 (w).31

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{31}H_{27}N_2O_4P^+$: 523.1781 $[M+H]^+$; found: 523.1784.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −0.4 (*c* = 0.68, DMSO).

(*S*)-3-((3,5-bis(Trifluoromethyl)benzyl)amino)-4-((1-(diphenylphosphanyl)-3-phenylpropan-2-yl)amino)cyclobut-3-ene-1,2-dione (26f)



According to general procedure **GP3**, (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (49.7 mg, 125 µmol) in MeOH (3.2 mL) and 3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (**24g**) (50.0 mg, 142 µmol) were stirred for two days to give the product **26f** (89.0 mg, 139 µmol, 98%) as a white solid.

$C_{34}H_{27}F_6N_2O_2P$ (520.57 g/mol):

MP: 240-241 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 8.08 (br s, 1H, N*H*), 8.03 (s, 2H, ar-*H*), 7.54 (br s, 1H, N*H*), 7.37-7.09 (m, 16H, ar-*H*), 4.82 (s, 2H, ar-CH_2), 4.24 (s, 1H, C*H*), 3.01 (dd, $^2J_{HP}$ = 13.6 Hz, $^3J_{HH}$ = 5.6 Hz, 1H, PCH_2), 2.90 (dd, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 8.3 Hz, 1H, PCH_2), 2.57-2.52 (m, 1H, Ph-CH_2), 2.43-2.35 (m, 1H, Ph-CH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d6) δ/ppm: 182.3, 167.6, 166.9, 142.6, 138.2 (d, J_{CP} = 12.8 Hz), 137.8, 132.5 (d, J_{CP} = 7.6 Hz), 132.3 (d, J_{CP} = 7.3 Hz), 130.9, 130.4 (d, J_{CP} = 32.7 Hz), 130.0, 129.3, 128.7, 128.5, 128.5, 128.4, 128.1, 127.4, 126.3, 124.7, 122.0, 53.9, 45.7, 43.1 (d, J_{CP} = 7.8 Hz), 34.2.

^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −23.2.

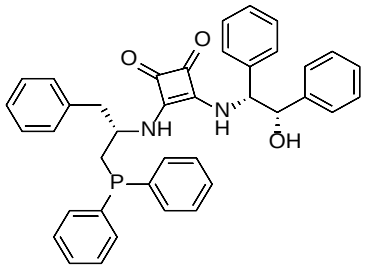
^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ/ppm = −61.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3169 (w), 3072 (w), 1642 (m), 1560 (s), 1475 (m), 1434 (m), 1380 (w), 1355 (w), 1278 (s), 1235 (w), 1182 (m), 1128 (s), 904 (w), 736 (m), 694 (s), 502 (m).

EA ($C_{34}H_{27}F_6N_2O_2P$) calc.: C 63.75, H 4.25, N 4.37; found: C 63.81, H 4.53, N 4.42.

$[\alpha]_D^{20}$ = −4.7 (*c* = 0.64, DMSO).

3-(((*S*)-1-(Diphenylphosphanyl)-3-phenylpropan-2-yl)amino)-4-(((1*R*,2*S*)-2-hydroxy-1,2-diphenylethyl)amino)cyclobut-3-ene-1,2-dione (26g)



According to general procedure **GP3**, (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (86.9 mg, 272 µmol) in MeOH (5.5 mL) and 3-(((1*R*,2*S*)-2-hydroxy-1,2-diphenylethyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (**24h**) (80.0 mg, 247 µmol) were stirred for two days to give the product **26g** (123 mg, 201 µmol, 82%) as a white solid.

$C_{39}H_{35}N_2O_3P$ (610.70 g/mol):

MP: >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.91 (d, $^3J_{HH}$ = 9.7 Hz, 1H, N*H*), 7.67 (d, $^3J_{HH}$ = 8.5 Hz, 1H, N*H*), 7.39-7.06 (m, 25H, ar-*H*), 5.86 (s, 1H, O*H*), 5.30 (s, 1H, NC*H*), 5.09 (s, 1H, OC*H*), 4.11 (s, 1H, C*H*), 3.00-2.85 (m, 2H, PCH_2), 2.54 (br s, 1H, Ph-CH_2), 2.33 (dd, $^4J_{HP}$ = 14.2 Hz, $^3J_{HH}$ = 9.4 Hz, 1H, Ph-CH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 182.3, 182.1, 167.3, 166.9, 142.0, 138.6, 138.2 (d, J_{CP} = 14.9 Hz), 137.8, 137.5 (d, J_{CP} = 13.3 Hz), 132.5 (d, J_{CP} = 5.9 Hz), 132.3 (d, J_{CP} = 5.9 Hz), 129.3, 128.8, 128.7, 128.6 (d, J_{CP} = 5.0 Hz), 128.5, 128.2, 128.0, 127.6, 127.1, 127.1, 126.5, 126.3, 75.1, 62.4, 53.6 (d, J_{CP} = 16.2 Hz), 43.2 (d, J_{CP} = 8.3 Hz), 33.9 (d, J_{CP} = 13.1 Hz).

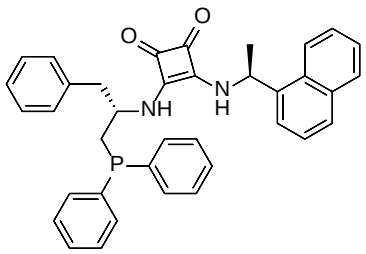
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −23.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3136 (w), 3092 (w), 2971 (w), 2939 (w), 1638 (m), 1553 (s), 1477 (m), 1017 (w), 734 (m), 695 (s), 615 (w), 499 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{39}H_{35}N_2O_3P^+$: 611.2458 $[M+H]^+$; found: 611.2454

$[\alpha]_D^{20}$ = +2.0 (*c* = 0.28, DMSO).

3-(((*S*)-1-(Diphenylphosphanyl)-3-phenylpropan-2-yl)amino)-4-(((*S*)-1-(naphthalen-1-yl)ethyl)amino)cyclobut-3-ene-1,2-dione (26h)



According to general procedure **GP3**, (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (60.0 mg, 188 µmol) in MeOH (3.8 mL) and (*S*)-3-methoxy-4-((1-(naphthalen-1-yl)ethyl)amino-)cyclobut-3-ene-1,2-dione (**24i**) (48.0 mg, 171 µmol) were stirred for two days to give the product **26h** (88.0 mg, 155 µmol, 91%) as a white solid. Because of the limited solubility in deuterated solvent, no carbon NMR was obtained.

$C_{37}H_{33}N_2O_2P$ (520.57 g/mol):

MP: >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 8.00-7.04 (m, 22H, ar-*H*), 5.28 (br s, 1H, C*H*), 4.22 (br s, 1H, C*H*), 3.04-2.95 (m, 1H, PCH_2), 2.93-2.87 (m, 1H, PCH_2), 2.46-2.32 (m, 2H, CH_2), 1.59 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3).

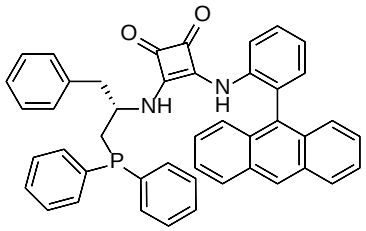
^{31}P NMR (162 MHz, DMSO-d_6): δ/ppm = −23.4.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3155 (w), 3054 (w), 1637 (m), 1551 (s), 1465 (m), 1185 (w), 1073 (w), 819 (m), 753 (s), 738 (s), 695 (s), 607 (w), 500 (m), 480 (m).

EA ($C_{37}H_{33}N_2O_2P$) calc.: C 78.15, H 5.85, N 4.93; found: C 77.86, H 5.77, N 5.02.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +28.5 (*c* = 0.14, DMSO).

(*S*)-3-((2-(Anthracen-9-yl)phenyl)amino)-4-((1-(diphenylphosphanyl)-3-phenylpropan-2-yl)amino)cyclobut-3-ene-1,2-dione (26i)



According to general procedure **GP3**, (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (50.9 mg, 159 µmol) in MeOH (3.2 mL) and 3-((2-(anthracen-9-yl)phenyl)amino)-4-methoxy-cyclobut-3-ene-1,2-dione (**24j**) (55.0 mg, 145 µmol) were stirred for two days to give the product **26i** (52.0 mg, 78.0 µmol, 54%) as a yellow solid.

$C_{45}H_{35}N_2O_2P$ (666.77 g/mol):

MP: 243-244 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.70 (s, 1H, N*H*), 8.44 (s, 1H, ar-*H*), 8.01 (d, $^3J_{HH}$ = 8.9 Hz, 2H, ar-*H*), 7.98 (d, $^3J_{HH}$ = 7.2 Hz, 1H, ar-*H*), 7.94 (d, $^3J_{HH}$ = 8.1 Hz, 1H, ar-*H*), 7.84 (d, $^3J_{HH}$ = 8.6 Hz, 1H, ar-*H*), 7.60 (d, $^3J_{HH}$ = 8.9 Hz, 1H, ar-*H*), 7.45-7.39 (m, 2H, ar-*H*), 7.35-7.25 (m, 12H, ar-*H*), 7.22-7.17 (m, 1H, ar-*H*), 7.15-7.07 (m, 3H, ar-*H*), 6.98 (d, $^3J_{HH}$ = 8.5 Hz, 1H, N*H*), 6.92-6.88 (m, 3H, ar-*H*), 4.17-4.03 (m, 1H, C*H*), 2.87 (dd, $^2J_{HP}$ = 13.5 Hz, $^3J_{HH}$ = 5.7 Hz, 1H, PCH_2), 2.79 (dd, $^2J_{HP}$ = 13.5, $^3J_{HH}$ = 7.5 Hz, 1H, PCH_2), 2.49-2.43 (m, 1H, Ph-CH_2), 2.26-2.19 (m, 1H, Ph-CH_2).

^{13}C{^{1}H} NMR (101 MHz DMSO-d_6): δ/ppm = 183.9, 180.5, 168.6, 164.2, 153.5, 138.0, 137.4, 134.8, 133.6, 132.5 (d, J_{CP} = 7.3 Hz), 132.3 (d, J_{CP} = 7.4 Hz), 130.7, 130.0, 129.3, 128.8, 128.7, 128.6 (d, J_{CP} = 4.0 Hz), 128.5 (d, J_{CP} = 3.9 Hz), 128.2 (d, J_{CP} = 5.5 Hz), 128.2, 128.0, 126.5, 126.4, 126.3, 125.2, 124.7, 123.7, 122.8, 122.7, 122.6, 118.7, 113.6, 53.6, 43.0, 33.7.

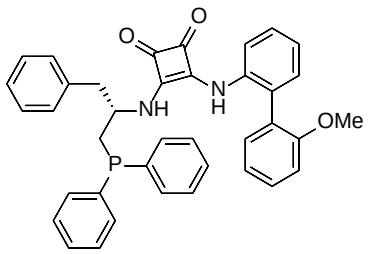
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −23.5.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3211 (w), 3053 (w), 1781 (w), 1665 (w), 1567 (s), 1519 (s), 1486 (m), 1427 (s), 1357 (w), 1305 (m), 1098 (w), 891 (w), 846 (w), 735 (s), 697 (s), 611 (w), 505 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{45}H_{35}N_2O_2P^+$: 667.2509 $[M+H]^+$; found: 667.2502.

$[\alpha]_D^{20}$ = +78.5 (*c* = 0.48, DMSO).

(*S*)-3-((1-(Diphenylphosphanyl)-3-phenylpropan-2-yl)amino)-4-((2'-methoxy-[1,1'-biphenyl]-2-yl)amino)cyclobut-3-ene-1,2-dione (26j)



According to general procedure **GP3**, (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (45.4 mg, 142 µmol) in MeOH (2.8 mL) and 3-methoxy-4-((2'-methoxy-[1,1'-biphenyl]-2-

yl)amino)cyclobut-3-ene-1,2-dione (**24k**) (40.0 mg, 129 µmol) were stirred for two days to give the product **26j** (25.0 mg, 42.0 µmol, 33%) as a white solid.

$C_{38}H_{33}N_2O_3P$ (596.67 g/mol):

MP: 84-85 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 8.44 (s, 1H, N*H*), 7.82 (d, $^3J_{HH}$ = 8.6 Hz, 1H, N*H*), 7.47-7.06 (m, 23H, ar-*H*), 4.26 and 4.11 (s, 1H, C*H*, rotamers), 3.56 (s, 3H, OCH_3), 3.08-2.84 (m, 1H, PCH_2), 2.58-2.52 (m, 1H, PCH_2), 2.41-2.26 (m, 2H, Ph-CH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 183.8, 180.2, 164.1, 156.4, 137.8, 135.8, 132.5 (d, J_{CP} = 7.5 Hz), 132.3 (d, J_{CP} = 7.4 Hz), 131.3, 131.0, 129.9, 129.6, 129.3, 128.7 (d, J_{CP} = 8.9 Hz), 128.6, 128.6, 128.5, 128.3, 127.7, 126.5, 126.4, 124.0, 122.6, 120.9, 111.8, 99.5, 55.2, 53.6, 43.1, 34.2 (d, J_{CP} = 12.8 Hz).

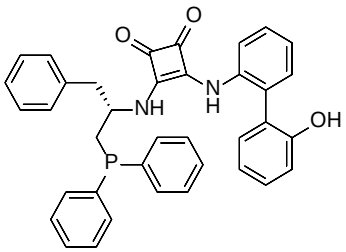
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −23.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3142 (w), 3053 (w), 3028 (w), 2946 (w), 1680 (w), 1583 (m), 1515 (s), 1429 (m), 1235 (w), 1055 (s), 1024 (s), 999 (s), 842 (w), 748 (m), 731 (m), 697 (s), 501 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{38}H_{33}N_2O_3P^+$: 597.2302 [M+H]$^+$; found: 597.2307.

$[\alpha]_D^{20}$ = +24.0 (*c* = 0.21, DMSO).

(*S*)-3-((1-(Diphenylphosphanyl)-3-phenylpropan-2-yl)amino)-4-((2'-hydroxy-[1,1'-biphenyl]-2-yl)amino)cyclobut-3-ene-1,2-dione (26k)



According to general procedure **GP3**, (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (59.5 mg, 186 µmol) in MeOH (3.7 mL) and 3-((2'-hydroxy-[1,1'-biphenyl]-2-yl)amino)-4-methoxycyclobut-3-ene-1,2-dione (**24l**) (50.0 mg, 169 µmol) were stirred for two days to give the product **26k** (76.0 mg, 130 µmol, 77%) as a white solid.

$C_{37}H_{31}N_2O_3P$ (582.64 g/mol):

MP: >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.61 (s, 1H, O*H*), 8.51 (s, 1H, N*H*), 7.85 (d, $^{3}J_{HH}$ = 8.6 Hz, 1H, N*H*), 7.36-7.10 (m, 21H, ar-*H*), 7.00 (d, $^{3}J_{HH}$ = 8.1 Hz, 1H, ar-*H*), 6.92 (t, $^{3}J_{HH}$ = 7.4 Hz, 1H, ar-*H*), 4.24 (br s, 1H, C*H*), 3.00 (dd, $^{2}J_{HP}$ = 13.5 Hz, $^{3}J_{HH}$ = 5.6 Hz, 1H, PCH_2), 2.90 (dd, $^{2}J_{HP}$ = 13.5 Hz, $^{3}J_{HH}$ = 7.7 Hz, 1H, PCH_2), 2.56-2.51 (m, 1H, Ph-CH_2), 2.38-2.27 (m, 1H, Ph-CH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 183.9, 180.5, 168.6, 164.1, 154.7, 138.1 (d, J_{CP} = 12.8 Hz), 137.7, 135.7, 132.5 (d, J_{CP} = 8.3 Hz), 132.3 (d, J_{CP} = 8.0 Hz), 131.3, 131.2, 130.2, 129.4, 129.2, 128.8, 128.7, 128.6 (d, J_{CP} = 4.8 Hz), 128.5 (d, J_{CP} = 5.0 Hz), 128.3, 127.6, 126.4, 124.8, 123.8, 122.3, 119.3, 116.0, 53.8 (d, J_{CP} = 16.3 Hz), 43.1 (d, J_{CP} = 8.6 Hz), 33.9 (d, J_{CP} = 14.0 Hz).

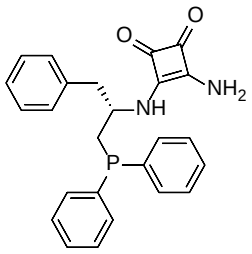
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −23.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3163 (w), 3027 (w), 2942 (w), 1789 (w), 1679 (m), 1579 (s), 1522 (s), 1478 (m) ,1431 (s), 1357 (m), 1283 (m), 1046 (s), 1021 (s), 996 (s), 820 (w), 751 (m), 696 (s), 502 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{37}H_{31}N_2O_3P^+$: 583.2145 [M+H]$^+$; found: 583.2143.

$[\alpha]_D^{20}$ = −4.7 (*c* = 0.41, DMSO).

(*S*)-3-Amino-4-((1-(diphenylphosphanyl)-3-phenylpropan-2-yl)amino)cyclobut-3-ene-1,2-dione (26l)



According to general procedure **GP3**, (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (69.1 mg, 186 µmol) in MeOH (4.3 mL) and 3-amino-4-methoxycyclobut-3-ene-1,2-dione (25.0 mg, 197 µmol) (**24m**) were stirred for two days to give the product **26l** (75.0 mg, 181 µmol, 92%) as a white solid

$C_{25}H_{23}N_2O_2P$ (520.57 g/mol):

MP: >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.49 (d, $^3J_{HH}$ = 8.1 Hz, 1H, N*H*), 7.40-7.12 (m, 16H, ar-*H,* N*H*), 4.14 (br s, 1H, C*H*), 3.04-2.88 (m, 2H, PCH_2), 2.43-2.32 (m, 2H, Ph-CH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 182.8, 168.1, 138.3 (d, J_{CP} = 16.1 Hz), 137.9, 137.6 (d, J_{CP} = 10.6 Hz), 132.5 (d, J_{CP} = 7.8 Hz), 132.3 (d, J_{CP} = 7.9 Hz), 129.3, 128.8, 128.6, 128.6, 128.5, 128.2, 126.3, 53.5 (d, J_{CP} = 15.1 Hz), 43.2 (d, J_{CP} = 8.0 Hz), 34.2 (d, J_{CP} = 13.4 Hz).

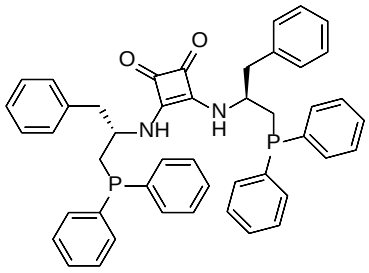
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −23.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3300 (w), 3130 (m), 2932 (w), 1631 (m), 1564 (s), 1529 (s), 1475 (m), 1359 (w), 1081 (w), 729 (m), 693 (s), 499 (m).

EA ($C_{25}H_{23}N_2O_2P$) calc.: C 72.45, H 5.59, N 6.76; found: C 72.20, H 5.66, N 6.95.

$[\alpha]_D^{20}$ = −14.0 (*c* = 0.21, DMSO).

3,4-bis(((*S*)-1-(Diphenylphosphanyl)-3-phenylpropan-2-yl)amino)cyclobut-3-ene-1,2-dione (26m)



Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with 3,4-dimethoxy-3-cyclobutene-1,2-dione (**22**) (20.0 mg, 131 µmol) and methanol (2.6 mL). Then, a solution of (*S*)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (112 mg, 352 µmol) in methanol (0.5 mL) was added in one portion. The corresponding mixture was stirred for two days at room temperature. The precipitate was filtered and washed with ice-cold methanol to yield the desired product **26m** (56.0 mg, 78.0 µmol, 55%) as a white solid. Because of the limited solubility in deuterated solvent, no carbon NMR was obtained.

$C_{46}H_{42}N_2O_2P_2$ (716.80 g/mol):

MP: >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.47-7.03 (m, 30H, ar-*H*), 4.11 (br s, 2H, C*H*), 3.01-2.86 (m, 4H, PCH_2), 2.47-2.28 (m, 4H, Ph-CH_2).

$^{31}P\{^{1}H\}$ NMR (162 MHz, DMSO-d_6): δ/ppm = −23.7.

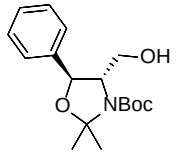
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3155 (w), 3056 (w), 3024 (w), 2929 (w), 1636 (m), 1562 (s), 1471 (m), 1433 (m), 1183 (w), 840 (w), 733 (s), 694 (s), 501 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{46}H_{42}N_2O_2P_2^+$: 717.2794 $[M+H]^+$; found: 717.2796

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −123.0 (*c* = 0.06, DMSO).

5.2.3 Synthesis of 3rd Generation Catalysts

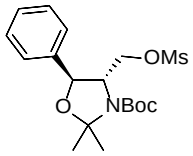
tert-Butyl (4*S*,5*S*)-4-(hydroxymethyl)-2,2-dimethyl-5-phenyloxazolidine-3-carboxylate (33)



Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (**32**) (5.00 g, 29.9 mmol), acetone (6 mL) and toluene (20 mL). Then, a Dean-Stark apparatus was attached and the solution was refluxed for 24 hours. Afterwards the reaction mixture was concentrated under vacuum and the residue was dissolved in THF (20 mL). To the reaction solution di-*tert*-butyldicarbonat (7.18 g, 7.04 mL, 32.9 mmol) was added dropwise over five minutes and the resulting mixture was stirred for 16 hours at room temperature. Then, the mixture was concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (3:1), d x h: 8 x 14 cm) to afford the product **33** (5.16 g, 29.9 mmol, 56%) as a pale yellow solid.

$C_{17}H_{25}NO_4$ (307.39 g/mol):
MP: 73-74 °C.
TLC: R_f = 0.38 (SiO_2, cyclohexane:ethyl acetate (3:1)).
^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.42 (d, $^3J_{HH}$ = 7.6 Hz, 2H, ar-*H*), 7.38 (t, $^3J_{HH}$ = 7.5 Hz, 2H, ar-*H*), 7.31 (t, $^3J_{HH}$ = 7.0 Hz, 1H, ar-*H*), 5.12-4.97 (br m, 2H, Ph-C*H*, O*H*), 3.81-3.70 (br m, 1 H, CH_2), 3.69-3.58 (br m, 1 H, NC*H*), 3.56-3.47 (br m, 1H, CH_2), 1.57 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.41 (s, 9H, C(CH_3)$_3$).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 151.0, 140.3, 128.3, 127.9, 126.6, 93.7, 79.0, 65.3, 58.9, 58.0, 28.0, 26.4, 25.7.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3456 (m), 2978 (w), 2934 (w), 2897 (w), 1666 (s), 1455 (s), 1404 (s), 1376 (m), 1256 (s), 1204 (m), 1166 (s); 1147 (s), 1103 (s), 1069 (m), 1049 (m); 1027 (m), 974 (m), 912 (m), 877 (m), 814 (m), 764 (s), 702 (m), 649 (m), 607 (w), 556 (w), 522 (w), 506 (m), 461 (w).
EA ($C_{17}H_{25}NO_4$) calc.: C 66.43, H 8.20, N 4.56; found: C 66.36, H 8.04, N 4.40.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +34.5 (*c* = 1.01, CH_2Cl_2).

tert-Butyl (4*S*,5*S*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carboxylate (34)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl (4*S*,5*S*)-4-(hydroxymethyl)-2,2-dimethyl-5-phenyloxazolidine-3-carboxylate (**33**) (5.10 g, 16.6 mmol), CH_2Cl_2 (53 mL) and this mixture was cooled in an ice-bath to 0 °C. Then, triethylamine (4.36 g, 5.83 mL, 41.5 mmol) was added, followed by dropwise addition of methanesulfonyl chloride (2.47 g, 1.67 mL, 21.6 mmol) over 10 minutes at 0 °C. After addition the mixture was stirred for four hours at 0 °C and 16 hours at room temperature. Water (20 mL) was added and the biphasic mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (4:1), d x h: 5 x 20 cm) to afford the product **34** (5.46 g, 14.14 mmol, 85%) as a white solid.

$C_{18}H_{27}NO_6S$ (385.48 g/mol):

MP: 107-108 °C.

TLC: R_f = 0.35 (SiO_2, cyclohexane:ethyl acetate (4:1)).

^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.50-7.33 (m, 5H, ar-*H*), 5.04 (d, $^3J_{HH}$ = 7.1 Hz, 1H, Ph-C*H*), 4.74-4.49 (br m, 1H, CH_2), 4.24 (d, $^3J_{HH}$ = 9.8 Hz, 1H, NC*H*), 3.90 (br s, 1H, CH_2), 3.22 (s, 3H, SCH_3), 1.61 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.44 (s, 9H, C(CH_3)$_3$).

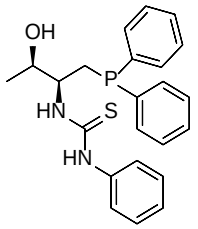
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 151.0, 138.4, 128.5, 128.4, 126.9, 94.2, 80.0. 77.7, 65.6, 62.1, 36.7, 27.9, 26.4, 25.5.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2989 (w), 2933 (w), 1691 (s), 1454 (w), 1391 (m), 1380 (s), 1356 (s), 1330 (m), 1281 (w), 1264 (m), 1238 (w), 1212 (w), 1175 (s), 1153 (s), 1101 (s), 1090 (m), 1075 (m), 1055 (m), 1021 (m), 976 (s), 950 (w), 917 (s), 888 (s), 848 (m), 813 (s), 770 (w), 757 (m), 704 (s), 694 (m), 528 (s), 517 (s), 456 (m).

EA ($C_{18}H_{27}NO_6$) calc.: C 56.09, H 7.06, N 3.63; found: C 56.08, H 6.83, N 3.47.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +5.2 (*c* = 1.45, CH_2Cl_2).

1-((2*S*,3*R*)-1-(Diphenylphosphanyl)-3-hydroxybutan-2-yl)-3-phenylthiourea (36)



According to general procedure **GP1**, (2*R*,3*S*)-3-amino-4-(diphenylphosphanyl)butan-2-ol (**35**) (140 mg, 512 µmol), phenyl isothiocyanate (77.7 mg, 68.7 µL, 563 µmol), CH_2Cl_2 (2.0 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (2:1), d x h: 2 x 10 cm) to afford the product **36** (187 mg, 511 µmol, 90%) as a white solid.

$C_{23}H_{25}N_2OPS$ (408.50 g/mol):

MP: 66-67 °C.

TLC: R_f = 0.20 (SiO_2, cyclohexane:ethyl acetate (1:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.80 (br s, 1H, N*H*), 7.49-7.35 (m, 4H, ar-*H*), 7.35-7.13 (m, 9H, ar-*H*), 7.03 (d, $^3J_{HH}$ = 8.1 Hz, 2H, ar-*H*), 6.54 (br s, 1H, N*H*), 4.64-4.49 (m, 1H, Ph-C*H*), 4.18-4.08 (m, 1H, NC*H*), 2.52-2.36 (m, 2H, PCH_2), 2.13 (br s, 1H, O*H*), 1.10 (d, $^3J_{HH}$ = 6.3 Hz, 3H, CHCH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 180.4, 136.2, 133.0 (d, J_{CP} = 9.3 Hz), 132.9 (d, J_{CP} = 8.9 Hz), 130.2, 129.2, 128.8 (d, J_{CP} = 2.2 Hz), 128.7 (d, J_{CP} = 2.4 Hz), 127.1, 124.9, 69.0 (d, J_{CP} = 8.8 Hz), 58.3 (d, J_{CP} = 14.9 Hz), 31.7 (d, J_{CP} = 12.5 Hz), 20.9.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −24.4.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3359 (w), 3226 (w), 1594 (w), 1519 (s), 1494 (s), 1450 (m), 1432 (m), 1314 (w), 1296 (w), 1237 (m), 1160 (w), 1095 (w), 1015 (w), 871 (m), 736 (s), 692 (s), 555 (w), 504 (m), 471 (m).

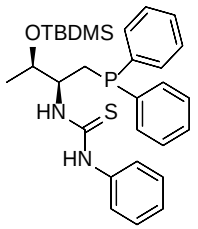
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{23}H_{25}N_2OPS^+$: 409.1498 $[M+H]^+$; found: 409.1501.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +59.2 (*c* = 0.96, $CHCl_3$).

General Procedure (GP4): Silylation of secondary alcohol

Under argon atmosphere, a heat-gun dried round bottomed flask was charged with the thiourea precursor (1.0 eq.), DIPEA (2.0 eq.) or triethylamine (2.0 eq.) and CH_2Cl_2 (11 mL per mmol). At 0 °C, silyl triflate (1.05 eq) was added dropwise to the reaction mixture over 5 minutes. After stirring for two hours at 0 °C and additional four hours at room temperature, the mixture was concentrated under vacuum and the crude product was purified by column chromatography.

1-((2*S*,3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-(diphenylphosphanyl)butan-2-yl)-3-phenyl thiourea (37)



According to general procedure **GP4**, 1-((2*S*,3*R*)-1-(diphenylphosphanyl)-3-hydroxybutan-2-yl)-3-phenylthiourea (**36**) (118 mg, 289 µmol), DIPEA (114 mg, 146 µL, 880 µmol), TBDMS triflate (83.7 mg, 72.8 µL, 317 µmol), CH_2Cl_2 (3.1 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1), d x h: 2 x 13 cm) to afford the product **37** (120 mg, 230 µmol, 79%) as a white solid.

$C_{29}H_{39}N_2OPSSi$ (522.76 g/mol):
MP: 60-61 °C.
TLC: R_f = 0.43 (SiO_2, cyclohexane:ethyl acetate (5:1)).
^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.93 (br s, 1H, N*H*), 7.70-7.58 (m, 2H, ar-*H*), 7.45-7.23 (m, 11H, ar-*H*), 7.19-7.14 (m, 2H, ar-*H*), 6.58 (d, $^3J_{HH}$ = 8.8 Hz, 1H, *N*H), 4.53-4.41 (m, 1H, Ph-C*H*), 4.36-4.30 (m, 1H, NC*H*), 2.62 (ddd, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 6.3 Hz, $^4J_{HH}$ = 3.1 Hz, 1H, PCH_2), 2.12 (ddd, $^2J_{HP}$ = 13.8 Hz, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.1 Hz, 1H, PCH_2), 1.12 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CHCH_3), 0.72 (s, 9H, SiC(CH_3)$_3$), 0.04 (s, 6H, SiCH_3).
^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.7, 136.8, 133.7 (d, J_{CP} = 19.4 Hz), 133.3 (d, J_{CP} = 19.1 Hz), 130.7, 129.4, 129.1, 129.0 (d, J_{CP} = 5.1 Hz), 128.9 (d, J_{CP} = 5.4 Hz), 127.5, 125.6, 69.5 (d, J_{CP} = 11.0 Hz), 59.1 (d, J_{CP} = 17.7 Hz), 32.3 (d, J_{CP} = 14.8 Hz), 26.07, 21.78, 18.20, −3.95, −4.31.

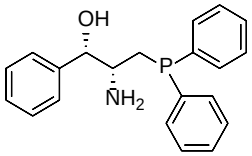
$^{31}P\{^{1}H\}$ NMR (162 MHz, CD_2Cl_2): δ/ppm = −24.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3366 (w), 3170 (w), 3052 (w), 2952 (m), 2926 (m), 1594 (w), 1510 (s), 1495 (s), 1470 (m), 1432 (m); 1316 (w), 1248 (m), 1125 (m), 1067 (m), 960 (m), 914 (m), 827 (s), 775 (s), 734 (s), 692 (s), 489 (w).

EA ($C_{29}H_{39}N_2OPSSi$) calc.: C 66.63, H 7.52, N 5.36; found: C 66.59, H 7.31, N 5.38.

$[\alpha]_D^{20}$ = +26.7 (*c* = 0.98, CH_2Cl_2).

(1*S*,2*R*)-2-Amino-3-(diphenylphosphanyl)-1-phenylpropan-1-ol (38)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl (4*S*,5*S*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carboxylate (**34**) (2.00 g, 5.19 mmol) and THF (17 mL). Then, the reaction mixture was degassed by three freeze-pump-thaw cycles. At 0 °C, potassium diphenylphosphide solution (0.5 M in THF, 1.48 g, 13.2 mL, 6.60 mmol) was added dropwise over five minutes and afterwards the mixture was stirred two hours at 0 °C and two hours at room temperature. At ambient temperature, aqueous HCl (37%, 3.82 g, 9.00 mL, 106 mmol) was added and then the mixture was stirred at room temperature for 16 hours. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed aqueous NaOH (2 M) and then the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (1:5) + 5% NEt_3, d x h: 3.5 x 14 cm) to afford the product **38** (1.49 g, 4.44 mmol, 86%) as a pale yellow gum.

$C_{21}H_{22}NOP$ (335,39 g/mol):

TLC: R_f = 0.29 (SiO_2, cyclohexane:ethyl acetate (1:5) + 5% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.28-7.16 (m, 15H, ar-*H*), 4.40 (d, $^{3}J_{HH}$ = 6.0 Hz, 1H, Ph-C*H*), 2.90-2.83 (m, 1H, NC*H*), 2.27 (dt, $^{2}J_{HP}$ = 13.9 Hz, $^{3}J_{HH}$ = 3.4 Hz, 1H, PCH_2), 2.20 (br s, 2H, NH_2), 1.95-1.88 (m, 1H, PCH_2).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ/ppm = 142.1, 138.9 (d, J_{CP} = 11.6 Hz), 137.1 (d, J_{CP} = 12.1 Hz), 133.2 (d, J_{CP} = 19.4 Hz), 132.5 (d, J_{CP} = 18.3 Hz), 129.1, 128.7, 128.7, 128.6, 128.5, 127.8, 126.8, 77.5, 55.2 (d, J_{CP} = 14.1 Hz), 34.0 (d, J_{CP} = 12.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ/ppm = −22.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3354 (w), 3052 (w), 3026 (w), 2897 (w), 1734 (w), 1583 (m), 1480 (m), 1450 (w), 1432 (s), 1240 (m), 1182 (w), 1125 (w), 1093 (w), 1046 (m), 1026 (m), 999 (w), 945 (w), 914 (w), 839 (w), 737 (s), 696 (s), 507 (m), 478 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{21}H_{22}NOP^+$: 336.1512 $[M+H]^+$; found: 336.1517.

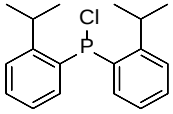
$[\alpha]_D^{20}$ = −86.1 (*c* = 0.89, $CHCl_3$).

General Procedure (GP5): Synthesis of chlorophosphine

Under argon atmosphere, a heat-gun dried two-neck flasked with a reflux condenser was charged with magnesium turnings (5.0 eq.) and THF (2 mL per mmol bromide). Then, the bromide (2.7 eq.) was added dropwise and the Grignard reagent formation was started by heating with a heat gun. After the reaction had started, the reaction mixture was refluxed for four hours at 68 °C.

Under argon atmosphere, a second heat-gun dried two-necked flask was charged with diethylphosphoramidous dichloride (1.0 eq.) and THF (1.1 mL per mmol phosphoramidous chloride). Then, this mixture was cooled in an ice-bath and at 0 °C the freshly prepared Grignard reagent was added dropwise. After complete addition, the mixture was stirred for six hours at room temperature. At 0 °C, the reaction mixture was treated with hydrogen chloride (4 M in dioxane, 10.0 eq.). Afterwards, the crude product was conctentrated under vacuum and the resulting residue was either purified by Kugelrohr distillation or directly used for the amino phoshine synthesis.

Chlorobis(2-isopropylphenyl)phosphane (39b)



According to general procedure **GP5**, magnesium (209 mg, 8.59 mmol), 2-isopropylphenyl bromide (**41b**) (910 g, 700 µL, 4.57 mmol) and THF (9 mL) were stirred for four hours at 68 °C. In a second two-necked flask, diethylphosphoramidous dichloride (299 mg, 250 µL, 1.72 mmol), and THF (2 mL) were treated with the Grignard reagent and stirred for six hours. After addition of hydrogen chloride (4 M in dioxane, 4.98 g, 4.30 mL, 17.2 mmol) the crude product **39b** (274 mg, 899 µmol, 52%) was yielded as a white gum and directly used for the amiono phosphine synthesis.

$C_{18}H_{22}ClP$ (304.11 g/mol):

^{1}H NMR (500 MHz, C_6D_6): δ/ppm = 7.56-7.42 (m, 2H, ar-*H*), 6.92-6.86 (m, 4H, ar-*H*), 6.77-6.72 (m, 2H, ar-*H*), 3.57 (sept, $^{3}J_{HH}$ = 6.8 Hz, 2H, C*H*$(CH_3)_2$), 0.99 (d, $^{3}J_{HH}$ = 6.7 Hz, 6H, CH(C*H*$_3)_2$), 0.75 (d, $^{3}J_{HH}$ = 6.8 Hz, 6H, CH(C*H*$_3)_2$).

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ/ppm = 152.3 (d, J_{CP} = 27.5 Hz), 135.6 (d, J_{CP} = 34.5 Hz), 132.4 (d, J_{CP} = 3.2 Hz), 130.9, 126.7, 125.7 (d, J_{CP} = 3.7 Hz), 31.6, 31.4, 24.1, 23.6.

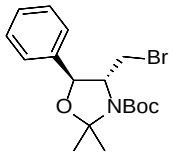
^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ/ppm = 72.4.

General Procedure: Synthesis of aminophosphines using chloro phosphines

Under argon atmosphere, a heat-gun dried two-necked flask was charged with the chlorophosphine (1.7 eq.) and THF (2 mL per mmol chlorophosphine). Then, the reaction mixture was degassed by three freeze-pump-thaw cycles. At 0 °C, potassium (4.0 eq.) was added in small portions over 20 minutes and afterwards the mixture was stirred for three hours at 75 °C. The red colored crude potassium phosphide solution was directly used for the next step without any purification.

Under argon atmosphere, a second heat-gun dried two-necked flask was charged with *tert*-butyl (4*S*,5*S*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carboxylate (1.0 eq.) and THF (1 mL per mmol oxazolidine). Then, the reaction mixture was degassed by three freeze-pump-thaw cycles. At 0 °C, the freshly prepared potassium phosphide solution was added dropwise over five minutes and afterwards the mixture was stirred for two hours at 0 °C and two hours at room temperature. At ambient temperature, aqueous HCl (37%, 40.0 eq.) was added and then the mixture was stirred at room temperature for 16 hours. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed aqueous NaOH (2 M) and then the mixture was extracted with EtOAc (3 x 5 mL per mmol oxazolidine). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography.

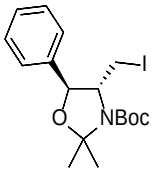
tert-Butyl (4*R*,5*S*)-4-(bromomethyl)-2,2-dimethyl-5-phenyloxazolidine-3-carboxylate (41)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl (4*S*,5*S*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carboxylate (**34**) (190 mg, 493 µmol), lithium bromide (173 mg, 1.97mmol), and THF (2 mL). Then, this mixture was refluxed for 16 hours and afterwards water (5 mL) was added and the biphasic mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 ml), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude mixture was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1), d x h: 3.5 x 10 cm) to afford the product **41** (117 mg, 315 µmol, 64%) as a colorless oil.

$C_{17}H_{24}BrNO_3$ (370.28 g/mol):
TLC: R_f = 0.72 (SiO_2, cyclohexane:ethyl acetate (10:1)).
^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.49-7.33 (m, 5H, ar-*H*), 4.92 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ph-C*H*), 4.11/3.95* (s, 1H, NC*H*), 3.84 (s, 1H, BrCH_2), 3.50 (d, $^3J_{HH}$ = 10.6 Hz, 1H, BrCH_2), 1.60 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.44 (s, 9H, C(CH_3)$_3$). [* refers to signal of rotamers]

tert-Butyl (4*R*,5*S*)-4-(iodomethyl)-2,2-dimethyl-5-phenyloxazolidine-3-carboxylate (42)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl (4*S*,5*S*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carboxylate (**34**) (385 mg, 1.00 mmol), lithium iodide (1.34 g, 10 mmol), and THF (6 mL). Then, this mixture was refluxed for 16 hours and afterwards water (20 mL) was added and the biphasic mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 ml), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude mixture was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (20:1), d x h: 3.5 x 15 cm) to afford the product **42** (358 mg, 858 µmol, 86%) as a white solid.

$C_{17}H_{24}INO_3$ (417.29 g/mol):

MP: 47-48 °C.

TLC: R_f = 0.36 (SiO_2, cyclohexane:ethyl acetate (20:1)).

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.46-7.33 (m, 5H, ar-*H*), 4.74 (d, $^3J_{HH}$ = 7.4 Hz, 1H, Ph-C*H*), 3.88/3.69* (s, 1H, NC*H*), 3.35 (br s, 1H, CH_2), 3.25 (d, $^3J_{HH}$ = 8.9 Hz, 1H, CH_2), 1.62 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.44 (s, 9H, C(CH_3)$_3$). [* refers to signal of rotamers]

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 151.2/150.6*, 137.7/128.7*, 128.6/127.2*, 94.5/94.0*, 80.9/80.6*, 79.9, 62.3/63.0*, 28.0, 26.8/26.4*, 9.6/8.6*.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2972 (w), 1678 (s), 1454 (w), 1396 (s), 1377 (s), 1364 (s), 1309 (m), 1270 (m), 1156 (s), 1108 (m), 1080 (m), 1058 (s), 939 (w), 892 (m), 761 (s), 704 (m), 641 (w), 604 (w), 504 (m).

EA ($C_{17}H_{24}INO_3$) calc.: C 48.93, H 5.80, N 3.36; found: C 49.02, H 5.82, N 3.66.

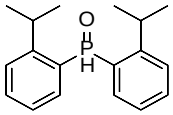
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −2.1 (*c* = 1.35, MeOH).

General Procedure (GP6): Synthesis of phosphine oxides

Under argon atmosphere, a heat-gun dried two-necked flask with a reflux condenser was charged with magnesium tunings (5.0 eq.) and THF (2 mL per mmol bromide). Then, the bromide (2.5 eq.) was added dropwise and the Grignard reagent formation was initiated by heating with a heat gun. After the reaction had started, the reaction mixture was refluxed for four hours at 68 °C.

Under argon atmosphere, a second heat-gun dried two-necked flask was charged with NaH (60% in mineral oil, 1.2 eq.) and THF (0.5 mL per mmol phosphite). Then this mixture was cooled in an ice-bath and at 0 °C diethyl phosphite (1.0 eq.) was added dropwise over 15 minutes. Afterwards the reaction mixture was stirred for 30 minutes at 0 °C and then the freshly prepared Grignard reagent was added dropwise. After complete addition, the mixture was stirred for 16 hours at room temperature and was then quenched with saturated aqueous NH_4Cl solution (5 mL per mmol phosphite). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL per mmol phosphite) and the combined organic layers were dried over $NaSO_4$. After concentration under vacuum the resulting crude product was purified by trituration with hexane/MTBE (3:1, 1 mL per mmol phosphite) to yield the phosphine oxide after filtration and drying under vacuum.

Bis(2-isopropylphenyl)phosphine oxide (43b)



According to general procedure **GP6**, magnesium (1.21 g, 49.9 mmol), 2-isopropylphenyl bromide (**41b**) (5.02 g, 3.86 mL, 25.0 mmol) and THF (50 mL) were stirred for four hours at 68 °C. In a second flask sodium hydride (60% in mineral oil, 479 mg, 12.1 mmol), diethyl phosphite (1.47 g, 1.37 mL, 9.98 mmol) and THF (5 mL) were stirred for 30 minutes at 0 °C and treated with the Grignard reagent. The crude product was purified by trituration with MTBE/hexane (3:1, 10 mL) to afford the product **43** (2.10 g, 7.33 mmol, 73%) as a white solid.

$C_{18}H_{23}OP$ (286.35 g/mol):

MP: 129-130 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm = 8.32 (d, $^{1}J_{HP}$ = 478.2 Hz, 1H, P*H*), 7.72 (ddd, $^{3}J_{HP}$ = 15.4 Hz, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.5 Hz, 2H, ar-*H*), 7.52 (tt, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.5 Hz, 2H, ar-*H*), 7.39 (dd, $^{3}J_{HH}$ = 8.0 Hz, $^{4}J_{HH}$ = 4.9 Hz, 2H, ar-*H*), 7.33-7.29 (m, 2H, ar-*H*), 3.25 (hept, $^{3}J_{HH}$ = 6.8 Hz, 2H, C*H*$(CH_3)_2$), 1.08 (d, $^{3}J_{HH}$ = 6.8 Hz, 6H, CH(C*H*$_3)_2$), 1.03 (d, $^{3}J_{HH}$ = 6.7 Hz, 6H, CH(C*H*$_3)_2$).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 152.5 (d, J_{CP} = 9.9 Hz), 132.9 (d, J_{CP} = 2.6 Hz), 132.4 (d, J_{CP} = 12.4 Hz), 129.21 (d, J_{CP} = 100.9 Hz), 126.6 (d, J_{CP} = 10.3 Hz), 126.3 (d, J_{CP} = 13.0 Hz), 31.1 (d, J_{CP} = 7.2 Hz), 23.9, 23.7.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = 20.7-14.5 (m).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3313 (w), 3237 (w), 3170 (w), 3079 (w), 1517 (m), 1379 (m), 1275 (s), 1174 (m), 1128 (s), 744 (m), 698 (m), 680 (m).

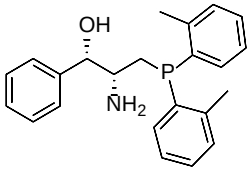
HRMS (ESI (+), 3600 V, 180 °C, MeOH, NaOAc): (*m/z*) calc. for $C_{18}H_{23}OP^{+}$: 309.1379 $[M+Na]^{+}$; found: 309.1382.

General Procedure (GP7): Synthesis of amino phosphines using phosphines

Non-commercial diarylphosphines were synthesized by reduction of the corresponding phosphine oxide following the procedure of C. A. Busacca.[68]

Under argon atmosphere, a heat gun dried two-necked flask was charged with the phosphine (1.5 eq), potassium hydride (95%, 1.5 eq.) and degassed THF (2 mL per mmol phosphine). The corresponding mixture was stirred for 30 minutes at 0 °C and afterwards *tert*-butyl (4*S*,5*S*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carboxylate (1.0 eq.) was added in one portion at 0 °C. The reaction mixture was stirred for 30 minutes at 0 °C and for additional four hours at room temperature. Then, aqueous HCl (37%, 20 eq.) was added dropwise to the solution and the pale yellow solution was stirred at room temperature over night. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed aqueous NaOH (2 M) and then the mixture was extracted with EtOAc (3 x 10 mL per mmol oxazolidine). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography.

(1*S*,2*R*)-2-Amino-3-(di-*o*-tolylphosphanyl)-1-phenylpropan-1-ol (40a)



According to general procedure **GP7**, di(*o*-tolyl)phosphine (**44a**) (390 mg, 1.82 mmol), potassium hydride (76.8 mg, 1.82 mmol) and THF (3.6 mL) were stirred for 30 minutes at 0 °C, followed by *tert*-butyl (4*S*,5*S*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carboxylate (**34**) (389 mg, 1.01 mmol) addition and after four hours aqueous HCl addition (37%, 1.99 g, 1.78 mL, 20.2 mmol). The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (1:5) + 5% NEt_3, d x h: 3.5 x 11 cm) to afford the product **40a** (286 mg, 787 µmol, 78%) as a pale yellow oil.

$C_{23}H_{26}NOP$ (363.44 g/mol):

TLC: R_f = 0.30 (SiO_2, cyclohexane:ethyl acetate (1:5) + 5% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.36-7.27 (m, 5H, ar-*H*), 7.23-7.13 (m, 4H, ar-*H*), 7.10-6.99 (m, 3H, ar-*H*), 6.86-6.82 (m, 1H, ar-*H*), 4.44 (d, $^3J_{HH}$ = 5.9 Hz, 1H, Ph-C*H*), 3.00-2.93 (m, 1H,

NC*H*), 2.47 (s, 3H, ar-CH_3), 2.36 (s, 3H, ar-CH_3), 2.27 (ddd, $^2J_{HP}$ = 14.1 Hz, $^3J_{HH}$ = 3.2 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, PCH_2), 1.86 (ddd, $^2J_{HP}$ = 14.1 Hz, $^3J_{HH}$ = 10.0 Hz, $^4J_{HH}$ = 4.1 Hz, 1H, PCH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 142.9, 142.6, 142.3, 142.1, 141.8, 136.7 (d, J_{CP} = 11.7 Hz), 135.4 (d, J_{CP} = 12.4 Hz), 131.5, 131.1, 130.3 (t, J_{CP} = 5.2 Hz), 128.7 (d, J_{CP} = 4.1 Hz), 128.5, 127.8, 126.9, 126.3 (d, J = 4.0 Hz), 77.8 (d, J_{CP} = 8.8 Hz), 55.2 (d, J_{CP} = 14.9 Hz), 32.9 (d, J_{CP} = 12.0 Hz), 21.5 (d, J_{CP} = 9.2 Hz), 21.2 (d, J_{CP} = 9.1 Hz).

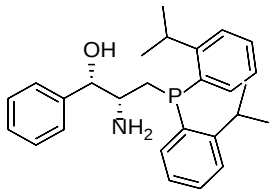
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −44.1.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3354 (w), 3054 (w), 3003 (w), 2912 (w), 1587 (m), 1450 (s), 1377 (m), 1270 (m), 1129 (w), 1042 (w), 835 (w), 744 (s), 699 (s), 546 (m), 451 (s).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{23}H_{26}NOP^+$: 364.1825 $[M+H]^+$; found: 364.1828.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −99.7 (*c* = 0.79, $CHCl_3$).

(1*S*,2*R*)-2-Amino-3-(bis(2-isopropylphenyl)phosphanyl)-1-phenylpropan-1-ol (40b)



According to general procedure **GP7**, di(*o*-isopropyl)phosphine (**44b**) (243 mg, 0.898 mmol), potassium hydride (37.9 mg, 0.898 mmol) and THF (2.0 mL) were stirred for 30 minutes at 0 °C, followed by *tert*-butyl (4*S*,5*S*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carbo-xylate (**34**) (192 mg, 0.50 mmol) addition and after four hours aqueous HCl addition (37%, 983 mg, 900 µL, 10.0 mmol). The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (1:2) + 5% NEt_3, d x h: 3.5 x 14 cm) to afford the product **40b** (150 mg, 357 µmol, 72%) as a pale yellow oil.

$C_{27}H_{34}NOP$ (419.55 g/mol):

TLC: R_f = 0.52 (SiO_2, cyclohexane:ethyl acetate (1:4) + 5% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.27-7.16 (m, 9H, ar-*H*), 7.04-6.95 (m, 2H, ar-*H*), 6.95-6.87 (m, 1H, ar-*H*), 6.77-6.73 (m, 1H, ar-*H*), 4.36 (d, $^3J_{HH}$ = 6.0 Hz, 1H, Ph-C*H*), 3.76-3.57 (m, 2H, ar-C*H*(CH_3)$_2$), 2.95-2.83 (m, 1H, NC*H*), 2.37 (br s, 2H, N*H*), 2.17 (ddd, $^2J_{HP}$ = 14.1 Hz, $^3J_{HH}$ = 3.0 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, PCH_2), 1.81-1.73 (m, 1H, PCH_2), 1.19 (d, $^3J_{HH}$ = 6.8 Hz, 3H,

CH(C*H*$_3$)$_2$), 1.14 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 0.93 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 0.83 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 153.4 (d, J_{CP} = 23.6 Hz), 152.7 (d, J_{CP} = 23.6 Hz), 142.2, 136.2 (d, J_{CP} = 10.3 Hz), 135.0 (d, J_{CP} = 11.6 Hz), 132.0, 131.4, 129.2, 128.5, 127.8, 126.9, 126.1 (d, J_{CP} = 7.0 Hz), 125.7 (d, J_{CP} = 4.7 Hz), 125.7 (d, J_{CP} = 4.8 Hz), 77.8 (d, J_{CP} = 8.7 Hz), 55.1 (d, J_{CP} = 15.1 Hz), 34.4 (d, J_{CP} = 13.1 Hz), 31.3 (d, J_{CP} = 10.5 Hz), 31.1 (d, J_{CP} = 10.9 Hz), 24.5, 24.3, 23.8, 23.7.

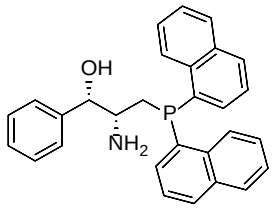
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −49.4.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3361 (w), 3054 (w), 2957 (m), 2924 (w), 2855 (w), 1471 (m), 1452 (w), 1436 (w), 1383 (w), 1361 (w), 1114 (m), 1051 (m), 1028 (w), 960 (s), 942 (s), 908 (s), 868 (w), 835 (w), 732 (m), 700 (m), 506 (s), 484 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{27}H_{34}NOP^+$: 420.2451 $[M+H]^+$; found: 420.2457.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −76.9 (*c* = 0.72, $CHCl_3$).

(1*S*,2*R*)-2-Amino-3-(di(naphthalen-1-yl)phosphanyl)-1-phenylpropan-1-ol (40c)



According to general procedure **GP7**, di(naphthalene-1-yl)phosphine (**44c**) (496 mg, 1.73 mmol), potassium hydride (73.2 mg, 1.73 mmol) and THF (3.5 mL) were stirred for 30 minutes at 0 °C, followed by *tert*-butyl (4*S*,5*S*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carboxylate (**34**) (393 mg, 1.02 mmol) addition and after four hours aqueous HCl addition (37%, 2.01 g, 1.79 mL, 20.4 mmol). The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (1:5) + 5% NEt_3, d x h: 3.5 x 12 cm) to afford the product **40c** (346 mg, 795 µmol, 78%) as a white solid.

$C_{29}H_{26}NOP$ (435.51 g/mol):

MP: 78-79 °C.

TLC: R_f = 0.35 (SiO_2, cyclohexane:ethyl acetate (1:5) + 5% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 8.67-8.56 (m, 1H, ar-*H*), 8.46-8.37 (m, 1H, ar-*H*), 7.83-7.67 (m, 4H, ar-*H*), 7.49-7.28 (m, 4H, ar-*H*), 7.30-7.13 (m, 7H, ar-*H*), 7.16-7.07 (m, 1H, ar-*H*), 7.05-6.96 (m, 1H, ar-*H*), 4.38 (d, $^{3}J_{HH}$ = 6.3 Hz, 1H, Ph-C*H*), 3.01-2.89 (m, 1H, PCH_2), 2.45-2.35 (m, 1H, NC*H*), 2.25 (br s, 2H, NH_2), 2.07-1.95 (m, 1H, PCH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 142.1, 136.0, 135.8, 135.4, 135.3, 135.1, 133.7 (t, J_{CP} = 4.2 Hz), 133.5, 133.4, 130.9, 130.3, 129.7, 129.5, 129.0, 128.9, 128.5, 127.9, 127.0, 126.6 – 126.5 (m), 126.2, 126.0, 125.8, 125.8, 125.7, 125.5, 77.72 (d, J_{CP} = 9.2 Hz), 55.47 (d, J_{CP} = 14.7 Hz), 33.33 (d, J_{CP} = 11.6 Hz).

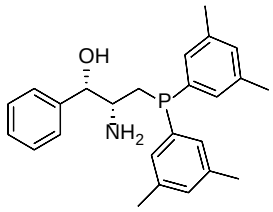
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −46.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3345 (w), 3049 (w), 2866 (w), 1732 (w), 1501 (s), 1450 (m), 1382 (m), 1328 (m), 1254 (w), 1045 (m), 1022 (m), 910 (w), 794 (s), 771 (s), 733 (s), 700 (s), 659 (w), 632 (w), 527 (w), 439 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{29}H_{26}NOP^{+}$: 436.1825 $[M+H]^{+}$; found: 436.1830.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −121.0 (*c* = 0.78, $CHCl_3$).

(1*S*,2*R*)-2-Amino-3-(bis(3,5-dimethylphenyl)phosphanyl)-1-phenylpropan-1-ol (40d)



According to general procedure **GP7**, bis(3,5-dimethylphenyl)phosphine (**44g**) (300 mg, 1.11 mmol), potassium hydride (45.6 mg, 1.11 mmol) and THF (4 mL) were stirred for 30 minutes at 0 °C, followed by *tert*-butyl (4*S*,5*S*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carboxylate (**34**) (286 mg, 740 µmol) addition and after four hours aqueous HCl addition (37%, 3.10 g, 2.67 mL, 20.4 mmol). The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (1:5) + 5% NEt_3, d x h: 2.5 x 12 cm) to afford the product **40d** (220 mg, 562 µmol, 76%) as a white solid.

$C_{25}H_{30}NOP$ (391.49 g/mol):

MP: 55-56 °C.

TLC: R_f = 0.21 (SiO_2, cyclohexane:ethyl acetate (1:5) + 5% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.26-7.16 (m, 5H, ar-*H*), 6.88-6.80 (m, 6H, ar-*H*), 4.37 (d, $^{3}J_{HH}$ = 6.3 Hz, 1H, Ph-C*H*), 2.87-2.80 (m, 1H, PCH_2), 2.27-2.22 (m, 1H, NC*H*), 2.17 (s, 3H, ar-CH_3), 2.26 (s, 3H, ar-CH_3), 1.81 (ddd, $^{2}J_{HP}$ = 14.0 Hz, $^{3}J_{HH}$ = 10.2 Hz, $^{4}J_{HH}$ = 3.8 Hz, 1H, PCH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 142.2, 138.7 (d, J_{CP} = 11.0 Hz), 138.0 (t, J_{CP} = 7.0 Hz), 136.4 (d, J_{CP} = 11.2 Hz), 131.0 (d, J_{CP} = 1.8 Hz), 130.8, 130.4, 130.1, 123.0, 128.5, 127.8, 126.9, 77.7 (d, J_{CP} = 8.7 Hz), 55.3 (d, J_{CP} = 13.8 Hz), 34.0 (d, J_{CP} = 11.8 Hz), 21.4, 21.3.

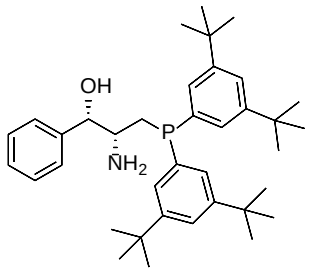
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −23.2.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3362 (w), 3027 (w), 2947 (w), 2912 (w), 2856 (w), 1597 (m), 1580 (m), 1450 (m), 1412 (m), 1264 (w), 1125 (m), 1039 (m), 909 (s), 841 (m), 762 (m), 690 (s), 635 (w), 544 (w), 420 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{25}H_{30}NOP^{+}$: 392.2138 $[M+H]^{+}$; found: 392.2144.

$[\alpha]_D^{20}$ = −100.0 (*c* = 0.49, $CHCl_3$).

(1*S*,2*R*)-2-Amino-3-(bis(3,5-di-*tert*-butylphenyl)phosphanyl)-1-phenylpropan-1-ol (40e)



According to general procedure **GP7**, bis(3,5-di-*tert*-butylphenyl)phosphine (**44d**) (490 mg, 1.19 mmol), potassium hydride (50.4 mg, 1.19 mmol) and THF (2.4 mL) were stirred for 30 minutes at 0 °C, followed by *tert*-butyl (4*S*,5*S*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carboxylate (**34**) (200 mg, 520 µmol) addition and after four hours aqueous HCl addition (37%, 1.02 g, 0.92 mL, 10.4 mmol). The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1) + 5% NEt_3, d x h: 2.5 x 10 cm) to afford the product **40e** (185 mg, 331 µmol, 64%) as a white solid.

$C_{37}H_{54}NOP$ (559.82 g/mol):

MP: 121-122 °C.

TLC: R_f = 0.21 (SiO_2, cyclohexane:ethyl acetate (10:1) + 5% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.33-7.30 (m, 1H, ar-*H*), 7.28-7.26 (m, 1H, ar-*H*), 7.24-7.13 (m, 7H, ar-*H*), 7.11-7.09 (m, 2H, ar-*H*), 4.40 (d, $^{3}J_{HH}$ = 5.7 Hz, 1H, Ph-C*H*), 2.96-2.90 (m, 1H, PCH_2), 2.36-2.34 (m, 1H, NC*H*), 1.92 (ddd, $^{2}J_{HP}$ = 13.8 Hz, $^{3}J_{HH}$ = 10.2 Hz, $^{4}J_{HH}$ = 3.3 Hz, 1H, PCH_2), 1.25 (s, 4H, ar-C(CH_3)$_3$), 1.18 (s, 32H, ar-C(CH_3)$_3$).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 150.9 (d, J_{CP} = 7.0 Hz), 150.8 (d, J_{CP} = 6.6 Hz), 142.4, 137.6 (d, J_{CP} = 10.2 Hz), 135.4 (d, J_{CP} = 10.2 Hz), 128.5, 127.7, 127.4, 127.2, 126.9, 126.7, 126.7, 123.3, 122.8, 77.7 (d, J_{CP} = 8.3 Hz), 55.5 (d, J_{CP} = 13.3 Hz), 35.1, 34.8 (d, J_{CP} = 12.1 Hz), 31.6, 31.5.

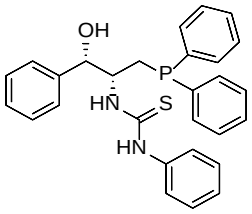
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −20.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3136 (w), 2959 (s), 2903 (m), 2867 (m), 1577 (m), 1476 (m), 1418 (m), 1361 (s), 1248 (m), 1135 (m), 1049 (m), 974 (m), 872 (m), 764 (m), 702 (s), 554 (w), 470 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{37}H_{54}NOP^{+}$: 560.4016 $[M+H]^{+}$; found: 560.4019.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −52.1 (*c* = 0.69, $CHCl_3$).

1-((1*S*,2*R*)-3-(Diphenylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (45a)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(diphenylphosphanyl)-1-phenylpropan-1-ol (**38**) (530 mg, 1.58 mmol), phenyl isothiocyanate (240 mg, 210 µL, 1.74 mmol), CH_2Cl_2 (4.7 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 3.5 x 17 cm) to afford the product **45a** (635 mg, 1.35 mmol, 85%) as a white solid.

$C_{28}H_{27}N_2OPS$ (470.57 g/mol):

MP: 78-79 °C.

TLC: R_f = 0.35 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm = 7.86 (s, 1H, N*H*), 7.54-7.50 (m, 2H, ar-*H*), 7.44-7.25 (m, 14H, ar-*H*), 7.20-7.18 (m, 2H, ar-*H*), 7.03-6.99 (m, 2H, ar-*H*), 6.48 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, N*H*), 5.12-5.06 (m, 1H, Ph-C*H*), 4.88 (br s, 1H, NC*H*), 3.06 (br s, 1H, O*H*), 3.06-2.47 (m, 2H, PCH_2).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ/ppm = 180.4, 141.1, 137.8, 137.4, 135.9, 133.1 (d, J_{CP} = 3.5 Hz), 132.9 (d, J_{CP} = 3.8 Hz), 130.1, 129.1 (d, J_{CP} = 2.2 Hz), 128.7 (d, $^3J_{CP}$ = 7.0 Hz), 128.5, 127.9, 127.3, 126.2, 125.3, 74.8 (d, J_{CP} = 9.3 Hz), 58.9 (d, J_{CP} = 15.5 Hz), 30.7 (d, J_{CP} = 14.5 Hz).

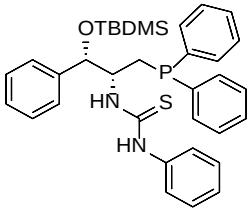
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ/ppm = −23.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3362 (w), 3190 (w), 3052 (w), 1594 (w), 1519 (s), 1494 (s), 1448 (m), 1432 (m), 1315 (w), 1296 (w), 1235 (m), 1182 (m), 1025 (w), 734 (s), 693 (s), 490 (m).

EA ($C_{28}H_{27}N_2OPS$) calc.: C 71.47, H 5.78, N 5.95; found: C 71.26, H 5.88, N 6.01.

$[\alpha]_D^{20}$ = −2.8 (*c* = 1.04, $CHCl_3$).

1-((1*S*,2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(diphenylphosphanyl)-1-phenylpropan-2-yl)-3-phenylthiourea (46a)



According to general procedure **GP4**, 1-((1S,2R)-3-(diphenylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (**45a**) (71.5 mg, 152 µmol), DIPEA (39.3 mg, 50.2 µL, 304 µmol), TBDMS triflate (42.3 mg, 36.7 µL, 160 µmol), CH_2Cl_2 (1.7 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1), d x h: 2 x 16 cm) to afford the product **46a** (77.0 mg, 132 µmol, 87%) as a white solid.

$C_{34}H_{41}N_2OPSSi$ (584.83 g/mol):

MP: 67-68 °C.

TLC: R_f = 0.22 (SiO_2, cyclohexane:ethyl acetate (10:1)).

^1H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.72-7.60 (m, 4H, ar-*H*), 7.49-7.20 (m, 12H, ar-*H*), 7.14-7.10 (m, 2H, ar-*H*), 7.09-7.04 (m, 2H, ar-*H*), 6.43 (d, $^3J_{HH}$ = 8.6 Hz, 1H, N*H*), 5.29 (s, 1H, Ph-C*H*), 4.63-4.50 (m, 1H, NC*H*), 2.51 (ddd, $^2J_{HP}$ = 13.8 Hz, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, PCH_2), 2.36 (ddd, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.1 Hz, 1H, PCH_2), 0.70 (s, 9H, SiC(CH_3)$_3$), 0.06 (s, 3H, SiCH_3), −0.02 (s, 3H, SiCH_3).

$^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.6, 142.2, 139.4, 138.0, 136.6, 133.9 (d, J_{CP} = 19.7 Hz), 133.3 (d, J_{CP} = 18.8 Hz), 130.7, 129.6, 129.2, 129.1 (d, J_{CP} = 2.6 Hz), 129.0 (d,

J_{CP} = 2.3 Hz), 128.4, 128.0, 127.9, 126.7, 126.3, 74.3 (d, J_{CP} = 7.5 Hz), 60.1 (d, J_{CP} = 16.5 Hz), 31.1 (d, J_{CP} = 14.6 Hz), 26.2, 18.4, −4.3.

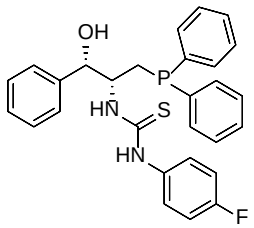
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −24.4.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3366 (w), 3180 (w), 3029 (w); 2952 (w), 2926 (w), 1588 (w), 1510 (s), 1495 (s), 1470 (w), 1449 (w), 1432 (w), 1313 (w), 1248 (m), 1090 (m), 1066 (s), 957 (m), 832 (s), 776 (s), 733 (s), 693 (s), 504 (w).

EA ($C_{34}H_{41}N_2OPSSi$) calc.: C 69.83, H 7.07, N 4.79; found: C 69.64, H 7.24, N 4.88.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +48.8 (*c* = 0.65, CH_2Cl_2).

1-((1*S*,2*R*)-3-(Diphenylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-(4-fluorophenyl) thiourea (45b)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(diphenylphosphanyl)-1-phenylpropan-1-ol (**38**) (100 mg, 298 µmol), 4-fluorophenyl isothiocyanate (48.8 mg, 318 µmol), CH_2Cl_2 (0.9 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (3:1), d x h: 2.5 x 17 cm) to afford the product **45b** (132 mg, 270 µmol, 91%) as a white solid.

$C_{28}H_{26}FN_2OPS$ (488.56 g/mol):

MP: 81-82 °C.

TLC: R_f = 0.29 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.77-7.59 (br m, 1H, N*H*), 7.43-7.39 (m, 2H, ar-*H*), 7.33-7.28 (m, 2H, ar-*H*), 7.26-7.14 (m, 11H, ar-*H*), 7.10-7.06 (m, 2H, ar-*H*), 6.92-6.86 (m, 2H, ar-*H*), 6.37 (d, $^{3}J_{HH}$ = 8.3 Hz, 1H, N*H*), 4.98 (d, $^{3}J_{HH}$ = 4.2 Hz, 1H, Ph-C*H*), 4.78 (br s, 1H, NC*H*), 2.91 (br s, 1H, O*H*), 2.47-2.37 (m, 2H, PCH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 180.8, 162.7, 160.2, 141.1, 137.4, 133.0 (d, J_{CP} = 18.8 Hz), 131.9, 129.2 (d, J_{CP} = 4.6 Hz), 128.8 (d, J_{CP} = 6.8 Hz), 128.6, 128.0, 127.8 (d, J_{CP} = 8.5 Hz), 126.1, 74.9 (d, J_{CP} = 9.2 Hz), 58.9 (d, J_{CP} = 14.8 Hz), 30.6 (d, J_{CP} = 13.6 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −23.4.

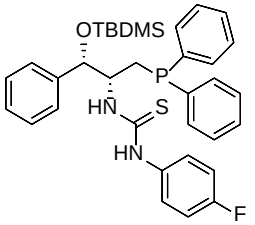
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ/ppm = −113.5.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3364 (w), 3205 (w), 3050 (w), 1504 (s), 1432 (w), 1214 (s), 1090 (m), 910 (m), 831 (m), 733 (s), 693 (s), 502 (s), 476 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{28}H_{26}FN_2OPS^+$: 489.1560 $[M+H]^+$; found: 489.1561.

$[\alpha]_D^{20}$ = −0.7 (*c* = 0.75, $CHCl_3$).

1-((1*S*,2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(diphenylphosphanyl)-1-phenylpropan-2-yl)-3-(4-fluorophenyl)thiourea (46b)



According to general procedure **GP4**, 1-((1*S*,2*R*)-3-(diphenylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-(4-fluorophenyl)thiourea (**45b**) (92.0 mg, 188 µmol), DIPEA (48.6 mg, 62.1 µL, 376 µmol), TBDMS triflate (52.2 mg, 45.4 µL, 197 µmol), CH_2Cl_2 (2.1 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (8:1), d x h: 3 x 18 cm) to afford the product **46b** (77.0 mg, 145 µmol, 77%) as a white solid.

$C_{34}H_{40}FN_2OPSSi$ (602.82 g/mol):

MP: 68-69 °C.

TLC: R_f = 0.25 (SiO_2, cyclohexane:ethyl acetate (5:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.75-7.69 (br m, 1H, N*H*), 7.67-7.60 (m, 2H, ar-*H*), 7.47-7.42 (m, 2H, ar-*H*), 6.23 (d, $^{3}J_{HH}$ = 8.5 Hz, 1H, N*H*), 5.29 (s, 1H, Ph-C*H*), 4.61-4.48 (m, 1H, NC*H*), 2.52 (ddd, $^{2}J_{HP}$ = 13.8 Hz, $^{3}J_{HH}$ = 7.0 Hz, $^{4}J_{HH}$ = 1.9 Hz, 1H, PCH_2), 2.34 (ddd, $^{2}J_{HP}$ = 13.8 Hz, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HH}$ = 2.3 Hz, 1H, PCH_2), 0.78 (s, 9H, SiC(CH_3)$_3$), 0.07 (s, 3H, SiCH_3), −0.20 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.9, 163.4, 161.0, 142.2, 139.4, 138.0 (d, J_{CP} = 12.8 Hz), 133.9 (d, J_{CP} = 19.8 Hz), 133.2 (d, J_{CP} = 19.0 Hz), 132.5, 129.6, 129.2, 129.1 (d, J_{CP} = 3.5 Hz), 129.0 (d, J_{CP} = 3.5 Hz), 128.5, 128.0, 126.6, 117.5 (d, J_{CP} = 22.7 Hz), 74.3 (d, J_{CP} = 7.2 Hz), 60.1 (d, J_{CP} = 17.0 Hz), 31.2 (d, J_{CP} = 15.0 Hz), 26.1, 18.4, −4.4.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −22.7.

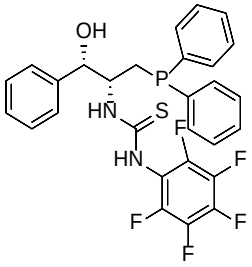
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ/ppm = −112.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3367 (w), 3206 (w), 3053 (w), 2951 (w), 2927 (w), 2855 (w), 1504 (s), 1470 (m), 1433 (w), 1251 (m), 1214 (s), 1089 (s), 1065 (m), 957 (w), 833 (s), 777 (s), 734 (s), 694 (s), 554 (w), 503 (m), 476 (w).

EA ($C_{34}H_{40}FN_2OPSSi$) calc.: C 67.74, H 6.69, N 4.65; found: C 67.60, H 6.69, N 4.56.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +38.9 (*c* = 0.86, CH_2Cl_2)

1-((1*S*,2*R*)-3-(diphenylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-(perfluorophenyl)-thiourea (45c)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(diphenylphosphanyl)-1-phenylpropan-1-ol (**38**) (100 mg, 298 µmol), pentafluorophenyl isothiocyanate (78.0 mg, 48 µL, 328 µmol), CH_2Cl_2 (0.9 mL) were stirred for 16 hours and the crude product was purified by flash column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), 2.5 x 19 cm) to afford the product **45c** (55.0 mg, 172 µmol, 58%) as a white solid.

$C_{28}H_{22}F_5N_2OPS$ (560.52 g/mol):

MP: 84-85 °C.

TLC: R_f = 0.25 (SiO_2, cyclohexane:ethyl acetate (4:1)).

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.11 (br s, 1H, O*H*), 8.18 (d, $^{3}J_{HH}$ = 8.3 Hz, 1H, N*H*), 7.52-7.43 (m, 4H, ar-*H*), 7.40-7.33 (m, 6H, ar-*H*), 7.31-7.20 (m, 5H, ar-*H*), 6.01 (d, $^{3}J_{HH}$ = 4.1 Hz, 1H, N*H*), 6.16-5.11 (br m, 1H, Ph-C*H*), 4.54-4.46 (m, 1H, NC*H*), 2.63 (dd, $^{2}J_{HP}$ = 13.7 Hz, $^{3}J_{HH}$ = 7.3 Hz, 1H, PCH_2), 2.26 (dd, $^{2}J_{HP}$ = 13.7 Hz, $^{3}J_{HH}$ = 7.5 Hz, 1H, PCH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 182.4, 145.1, 142.8, 142.5, 138.6 (d, J_{CP} = 14.1 Hz), 138.2, 138.0 (d, J_{CP} = 13.4 Hz), 135.8, 132.2, 128.8, 128.5 (d, J_{CP} = 3.3 Hz), 128.5 (d, J_{CP} = 3.6 Hz), 127.7, 126.9, 126.3, 115.4, 71.5 (d, J_{CP} = 9.9 Hz), 58.0 (d, J_{CP} = 17.1 Hz), 29.5 (d, J_{CP} = 14.1 Hz).

^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = − 24.1.

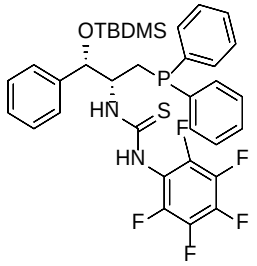
^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ/ppm = −144.6 (d, $^{3}J_{FF}$ = 24.4 Hz), −157.7 (t, $^{3}J_{FF}$ = 24.0 Hz), −164.5 (t, $^{3}J_{FF}$ = 23.4 Hz).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3032 (w), 2944 (w), 2905 (w), 2856 (w), 1515 (s), 1462 (s), 1359 (m), 1241 (m), 1136 (m), 989 (s), 948 (w), 871 (m), 777 (s), 718 (m), 676 (m), 576 (w), 477 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{28}H_{22}F_5N_2OPS^+$: 561.1183 $[M+H]^+$; found: 561.1190.

$[\alpha]_D^{20}$ = −1.7 (*c* = 0.67, $CHCl_3$).

1-((1S,2R)-1-((tert-butyldimethylsilyl)oxy)-3-(diphenylphosphanyl)-1-phenylpropan-2-yl)-3-(perfluorophenyl)thiourea (46c)



According to general procedure **GP4**, 1-((1*S*,2*R*)-3-(diphenylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-(perfluorophenyl)thiourea (**45c**) (84.1 mg, 150 µmol), DIPEA (58.0 mg, 74.0 µL, 450 µmol), TBDMS triflate (43.6 mg, 38.0 µL, 165 µmol), CH_2Cl_2 (1.2 mL) were stirred for six hours and the crude product was purified by flash column chromatography (SiO_2, cyclohexane:ethyl acetate (8:1), 2 x 14 cm) to afford the product **46c** (72.5 mg, 107 µmol, 73%) as a white solid.

$C_{34}H_{36}F_5N_2OPSSi$ (674.79 g/mol):

MP: 77-78 °C.

TLC: R_f = 0.50 (SiO_2, cyclohexane:ethyl acetate (5:1)).

^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 9.06 (s, 1H, N*H*), 7.99 (d, $^{3}J_{HH}$ = 8.1 Hz, 1H, N*H*), 7.46 – 7.18 (m, 15H, ar-*H*), 5.29 (d, $^{3}J_{HH}$ = 4.0 Hz, 1H, Ph-C*H*), 4.49-4.39 (m, 1H, NC*H*), 2.63 (dt, $^{2}J_{HP}$ = 13.7 Hz, $^{3}J_{HH}$ = 3.5 Hz, 1H, PCH_2), 1.79 (ddd, $^{2}J_{HP}$ = 14.1, $^{3}J_{HH}$ = 10.8 Hz, $^{4}J_{HH}$ = 3.6 Hz, 1H, PCH_2), 0.83 (s, 9H, SiC(CH_3)$_3$), −0.02 (s, 3H, SiCH_3), −0.16 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 182.6, 140.5, 138.5 (d, J_{CP} = 12.9 Hz), 137.8 (d, J_{CP} = 15.1 Hz), 132.6 (d, J_{CP} = 19.2 Hz), 132.1 (d, J_{CP} = 18.8 Hz), 128.8, 128.6, 128.5, 127.8, 127.3, 126.7, 73.1, 57.5 (d, J_{CP} = 15.4 Hz), 27.8 (d, J_{CP} = 13.7 Hz), 25.6, 17.7, −4.8, −5.0.

^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −25.1.

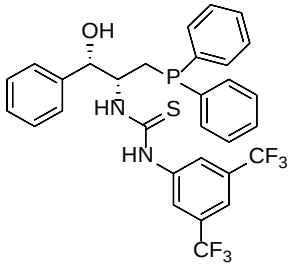
^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ/ppm = −144.55 (d, J_{FF} = 23.8 Hz), −157.41 (t, J_{FF} = 22.9 Hz), −164.35 (t, J_{FF} = 23.1 Hz).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3032 (w), 2944 (w), 2905 (w), 2856 (w), 1515 (s), 1462 (s), 1359 (m), 1241 (m), 1136 (m), 989 (s), 948 (w), 871 (m), 777 (s), 718 (m), 676 (m), 576 (w), 477 (w).

EA ($C_{34}H_{36}F_5N_2OPSSi$) calc.: C 60.52, H 5.38, N 4.15; found: C 60.46, H 5.75, N 4.46.

$[\alpha]_D^{20}$ = +4.0 (*c* = 0.23, MeOH).

1-(3,5-bis(Trifluoromethyl)phenyl)-3-((1*S*,2*R*)-3-(diphenylphosphanyl)-1-hydroxy-1-phenyl propan-2-yl)thiourea (45d)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(diphenylphosphanyl)-1-phenylpropan-1-ol (**38**) (100 mg, 298 µmol), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (91.0 mg, 61.0 µL, 328 µmol), CH_2Cl_2 (0.9 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 2.5 x 19 cm) to afford the product **45d** (158 mg, 260 µmol, 87%) as a white solid.

$C_{30}H_{25}F_6N_2OPS$ (606.57 g/mol):

MP: 78-79 °C.

TLC: R_f = 0.43 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 10.2 (s, 1H, O*H*), 8.25 (s, 2H, ar-*H*), 8.05 (d, $^{3}J_{HH}$ = 8.4 Hz, 1H, N*H*), 7.69 (s, 1H, ar-*H*), 7.56-7.52 (m, 2H, ar-*H*), 7.45-7.42 (m, 2H, ar-*H*), 7.40-7.25 (m, 10H, ar-*H*), 7.23-7.18 (m, 1H, ar-*H*), 6.10 (br s, 1H, N*H*), 5.17-5.11 (m, 1H, Ph-C*H*), 4.65-4.57 (m, 1H, NC*H*), 2.58 (dd, $^{2}J_{HP}$ = 13.6 Hz, $^{3}J_{HH}$ = 7.8 Hz, 1H, PCH_2), 2.45 (dd, $^{2}J_{HP}$ = 13.6 Hz, $^{3}J_{HH}$ = 6.9 Hz, 1H, PCH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 179.6, 142.8, 141.8, 138.8 (d, J_{CP} = 13.6 Hz), 137.7 (d, J_{CP} = 13.3 Hz), 132.9 (d, J_{CP} = 19.6 Hz), 132.2 (d, J_{CP} = 18.5 Hz), 130.2, 129.9, 128.8, 128.5 (d, J_{CP} = 4.1 Hz), 128.4 (d, J_{CP} = 3.6 Hz), 127.8, 126.9, 126.1, 124.6, 121.9, 121.1, 115.8, 71.8 (d, J_{CP} = 10.3 Hz), 57.1 (d, J_{CP} = 16.6 Hz), 30.1 (d, J_{CP} = 14.8 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, DMSO-d_6): δ/ppm = −24.1.

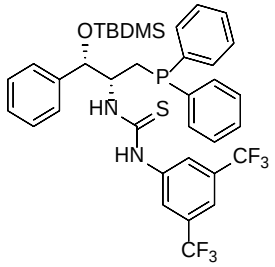
$^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6): δ/ppm = −61.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3246 (br s), 3070 (w), 3033 (w), 1521 (m), 1470 (w), 1380 (w), 1274 (s), 1171 (s), 1126 (s), 885 (w), 846 (w), 736 (s), 646 (m), 503 (m), 475 (w).

EA ($C_{30}H_{25}F_6N_2OPS$) calc.: C 59.40, H 4.50, N 4.62; found: C 59.28, H 4.62, N 4.88.

$[\alpha]_D^{20}$ = +9.3 (*c* = 1.0, $CHCl_3$).

1-(3,5-bis(Trifluoromethyl)phenyl)-3-((1*S*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-3-(diphenyl phosphanyl)-1-phenylpropan-2-yl)thiourea (46d)



According to general procedure **GP4**, 1-(3,5-bis(trifluoromethyl)phenyl-3-((1*S*,2*R*)-3-(diphenyl-phosphanyl)-1-hydroxy-1-phenylpropan-2-yl)thiourea (**45d**) (101 mg, 167 µmol), DIPEA (43.2 mg, 55.2 µL, 334 µmol), TBDMS triflate (46.4 mg, 40.3 µL, 175 µmol), CH_2Cl_2 (1.8 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (8:1), d x h: 3.5 x 19 cm) to afford the product **46d** (97.0 mg, 134 µmol, 80%) as a white solid.

$C_{36}H_{39}F_6N_2OPSSi$ (720.83 g/mol):

MP: 67-68 °C.

TLC: R_f = 0.43 (SiO_2, cyclohexane:ethyl acetate (5:1)).

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 10.08 (s, 1H, N*H*), 8.28 (s, 2H, ar-*H*), 7.84 (d, $^{3}J_{HH}$ = 8.5 Hz, 1H, ar-*H*), 7.74 (s, 1H, ar-*H*), 7.46-7.22 (m, 15H, ar-*H*), 5.22 (d, $^{3}J_{HH}$ = 3.8 Hz, 1H, Ph-C*H*), 4.70-4.57 (m, 1H, NC*H*), 2.58 (ddd, $^{2}J_{HP}$ = 13.9 Hz, $^{3}J_{HH}$ = 4.3 Hz, $^{4}J_{HH}$ = 1.9 Hz, 1H, PCH_2), 1.89 (ddd, $^{2}J_{HP}$ = 13.6 Hz, $^{3}J_{HH}$ = 10.3 Hz, $^{4}J_{HH}$ = 2.7 Hz, 1H, PCH_2), 0.84 (s, 9H, SiC(CH_3)$_3$), 0.01 (s, 3H, SiCH_3), −0.15 (s, 3H, SiCH_3).

$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6): δ/ppm = 180.2, 141.7, 140.7, 138.3 (d, J_{CP} = 13.1 Hz), 137.9 (d, J_{CP} = 14.6 Hz), 132.6, 132.4 (d, J_{CP} = 3.7 Hz), 132.2, 130.6, 130.3, 129.9, 129.6, 128.8, 128.6, 128.5 (d, J_{CP} = 3.7 Hz), 128.5 (d, J_{CP} = 3.6 Hz), 127.8, 127.3, 126.7, 124.6, 122.0 (d,

J_{CP} = 4.3 Hz), 121.9, 119.2, 116.2, 73.9 (d, J_{CP} = 8.9 Hz), 56.7 (d, J_{CP} = 15.5 Hz), 28.5 (d, J_{CP} = 13.3 Hz), 25.7, 17.8, −4.9, −4.8.

^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −25.0.

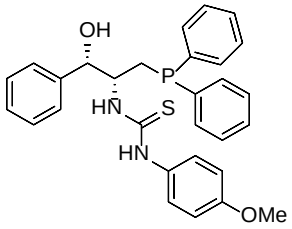
^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ/ppm = −61.5.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3376 (w), 3055 (w), 2952 (w), 2929 (w), 2856 (w), 1510 (m), 1470 (m), 1380 (s), 1173 (s), 1131 (s), 1092 (s), 1066 (m), 961 (w), 943 (w), 883 (m), 778 (m), 734 (m), 695 (s), 680 (s), 503 (m), 475 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{36}H_{39}F_6N_2OPSSi^+$: 721.2267 $[M+H]^+$; found: 721.2273.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +18.2 (*c* = 0.76, CH_2Cl_2).

1-((1*S*,2*R*)-3-(Diphenylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-(4-methoxyphenyl) thiourea (45e)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(diphenylphosphanyl)-1-phenylpropan-1-ol (**38**) (100 mg, 298 µmol), 4-methoxyphenyl isothiocyanate (54.0 mg, 45.0 µL, 328 µmol), CH_2Cl_2 (0.9 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 2.5 x 17 cm) to afford the product **45e** (136 mg, 272 µmol, 91%) as a white solid.

$C_{29}H_{29}N_2O_2PS$ (500.60 g/mol):

MP: 86-87 °C.

TLC: R_f = 0.21 (SiO_2, cyclohexane:ethyl acetate (10:3)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.45-7.39 (m, 2H, ar-*H*), 7.39-7.36 (m, 12H, ar-*H**, N*H**), 7.09-7.07 (m, 2H, ar-*H*), 6.84-6.78 (m, 4H, ar-*H*), 6.14 (br s, 1H, N*H*), 4.97 (d, $^3J_{HH}$ = 4.2 Hz,1H, Ph-C*H*), 4.81-4.71 (br m, 1H, NC*H*), 3.75 (s, 3H, OCH_3), 2.81 (br s, 1H, O*H*), 2.43 (d, $^3J_{HH}$ = 7.0 Hz, 2H, PCH_2).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ/ppm = 181.0, 159.0, 141.2, 133.1 (d, J_{CP} = 3.3 Hz), 132.9 (d, J_{CP} = 2.9 Hz), 129.2 (d, J_{CP} = 6.3 Hz), 128.8 (d, J_{CP} = 7.0 Hz), 128.5, 128.2, 127.9, 127.8, 126.2, 115.2, 75.0 (d, J_{CP} = 8.8 Hz), 58.8 (d, J_{CP} = 15.0 Hz), 55.6, 30.6 (d, J_{CP} = 13.3 Hz).

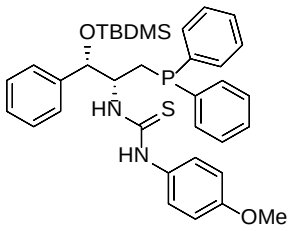
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ/ppm = −23.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3360 (w), 3235 (w), 3049 (w), 1506 (s), 1432 (w), 1297 (w), 1163 (w); 1091 (m), 1025 (m), 828 (m), 734 (s), 633 (w), 568 (w), 473 (m).

EA ($C_{29}H_{29}N_2O_2PS$) calc.: C 69.58, H 5.84, N 5.60; found: C 69.34, H 5.88, N 5.69.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −4.6 (*c* = 0.76, $CHCl_3$).

1-((1*S*,2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(diphenylphosphanyl)-1-phenylpropan-2-yl)-3-(4-methoxyphenyl)thiourea (46e)



According to general procedure **GP4**, 1-((1*S*,2*R*)-3-(diphenylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-(4-methoxyphenylthiourea (**45e**) (130 mg, 260 µmol), DIPEA (67.2 mg, 85.9 µL, 520 µmol), TBDMS triflate (75.6 mg, 65.7 µL, 290 µmol), CH_2Cl_2 (1.4 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 2 x 14 cm) to afford the product **46e** (103 mg, 0.17 mmol, 64%) as a white solid.

$C_{35}H_{43}N_2O_2PSSi$ (614.86 g/mol):

MP: 67-68 °C.

TLC: R_f = 0.47 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^1H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.68-7.63 (m, 2H, ar-*H*), 7.47-7.42 (m, 2H, ar-*H*), 7.38-7.32 (m, 6H, ar-*H*), 7.29-7.21 (m, 3H, ar-*H*), 7.06-7.04 (m, 4H, ar-*H*), 6.95-6.91 (m, 2H, ar-*H*), 6.26 (br s, 1H, N*H*), 5.27 (s, 1H, Ph-C*H*), 4.56-4.48 (m, 1H, NC*H*), 3.82 (s, 3H, OCH_3), 2.53 (ddd, $^2J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 2.3 Hz, 1H, PCH_2), 2.30 (ddd, $^2J_{HP}$ = 13.8 Hz, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, PCH_2), 0.75 (s, 9H, SiC(CH_3)$_3$), 0.05 (s, 3H, SiCH_3), −0.23 (s, 3H, SiCH_3).

$^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2): δ/ppm = 181.2, 159.8, 142.3, 139.4, 137.8, 133.9 (d, J_{CP} = 19.8 Hz), 133.3 (d, J_{CP} = 18.8 Hz), 129.6, 129.2, 129.1 (d, J_{CP} = 3.0 Hz), 129.0 (d,

J_{CP} = 2.6 Hz), 128.9, 128.4, 127.9, 126.7, 115.7, 74.2 (d, J_{CP} = 10.0 Hz), 60.0 (d, J_{CP} = 16.5 Hz), 56.0, 31.2 (d, J_{CP} = 14.6 Hz), 26.1, 18.4, −4.4.

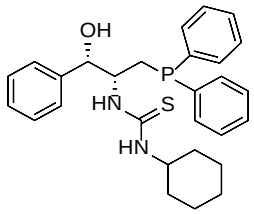
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −24.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3365 (w), 3182 (w), 3051 (w), 2927 (w), 1507 (s), 2397 (w), 1239 (s), 1164 (w), 1090 (m), 1066 (m), 1027 (m), 957 (w), 831 (s), 776 (s), 734 (s), 694 (s), 562 (w), 504 (w).

EA ($C_{35}H_{43}N_2O_2PSSi$) calc.: C 68.37, H 7.05, N 4.56; found: C 68.46, H 7.12, N 4.68.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −25.4 (*c* = 0.87, CH_2Cl_2).

1-Cyclohexyl-3-((1*S*,2*R*)-3-(diphenylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)thiourea (45f)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(diphenylphosphanyl)-1-phenylpropan-1-ol (**38**) (100 mg, 298 µmol), cyclohexyl isothiocyanate (46.0 mg, 46.5 µL, 328 µmol), CH_2Cl_2 (0.9 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 2.5 x 10 cm) to afford the product **45f** (55.0 mg, 115 µmol, 39%) as a white solid.

$C_{28}H_{33}N_2OPS$ (476.62 g/mol):

MP: 186-187 °C.

TLC: R_f = 0.36 (SiO_2, cyclohexane:ethyl acetate (5:1)).

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.56-7.31 (m, 11H, ar-*H*, N*H*), 7.27-7.24 (m, 2H, ar-*H*), 7.20-7.15 (m, 3H, ar-*H*), 5.84 (d, $^{3}J_{HH}$ = 4.1 Hz, N*H*), 5.07 (s, 1H, Ph-C*H*), 4.50 (s, 1H, NC*H*), 3.89 (br s, 1H, C*H*), 2.53-2.45 (br m, 1H, PCH_2), 2.18 (dd, $^{2}J_{HP}$ = 13.7 Hz, $^{3}J_{HH}$ = 7.3 Hz, 1H, PCH_2), 1.81-1.73 (m, 2H, cy-CH_2), 1.67-1.55 (m, 2H, cy-CH_2), 1.52-1.49 (m, 1H, cy-C*H*), 1.29-1.02 (m, 5H, cy-CH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 181.0, 142.9, 138.9 (d, J_{CP} = 14.6 Hz), 138.2 (d, J_{CP} = 13.3 Hz), 132.7 (d, J_{CP} = 19.2 Hz), 132.2 (d, J_{CP} = 18.5 Hz), 128.6, 128.5, 128.4 (d, J_{CP} = 2.4 Hz), 128.4, 127.6, 126.7, 126.3, 71.8, 56.5 (d, J_{CP} = 16.9 Hz), 51.4, 32.2, 32.2, 29.9 (d, J_{CP} = 9.2 Hz), 25.2, 24.2, 24.2.

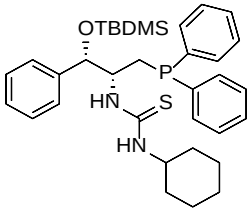
$^{31}P\{^{1}H\}$ NMR (162 MHz, DMSO-d_6): δ/ppm = −23.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3410 (w), 3308 (m), 1531 (s), 1361 (m), 1256 (m), 1176 (w), 1056 (w), 973 (w), 846 (w), 732 (s), 693 (s), 650 (m), 592 (w), 509 (m), 463 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{28}H_{33}N_2OPS^+$: 477.2124 $[M+H]^+$; found: 477.2130.

$[\alpha]_D^{20}$ = −4.7 (*c* = 0.62, DMSO).

1-((1*S*,2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(diphenylphosphanyl)-1-phenylpropan-2-yl)-3-cyclohexylthiourea (46f)



According to general procedure **GP4**, 1-cyclohexyl-3-((1S,2R)-3-(diphenylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-thiourea (**45f**) (45 mg, 94.4 µmol), DIPEA (24.4 mg, 31.2 µL, 189 µmol), TBDMS triflate (27.5 mg, 23.9 µL, 104 µmol), CH_2Cl_2 (1.0 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (8:1), d x h: 2 x 16 cm) to afford the product **46f** (38 mg, 64 µmol, 68%) as a white solid.

$C_{34}H_{47}N_2OPSSi$ (590.88 g/mol):

MP: 66-67 °C.

TLC: R_f = 0.30 (SiO_2, cyclohexane:ethyl acetate (5:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.59-7.50 (m, 2H, ar-*H*), 7.47-7.40 (m, 2H, ar-*H*), 7.37-7.19 (m, 11H, ar-*H*), 5.75 (s, 1H, Ph-C*H*), 5.26 (s, 1H, NC*H*), 4.44 (br s, 1H, N*H*), 3.31 (s, 1H, N*H*), 2.47 (dd, $^{2}J_{HP}$ = 13.7 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, PCH_2), 2.39-2.30 (m, 1H, PCH_2), 1.90-1.83 (m, 2H, cy-CH_2), 1.72-1.64 (m, 2H, cy-CH_2), 1.63-1.55 (m, 1H, cy-C*H*), 1.33-1.05 (m, 6H, cy-CH_2), 0.93 (s, 9H, SiC(CH_3)$_3$), 0.11 (s, 3H, SiCH_3), −0.10 (s, 3H, SiCH_3).

$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.7, 142.0, 138.9, 138.4, 133.6 (d, J_{CP} = 19.6 Hz), 133.4 (d, J_{CP} = 19.1 Hz), 129.5, 129.3, 129.2, 129.1, 129.1, 129.1, 128.6, 128.1, 127.0, 75.0, 59.1 (d, J_{CP} = 15.2 Hz), 53.0, 33.4, 33.3, 30.9, 26.3, 25.9, 25.3, 25.2, 18.6, −4.3.

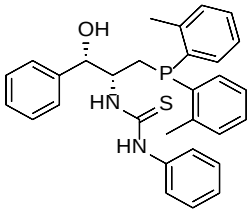
$^{31}P\{^{1}H\}$ NMR (162 MHz, CD_2Cl_2): δ/ppm = −23.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3255 (w), 3051 (w), 2926 (m), 2853 (m), 1525 (s), 1433 (w), 1360 (w), 1251 (m), 1090 (s), 1065 (s), 834 (m), 777 (s), 735 (s), 694 (s), 504 (m).

EA ($C_{34}H_{47}N_2OPSSi$) calc.: C 69.11, H 8.02, N 4.74; found: C 68.97, H 8.17, N 4.82.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −10.8 (*c* = 0.77, CH_2Cl_2)

1-((1*S*,2*R*)-3-(di-*o*-Tolylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (47a)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(di-*o*-tolylphosphanyl)-1-phenylpropan-1-ol (**40a**) (180 mg, 495 µmol), phenyl isothiocyanate (75.1 mg, 66.4 µL, 545 µmol), CH_2Cl_2 (1.4 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (4:1), d x h: 3.5 x 15 cm) to afford the product **47a** (222 mg, 445 µmol, 90%) as a white solid.

$C_{30}H_{31}N_2OPS$ (498.62 g/mol):

MP: 84-85 °C.

TLC: R_f = 0.36 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.88 (br s, 1H, N*H*), 7.44-7.09 (m, 16H, ar-*H*), 7.03 (d, $^3J_{HH}$ = 7.6 Hz, 2H, ar-*H*), 6.48 (d, $^3J_{HH}$ = 8.2 Hz, 1H, N*H*), 5.11-5.05 (br m, 1H, Ph-C*H*), 4.98-4.83 (br m, 1H, NC*H*), 3.15 (br s, 1H, O*H*), 2.47 (s, 3H, ar-CH_3), 2.43 (s, 3H, ar-CH_3), 2.42-2.34 (m, 2H, PCH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 180.4, 142.6, 142.3 (d, J_{CP} = 4.5 Hz), 142.0, 141.2, 135.9, 131.8, 131.6, 130.3 (t, J_{CP} = 4.7 Hz), 130.1, 128.9 (d, J_{CP} = 4.2 Hz), 128.5, 127.9, 127.3, 126.4 (d, J_{CP} = 4.9 Hz), 126.3, 125.3, 75.3 (d, J_{CP} = 8.2 Hz), 58.8 (d, J_{CP} = 16.9 Hz), 29.1 (d, J_{CP} = 14.4 Hz), 21.5, 21.3.

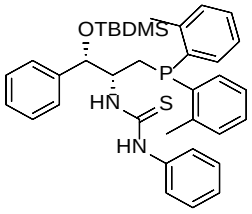
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −45.4.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3356 (w), 3256 (w), 3193 (w), 3054 (w), 1589 (w), 1518 (s), 1448 (m), 1235 (m), 1184 (m), 1050 (w), 1027 (w), 938 (w), 858 (w), 739 (s), 695 (s), 602 (w), 491 (m), 451 (s).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{30}H_{31}N_2OPS^+$: 499.1967 $[M+H]^+$; found: 499.1974.

$[\alpha]_D^{20}$ = +0.4 (*c* = 0.61, $CHCl_3$).

1-((1*S*,2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(di-*o*-tolylphosphanyl)-1-phenylpropan-2-yl)-3-phenylthiourea (48a)



According to general procedure **GP4**, 1-((1*S*,2*R*)-3-(di-*o*-tolylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (**47a**) (50.0 mg, 100 µmol), triethylamine (20.2 mg, 28.0 µL, 200 µmol), TBDMS triflate (27.8 mg, 24.0 µL, 105 µmol), CH_2Cl_2 (1.4 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (8:1), d x h: 2 x 14 cm) to afford the product **48a** (42.0 mg, 69.0 µmol, 69%) as a white solid.

$C_{36}H_{45}N_2OPSSi$ (612.89 g/mol):

MP: 73-74 °C.

TLC: R_f = 0.23 (SiO_2, cyclohexane:ethyl acetate (8:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.70 (s, 1H, N*H*), 7.39-7.06 (m, 17H, ar-*H*), 6.17 (d, $^3J_{HH}$ = 8.4 Hz, 1H, N*H*), 5.26 (s, 1H, Ph-C*H*), 4.54 (s, 1H, NC*H*), 2.46-2.41 (m, 1H, PCH_2), 2.40 (s, 6H, ar-CH_3), 2.06 (ddd, $^2J_{HP}$ = 13.9 Hz, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, PCH_2), 0.77 (s, 9H, SiC(CH_3)$_3$), 0.00 (s, 3H, SiCH_3), −0.22 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.7, 143.2 (d, J_{CP} = 16.5 Hz), 143.0 (d, J_{CP} = 16.7 Hz), 141.7, 137.2, 137.0, 136.9, 136.6, 132.6, 131.9, 130.7, 130.6 (d, J_{CP} = 5.0 Hz), 129.2 (d, J_{CP} = 4.8 Hz), 128.4, 128.0, 127.8, 127.0, 126.7 (d, J_{CP} = 4.8 Hz), 126.1, 74.3, 59.4 (d, J_{CP} = 16.8 Hz), 29.2 (d, J_{CP} = 14.5 Hz), 26.2, 21.8 (d, J_{CP} = 4.3 Hz), 21.6 (d, J_{CP} = 4.7 Hz), 18.5, −4.4, −4.5.

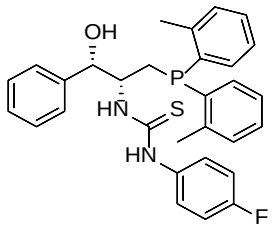
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −47.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3374 (w), 3158 (w), 2927 (w), 1516 (m), 1494 (m), 1449 (m), 1376 (w), 1247 (m), 1186 (w), 1091 (m), 1065 (m), 958 (w), 883 (w), 834 (s), 774 (m), 740 (s), 696 (s), 498 (m), 449 (m).

EA ($C_{36}H_{45}N_2OPSSi$) calc.: C 70.55, H 7.40, N 4.57; found: C 70.62, H 7.42, N 4.62.

$[\alpha]_D^{20}$ = +6.6 (*c* = 0.61, CH_2Cl_2)

1-((1*S*,2*R*)-3-(di-*o*-Tolylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (47b)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(di-*o*-tolylphosphanyl)-1-phenylpropan-1-ol (**40a**) (50.2 mg, 138 µmol), 4-fluorophenyl isothiocyanate (22.2 mg, 10.2 µL, 152 µmol), CH_2Cl_2 (0.5 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (4:1), d x h: 3.5 x 13 cm) to afford the product **47b** (69.0 mg, 134 µmol, 97%) as a white solid.

$C_{30}H_{30}FN_2OPS$ (516,62 g/mol):

MP: 81-82 °C.

TLC: R_f = 0.33 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.52 (s, 1H, N*H*), 7.40-7.38 (m, 1H, ar-*H*), 7.33-7.27 (m, 3H, ar-*H*), 7.24-7.08 (m, 9H, ar-*H*), 7.06 (m, 2H, ar-*H*), 6.96-6.91 (m, 2H, ar-*H*), 6.23 (d, $^3J_{HH}$ = 8.2 Hz, 1H, N*H*), 6.10-6.03 (br m, 1H, Ph-C*H*), 4.87 (br s, 1H, NC*H*), 2.95 (br s, 1H, O*H*), 2.44 (s, 3H, ar-CH_3), 2.43-2.33 (m, 5H, ar-CH_3^*, PCH_2^*).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 180.9, 160.3, 142.6, 142.3, 142.1, 141.1, 135.6 (d, J_{CP} = 6.0 Hz), 135.5 (d, J_{CP} = 6.1 Hz), 131.8, 131.6, 130.4 (d, J_{CP} = 2.5 Hz), 130.3 (d, J_{CP} = 2.0 Hz), 129.0 (d, J_{CP} = 4.9 Hz), 128.6, 128.0, 127.9, 126.4 (d, J_{CP} = 5.8 Hz), 126.2, 117.0 (d, J_{CP} = 22.7 Hz), 75.1, 58.9 (d, J_{CP} = 16.6 Hz), 29.2 (d, J_{CP} = 14.8 Hz), 21.6 (d, J_{CP} = 2.0 Hz), 21.3 (d, J_{CP} = 1.1 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −45.7.

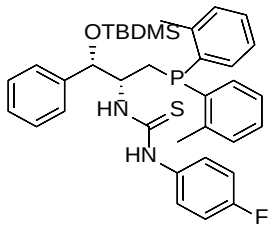
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ/ppm = −113.1.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3356 (w), 3222 (w), 3055 (w), 1504 (s), 1449 (w), 1334 (w), 1215 (s), 1152 (m), 1089 (w), 1052 (w), 1028 (w), 832 (m), 744 (s), 699 (s), 634 (m), 504 (m), 454 (s).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{30}H_{30}FN_2OPS^+$: 517.1873 $[M+H]^+$; found: 517.1880.

$[\alpha]_D^{20}$ = −0.9 (*c* = 0.34, $CHCl_3$).

1-((1S,2R)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(di-*o*-tolylphosphanyl)-1-phenylpropan-2-yl)-3-(4-fluorophenyl)thiourea (48b)



According to general procedure **GP4**, 1-((1*S*,2*R*)-3-(di-*o*-tolylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (**47b**) (70.0 mg, 135 µmol), DIPEA (52.5 mg, 67.0 µL, 406 µmol), TBDMS triflate (43.0 mg, 37.0 µL, 163 µmol), CH_2Cl_2 (1.4 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 3.5 x 17 cm) to afford the product **48b** (61.3 mg, 97 µmol, 72%) as a white solid.

$C_{36}H_{44}FN_2OPSSi$ (630.88 g/mol):

MP: 84-85 °C.

TLC: R_f = 0.36 (SiO_2, cyclohexane:ethyl acetate (5:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.67 (s, 1H, N*H*), 7.40-7.04 (m, 17H, ar-*H*), 6.02 (s, 1H, N*H*), 5.28 (s, 1H, Ph-C*H*), 4.56 (s, 1H, NC*H*), 2.49-2.38 (m, 7H, ar-CH_3, PCH_2), 2.17-2.08 (m, 1H, PCH_2), 0.80 (s, 9H, SiC(CH_3)$_3$), 0.04 (s, 3H, SiCH_3), −0.19 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): 181.0, 163.4, 160.9, 143.2 (d, J_{CP} = 9.4 Hz), 143.0 (d, J_{CP} = 9.8 Hz), 141.7, 137.2, 136.9 (d, J_{CP} = 13.4 Hz), 132.6, 131.9, 130.8 (d, J_{CP} = 5.0 Hz), 130.6 (d, J_{CP} = 5.2 Hz), 129.2 (d, J_{CP} = 5.1 Hz), 128.9 (d, J_{CP} = 8.5 Hz), 128.4, 128.0, 127.0, 126.7 (d, J_{CP} = 3.4 Hz), 117.4 (d, J_{CP} = 22.9 Hz), 74.3, 59.4 (d, J_{CP} = 17.0 Hz), 29.3 (d, J_{CP} = 14.7 Hz), 26.1, 21.8 (d, J_{CP} = 4.5 Hz), 21.6 (d, J_{CP} = 5.0 Hz), 18.4, −4.4, −4.5.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −47.4.

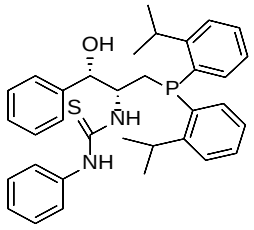
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ/ppm = −14.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3691 (m), 1506 (s), 1433 (m), 1335 (m), 1243 (m), 987 (s), 737 (m), 693 (s), 503 (w), 475 (w).

EA ($C_{36}H_{44}FN_2OPSSi$) calc.: C 68.54, H 7.03, N 4.44; found: C 68.46, H 7.32, N 4.37.

$[\alpha]_D^{20}$ = +13.1 (*c* = 0.49, CH_2Cl_2).

1-((1*S*,2*R*)-3-(bis(2-Isopropylphenyl)phosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (47c)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(bis(2-isopropylphenyl)phosphanyl)-1-phenylpropan-1-ol (**40b**) (80.0 mg, 191 µmol), phenyl isothiocyanate (28.9 mg, 25.6 µL, 210 µmol), CH_2Cl_2 (0.6 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (4:1), d x h: 2.5 x 11 cm) to afford the product **47c** (138 mg, 195 µmol, 85%) as a white solid.

$C_{34}H_{39}N_2OPS$ (554,73):

MP: 87-88 °C.

TLC: R_f = 0.43 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.49-7.39 (m, 2H, ar-*H**, N*H**), 7.30-7.13 (m, 13H, ar-*H*), 7.12-7.08 (m, 1H, ar-*H*), 7.05-7.01 (m, 1H, ar-*H*), 6.85 (d, $^3J_{HH}$ = 7.5 Hz, 2H, ar-*H*), 6.36 (br s, 1H, N*H*), 5.07 (s, 1H, Ph-C*H*), 4.92-4.79 (br m, 1H, NC*H*), 3.79-3.57 (m, 2H, ar-C*H*$(CH_3)_2$), 2.83 (br s, 1H, O*H*), 2.44-2.29 (m, 2H, PCH_2), 1.16 (d, $^3J_{HH}$ = 6.8 Hz, 6H, CH(CH_3)$_2$), 0.93 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(CH_3)$_2$)), 0.90 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(CH_3)$_2$).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 180.4, 153.1, 152.9, 152.9, 152.7, 141.2, 135.9, 134.8, 132.4, 132.2, 130.1, 129.5, 128.5, 127.9, 127.3, 126.3 (d, J_{CP} = 13.6 Hz), 126.2 (d, J_{CP} = 2.6 Hz), 125.8, 125.4, 74.8 (d, J_{CP} = 9.0 Hz), 58.9 (d, J_{CP} = 16.2 Hz), 31.5 (d, J_{CP} = 6.6 Hz), 31.2 (d, J_{CP} = 7.3 Hz), 30.5, 24.5, 24.4, 23.9, 23.8.

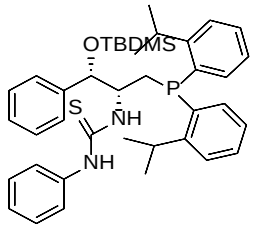
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −50.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3370 (w), 3274 (w), 3048 (w), 1589 (m), 1519 (s), 1495 (s), 1470 (m), 1380 (w), 1316 (s), 1295 (w), 1232 (m), 1054 (w), 1026 (w), 939 (w), 870 (w), 832 (w), 735 (s), 695 (s), 604 (w), 507 (m).

EA ($C_{34}H_{39}N_2OPS$) calc.: C 73.62, H 7.09, N 5.05; found: C 73.68, H 6.93, N 5.29.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +17.1 (*c* = 0.72, $CHCl_3$).

1-((1*S*,2*R*)-3-(bis(2-Isopropylphenyl)phosphanyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-3-phenylthiourea (48c)



According to general procedure **GP4**, 1-((1S,2R)-3-(bis(2-isopropylphenyl)phosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (**47c**) (73.6 mg, 133 µmol), DIPEA (52.3 mg, 66.8 µL, 404 µmol), TBDMS triflate (38.4 mg, 33.0 µL, 145 µmol), CH_2Cl_2 (1.5 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1), d x h: 2 x 13 cm) to afford the product **48c** (81 mg, 121 µmol, 91%) as a white solid.

$C_{40}H_{53}N_2OPSSi$ (668.99 g/mol):

MP: 78-79 °C.

TLC: R_f = 0.57 (SiO_2, cyclohexane:ethyl acetate (5:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.71 (s, 1H, N*H*), 7.46-7.05 (m, 16H, ar-*H*), 6.28 (d, $^3J_{HH}$ = 8.4 Hz, 1H, N*H*), 5.34 (s, 1H, Ph-C*H*), 4.60 (s, 1H, NC*H*), 3.87-3.71 (m, 2H, ar-C*H*$(CH_3)_2$), 2.46 (ddd, $^2J_{HP}$ = 14.0 Hz, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 2.3 Hz, 1H, PCH_2), 2.05 (ddd, $^2J_{HP}$ = 14.0 Hz, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, PCH_2), 1.28 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(CH_3)$_2$), 1.18 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH(CH_3)$_2$), 1.06 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH(CH_3)$_2$), 0.95 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(CH_3)$_2$), 0.80 (s, 9H, SiC(CH_3)$_3$), 0.04 (s, 3H, SiCH_3), −0.19 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): 180.5, 153.6 (d, J_{CP} = 6.9 Hz), 153.4 (d, J_{CP} = 7.5 Hz), 141.7, 136.4, 135.8 (d, J_{CP} = 12.5 Hz), 133.1, 132.0, 130.5, 129.4 (d, J_{CP} = 9.2 Hz), 128.2, 127.8, 127.7, 126.8, 126.4 (d, J_{CP} = 5.6 Hz), 126.0, 126.0, 125.8 (d, J_{CP} = 5.0 Hz), 74.1, 59.2 (d, J_{CP} = 17.0 Hz), 31.5 (d, J_{CP} = 6.7 Hz), 31.3 (d, $^3J_{CP}$ = 7.8 Hz), 30.5 (d, J_{CP} = 16.3 Hz), 26.0, 24.5, 24.4, 24.1, 23.9, 18.3, −4.5, −4.7.

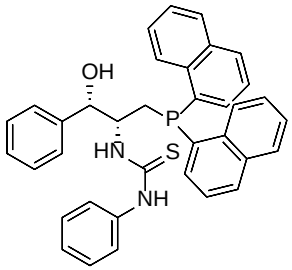
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −52.2.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3372 (w), 3163 (w), 3052 (w), 2955 (m), 2856 (w), 1589 (w), 1496 (s), 1470 (s), 1249 (m), 1091 (s), 1065 (s), 833 (s), 734 (s), 696 (s), 506 (m), 485 (m).

EA ($C_{40}H_{53}N_2OPSSi$) calc.: C 71.82, H 7.99, N 4.19; found: C 71.62, H 8.05, N 4.21.

$[\alpha]_D^{20}$ = +1.4 (*c* = 0.85, CH_2Cl_2).

1-((1S,2R)-3-(di(naphthalen-1-yl)phosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenyl-thiourea (47d)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(di(naphthalen-1-yl phosphanyl)-1-phenylpropan-1-ol (**40c**) (210 mg, 482 µmol), phenyl isothiocyanate (69.8 mg, 61.8 µL, 506 µmol), CH_2Cl_2 (1.5 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (3:1), d x h: 2.5 x 12 cm) to afford the product **47d** (215 mg, 377 µmol, 78%) as a white solid.

$C_{36}H_{31}N_2OPS$ (570.69 g/mol):

MP: 197-198 °C.

TLC: R_f = 0.40 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.70 (br s, 1H, O*H*), 8.65-8.58 (m, 1H, ar-*H*), 8.57-8.52 (m, 1H, ar-*H*), 8.02-7.90 (m, 4H, ar-*H*), 7.85-7.78 (m, 1H, N*H*), 7.65-7.44 (m, 8H, ar-*H*), 7.42-7.35 (m, 2H, ar-*H*), 7.33-7.15 (m, 7H, ar-*H*), 7.03 (t, $^3J_{HH}$ = 7.3 Hz, 1H, ar-*H*), 6.16 (d, $^3J_{HH}$ = 3.7 Hz, 1H, N*H*), 5.28 (s, 1H, Ph-C*H*), 4.78-4.71 (m, 1H, NC*H*), 2.72-2.67 (m, 1H, PCH_2), 2.57-2.53 (m, 1H, PCH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 179.7, 143.0, 139.1, 135.1, 135.0 (d, J_{CP} = 3.8 Hz), 134.8, 134.6, 134.4, 134.2, 133.2 (t, J_{CP} = 4.1 Hz), 131.2, 130.2, 129.4, 129.1, 128.8 (d, J_{CP} = 6.0 Hz), 128.5, 127.8, 126.9, 126.5-126.2 (m), 126.0 (d, J_{CP} = 6.4 Hz), 125.8, 125.4 (d, J_{CP} = 3.7 Hz), 125.2 (d, J_{CP} = 4.9 Hz), 124.1, 122.6, 71.6 (d, J_{CP} = 10.7 Hz), 57.0 (d, J_{CP} = 17.6 Hz), 29.5 (d, J_{CP} = 14.6 Hz).

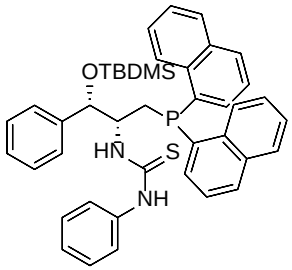
^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ/ppm = −47.0.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3405 (m), 3351 (m), 3257 (w), 1519 (s), 1495 (s), 1452 (m), 1377 (m), 1232 (m), 1094 (m), 1022 (m), 925 (w), 797 (s), 772 (s), 741 (s), 691 (m), 642 (m), 609 (w), 507 (m), 437 (s).

EA ($C_{36}H_{31}N_2OPS$) calc.: C 75.77, H 5.48, N 4.91; found: C 75.57, H 5.67, N 5.01.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +37.3 (*c* = 0.91, DMSO).

1-((1S,2R)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(di(naphthalen-1-yl)phosphanyl)-1-phenyl propan-2-yl)-3-phenylthiourea (48d)



According to general procedure **GP4**, 1-((1*S*,2*R*)-3-(di(naphthalen-1-yl)phosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (**47d**) (184 mg, 322 µmol), DIPEA (125 mg, 160 µL, 966 µmol), TBDMS triflate (93.6 mg, 81.5 µL, 354 µmol), CH_2Cl_2 (3.3 mL) were stirred for six hours and the crude product was purified by flash column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 3.5 x 12 cm) to afford the product **48d** (102 mg, 148 µmol, 46%) as a white solid.

$C_{42}H_{45}N_2OPSSi$ (684.95 g/mol):

MP: 94-95 °C.

TLC: R_f = 0.55 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (500 MHz, CD_2Cl_2): δ/ppm = 8.79-8.69 (m, 1H, ar-*H*), 8.65-8.58 (m, 1H, ar-*H*), 7.93-7.76 (m, 5H, ar-*H**, N*H**), 7.69-7.60 (m, 2H, ar-*H*), 7.55-7.36 (m, 8H, ar-*H*), 7.31 (t, $^3J_{HH}$ = 7.5 Hz, 1H, ar-*H*), 7.23-7.17 (m, 3H, ar-*H*), 7.14-7.10 (m, 2H, ar-*H*), 7.03-6.96 (m, 2H, ar-*H*), 6.42 (d, $^3J_{HH}$ = 8.4 Hz, 1H, N*H*), 5.35 (s, 1H, Ph-C*H*), 4.66 (s, 1H, NC*H*), 2.64-2.51 (m, 2H, PCH_2), 0.76 (s, 9H, SiC(CH_3)$_3$), 0.05 (s, 3H, SiCH_3), −0.20 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.7, 142.0, 136.5, 136.3, 136.1, 135.9, 135.8, 135.7, 135.1 (d, J_{CP} = 14.5 Hz), 134.3 (d, J_{CP} = 1.7 Hz), 134.2 (d, J_{CP} = 2.0 Hz), 132.3, 131.0, 130.7, 123.0 (d, J = 11.7 Hz), 129.3 (d, J_{CP} = 9.2 Hz), 128.4, 128.0, 126.9 (d, J_{CP} = 2.5 Hz), 126.8 (d, J_{CP} = 1.9 Hz), 126.6, 126.5 (d, J_{CP} = 1.4 Hz), 126.5 (d, J_{CP} = 1.5 Hz), 126.4, 126.3, 126.2 (d, J_{CP} = 1.5 Hz), 126.0, 74.5, 59.9 (d, J_{CP} = 17.0 Hz), 30.4 (d, J_{CP} = 15.5 Hz), 26.2, 18.5, −4.3, −4.4.

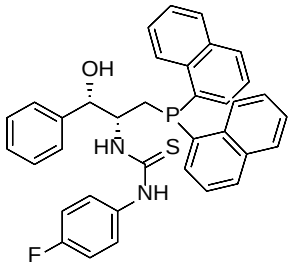
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −50.1.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3369 (w), 3169 (w), 3052 (w), 2950 (w), 2925 (w), 2853 (w), 1590 (s), 1495 (m), 1379 (w), 1316 (w), 1249 (m), 1185 (w), 1090 (m), 1065 (m), 833 (m), 771 (s), 695 (m), 498 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{42}H_{45}N_2OPSSi^+$: 685.2832 $[M+H]^+$; found: 685.2832.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +12.6 (*c* = 0.62, CH_2Cl_2).

1-((1*S*,2*R*)-3-(Di(naphthalen-1-yl)phosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-(4-fluorophenyl)thiourea (47e)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(di(naphthalen-1-yl phosphanyl)-1-phenylpropan-1-ol (**40c**) (145 mg, 333 µmol), 4-fluorophenyl isothiocyanate (54.7 mg, 350 µmol), CH_2Cl_2 (1 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (4:1), d x h: 3.5 x 13 cm) to afford the product **47e** (153 mg, 260 µmol, 78%) as a white solid.

$C_{36}H_{30}FN_2OPS$ (588,68):

MP: 141-142 °C.

TLC: R_f = 0.35 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm = 8.55-8.50 (m, 1H, ar-*H*), 8.41 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 4.4 Hz, 1H, ar-*H*), 7.77-7.74 (m, 3H, ar-*H*), 7.72-7.65 (m, 3H, ar-*H*), 7.40-7.31 (m, 5H, ar-*H*), 7.27-7.20 (m, 2H, ar-*H*), 7.17-7.12 (m, 3H, ar-*H*), 7.06-7.03 (m, 2H, ar-*H*), 6.84-6.80 (m, 2H, ar-*H*), 6.76-6.72 (m, 2H, ar-*H*), 6.29 (br s, 1H, N*H*), 5.14 (br s, 1H, Ph-C*H*), 4.88 (br s, 1H, NC*H*), 3.12 (br s, 1H, O*H*), 2.61-2.51 (m, 2H, PCH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 180.8, 162.6, 160.2, 141.2, 135.4 (d, J_{CP} = 4.3 Hz), 135.2 (d, J_{CP} = 4.5 Hz), 133.7 (d, J_{CP} = 4.9 Hz), 131.7, 131.5, 131.1, 129.9 (d, J_{CP} = 9.0 Hz), 129.0, 128.5, 128.00, 127.8 (d, J_{CP} = 8.5 Hz), 126.6 (d, J_{CP} = 5.4 Hz), 126.2, 126.1, 126.0 (d, J_{CP} = 1.9 Hz), 125.9, 125.8, 125.6 (d, J_{CP} = 5.0 Hz), 116.8 (d, J_{CP} = 22.9 Hz), 74.7 (d, J_{CP} = 10.1 Hz), 58.9 (d, J_{CP} = 16.0 Hz), 29.4 (d, J_{CP} = 13.4 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −46.9.

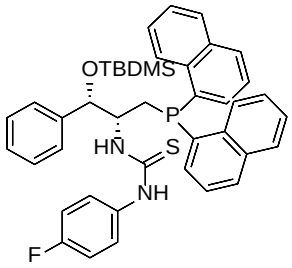
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ/ppm = −113.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3398 (w), 3355 (m), 3261 (w), 3043 (w), 1508 (s), 1478 (s), 1373 (w), 1218 (m), 1089 (w), 1020 (m), 826 (w), 796 (s), 771 (s), 739 (s), 698 (m), 640 (w), 537 (w), 486 (w), 439 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{30}H_{30}FNOPS^+$: 589.1873 $[M+H]^+$; found: 589.1883.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +12.4 (*c* = 0.92, $CHCl_3$).

1-((1*S*,2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(di(naphthalen-1-yl)phosphanyl)-1-phenyl propan-2-yl)-3-(4-fluorophenyl)thiourea (48e)



According to general procedure **GP4**, 1-((1*S*,2*R*)-3-(di(naphthalen-1-yl)phosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-(4-fluorophenyl)thiourea (**47e**) (108 mg, 183 µmol), triethylamine (37.0 mg, 51.0 µL, 366 µmol), TBDMS triflate (50.8 mg, 44.0 µL, 192 µmol), CH_2Cl_2 (1.8 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1), d x h: 2 x 12 cm) to afford the product **48e** (98 mg, 139 µmol, 76%) as a white solid.

$C_{42}H_{44}FN_2OPSSi$ (702.94 g/mol):

MP: 108-109 °C.

TLC: R_f = 0.51 (SiO_2, cyclohexane:ethyl acetate (4:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 8.76-8.68 (m, 1H, ar-*H*), 8.64-8.57 (m, 1H, ar-*H*), 7.92-7.84 (m, 4H, ar-*H,* N*H*), 7.68-7.60 (m, 1H, ar-*H*), 7.55-7.37 (m, 7H, ar-*H*), 7.25-7.20 (m, 3H, ar-*H*), 7.08 (d, $^3J_{HH}$ = 6.6 Hz, 4H, ar-*H*), 7.03-6.99 (m, 2H, ar-*H*), 6.28 (s, 1H, N*H*), 5.45 (s, 1H, Ph-C*H*), 4.65 (s, 1H, NC*H*), 2.59 (d, $^3J_{HH}$ = 7.5 Hz, 2H, PCH_2), 0.78 (s, 9H, SiC(CH_3)$_3$), 0.07 (s, 3H, SiCH_3), −0.19 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 181.1, 163.4, 160.9, 141.9, 136.2 (d, J_{CP} = 23.5 Hz), 135.7 (d, J_{CP} = 22.4 Hz), 134.2 (d, J_{CP} = 4.7 Hz), 132.5, 132.3, 131.1, 130.2, 130.1, 129.4 (d, J_{CP} = 9.2 Hz), 129.0 (d, J_{CP} = 8.4 Hz), 128.4, 128.0, 126.9 (d, J_{CP} = 4.7 Hz), 126.8, 126.6, 126.3, 126.2, 126.0, 117.4 (d, J_{CP} = 22.8 Hz), 74.4, 59.8 (d, J_{CP} = 16.8 Hz), 30.3, 26.1, 18.4, −4.3, −4.4.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −50.1.

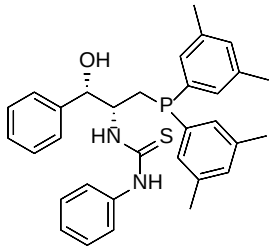
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ/ppm = −114.1.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3366 (w), 3055 (w), 2950 (w), 2927 (w), 2854 (w), 1503 (s), 1251 (w), 1214 (m), 1098 (m), 1065 (m), 958 (w), 833 (m), 795 (m), 771 (s), 700 (w), 508 (w), 422 (w).

EA ($C_{42}H_{44}FN_2OPSSi$) calc.: C 71.76, H 6.31, N 3.99; found: C 71.58, H 6.59, N 4.02.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +12.4 (*c* = 0.92, $CHCl_3$).

1-((1*S*,2*R*)-3-(bis(3,5-Dimethylphenyl)phosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (47g)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(bis(3,5-dimethylphenyl)phosphanyl)-1-phenylpropan-1-ol (**40f**) (152 mg, 388 µmol), phenyl isothiocyanate (58.9 mg, 52.0 µL, 427 µmol), CH_2Cl_2 (1.5 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 2.5 x 16 cm) to afford the product **47g** (195 mg, 370 µmol, 95%) as a white solid.

$C_{32}H_{35}N_2OPS$ (526,68 g/mol):

MP: 86-87 °C.

TLC: R_f = 0.43 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.86-7.51 (br m, 1H, N*H*), 7.31-7.15 (m, 6H, ar-*H*), 7.11-7.04 (m, 4H, ar-*H*), 6.95 (d, $^3J_{HH}$ = 8.3 Hz, 2H, ar-*H*), 6.88 (d, $^3J_{HH}$ = 8.6 Hz, 4H, ar-*H*), 6.41 (br s, 1H, N*H*), 5.03-4.97 (m, 1H, Ph-C*H*), 4.84-4.69 (m, 1H, NC*H*), 3.13-2.84 (br m, 1H, O*H*), 2.48-2.34 (m, 2H, PCH_2), 2.21 (s, 6H, ar-CH_3), 2.19 (s, 6H, ar-CH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 180.4, 141.3, 138.2 (d, J_{CP} = 3.4 Hz), 138.1 (d, J_{CP} = 3.4 Hz), 136.0, 131.0 (d, J_{CP} = 6.1 Hz), 130.7, 130.7, 130.6, 130.5, 130.0, 128.5, 127.8, 127.2, 126.2, 125.2, 74.9 (d, $^3J_{CP}$ = 8.7 Hz), 59.1 (d, $^2J_{CP}$ = 14.4 Hz), 30.5 (d, $^1J_{CP}$ = 13.7 Hz), 21.5, 21.4.

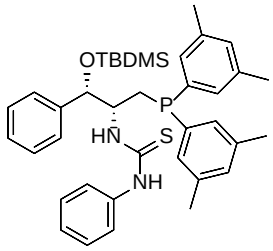
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −24.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3360 (w), 3022 (w), 1596 (m), 1517 (s), 1494 (s), 1448 (m), 1375 (w), 1296 (w), 1235 (w), 1184 (m), 1028 (w), 935 (w), 842 (s), 737 (s), 692 (s), 603 (w), 493 (w).

EA ($C_{32}H_{35}N_2OPS$) calc.: C 72.98, H 6.70, N 5.32; found: C 72.70, H 6.72, N 5.36.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −0.3 (*c* = 0.78, $CHCl_3$).

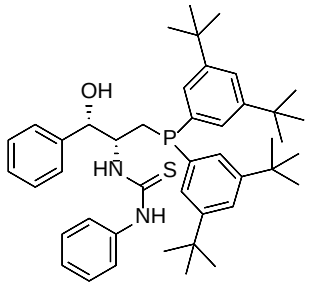
1-((1*S*,2*R*)-3-(bis(3,5-Dimethylphenyl)phosphanyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-3-phenylthiourea (48g)



According to general procedure **GP4**, 1-((1*S*,2*R*)-3-(bis(3,5-dimethylphenyl)phosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (**47g**) (100 mg, 190 µmol), DIPEA (74.8 mg, 95.5 µL, 579 µmol), TBDMS triflate (55.0 mg, 47.5 µL, 208 µmol), CH_2Cl_2 (2.0 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1), d x h: 2 x 13 cm) to afford the product **48g** (107 mg, 167 µmol, 88%) as a white solid.

$C_{38}H_{49}N_2OPSSi$ (640.94 g/mol):
MP: 66-67 °C.
TLC: R_f = 0.38 (SiO_2, cyclohexane:ethyl acetate (5:1)).
^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 8.03 (br s, 1H, N*H*), 7.42 (t, $^3J_{HH}$ = 7.7 Hz, 2H, ar-*H*), 7.35-7.19 (m, 6H, ar-*H*), 7.17-6.95 (m, 8H, ar-*H*), 6.56 (br s, 1H, N*H*); 5.31 (s, 1H, Ph-C*H*), 4.52 (s, 1H, NC*H*), 2.66-2.57 (m, 1H, PCH_2), 2.40-2.20 (m, 13H, CH_2, ar-CH_3), 0.79 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 3H, SiCH_3), −0.20 (s, 3H, SiCH_3).
^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.1, 142.2, 138.5, 138.4, 138.3, 136.6, 131.5, 131.3, 130.7, 130.5, 130.4, 128.2, 127.7, 127.6, 126.5, 126.0, 74.1 (d, J_{CP} = 12.0 Hz), 60.0 (d, J_{CP} = 18.0 Hz), 30.7, 26.0, 21.4, 18.3, −4.5.
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −25.4.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3370 (w), 3167 (w), 2927 (m), 2855 (m), 1597 (m), 1513 (s), 1469 (m), 1377 (w), 1314 (w), 1250 (s), 1187 (w), 1093 (s), 1037 (w), 961 (m), 837 (s), 778 (s), 739 (s), 694 (s).
EA ($C_{38}H_{49}N_2OPSSi$) calc.: C 71.21, H 7.71, N 4.37; found: C 70.86, H 7.66, N 4.43.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +63.3 (*c* = 1.00, CH_2Cl_2).

1-((1*S*,2*R*)-3-(bis(3,5-di-*tert*-Butylphenyl)phosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (47h)



According to general procedure **GP1**, (1*S*,2*R*)-2-amino-3-(bis(3,5-di-*tert*-butylphenyl)-phosphanyl)-1-phenylpropan-1-ol (**40d**) (100 mg, 179 µmol), phenyl isothiocyanate (24.7 mg, 22.0 µL, 179 µmol), CH_2Cl_2 (0.6 mL) were stirred for 16 hours and the crude was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 2.5 x 13 cm) to afford the product **47h** (81.0 mg, 117 µmol, 65%) as a white solid.

$C_{44}H_{59}N_2OPS$ (695.00 g/mol):

MP: 95-96 °C.

TLC: R_f = 0.33 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.70-7-65 (br m, 1H, N*H*), 7.46-7.40 (m, 2H, ar-*H*), 7.39-7.22 (m, 12H, ar-*H*), 7.19-7.11 (m, 2H, ar-H), 6.97 (d, $^3J_{HH}$ = 7.7 Hz, 1H, ar-*H*), 6.51 (d, $^3J_{HH}$ = 8.1 Hz, 1H, N*H*), 5.16-5.12 (br m, 1H, Ph-C*H*), 4.94-4.83 (br m, 1H, NC*H*), 2.93 (br s, 1H, O*H*), 2.62 (dd, $^2J_{HP}$ = 14.1 Hz, $^3J_{HH}$ = 6.5 Hz, 1H, PCH_2), 2.53 (dd, $^2J_{HP}$ = 14.1 Hz, $^3J_{HH}$ = 7.7 Hz, 1H, PCH_2), 1.32 (s, 18H, ar-C(CH_3)$_3$), 1.31 (s, 18H, ar-C(CH_3)$_3$).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 180.4, 151.0 (d, J_{CP} = 3.2 Hz), 150.9 (d, J_{CP} = 3.0 Hz), 141.3, 136.5 (d, J_{CP} = 9.9 Hz), 136.0 (d, J_{CP} = 5.0 Hz), 135.9, 130.1, 128.5, 127.8, 127.6, 127.4, 127.2, 127.0, 126.1, 125.3, 123.3 (d, J_{CP} = 8.8 Hz), 74.8 (d, J_{CP} = 9.5 Hz), 59.4 (d, J_{CP} = 14.7 Hz), 35.1, 31.6, 31.3 (d, J_{CP} = 15.7 Hz).

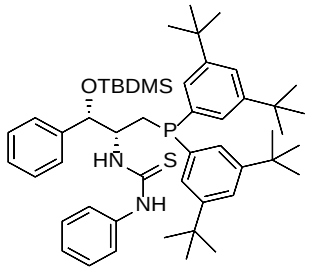
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −21.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3362 (w), 3021 (w), 1599 (m), 1527 (s), 1496 (s), 1446 (m), 1296 (w), 1233 (w), 1184 (m), 938 (w), 842 (s), 737 (s), 692 (s), 493 (w).

EA ($C_{44}H_{59}N_2OPS$) calc.: C 76.04, H 8.56, N 4.03; found: C 76.01, H 8.49, N 3.95.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −7.3 (*c* = 0.92, $CHCl_3$).

1-((1*S*,2*R*)-3-(bis(3,5-di-*tert*-Butylphenyl)phosphanyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-3-phenylthiourea (48h)



According to general procedure **GP4**, 1-((1*S*,2*R*)-3-(bis(3,5-di-*tert*-butylphenyl)phosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (**47h**) (53.0 mg, 76.3 µmol), triethylamine (15.4 mg, 21.5 µL, 153 µmol), TBDMS triflate (21.2 mg, 18.5 µL, 80.1 µmol), CH_2Cl_2 (0.9 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1), d x h: 2 x 13 cm) to afford the product **48h** (50.0 mg, 62.0 µmol, 81%) as a white solid.

$C_{50}H_{73}N_2OPSSi$ (809.27 g/mol):

MP: 86-87 °C.

TLC: R_f = 0.49 (SiO_2, cyclohexane:ethyl acetate (5:1)).

^{1}H NMR (500 MHz, CD_2Cl_2): δ/ppm = 7.62 (br s, 1H, N*H*), 7.52 (d, $^3J_{HH}$ = 8.4 Hz, 2H, ar-*H*), 7.48 (s, 1H, ar-*H*), 7.44-7.36 (m, 3H, ar-*H*), 7.34-7.19 (m, 6H, ar-*H*), 7.10-6.98 (m, 4H, ar-*H*), 6.46 (d, $^3J_{HH}$ = 8.6 Hz, 1H, N*H*), 5.29 (s, 1H, Ph-C*H*), 4.68-4.54 (m, 1H, NC*H*), 2.74-2.63 (m, 1H, PCH_2), 2.36-2.23 (m, 1H, PCH_2), 1.32 (s, 18H, ar-C(CH_3)$_3$), 1.29 (s, 18H, ar-C(CH_3)$_3$), 0.76 (s, 9H, SiC(CH_3)$_3$), 0.07 (s, 3H, SiCH_3), −0.21 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.5, 151.4 (d, J_{CP} = 7.5 Hz), 151.2 (d, J_{CP} = 6.8 Hz), 142.5, 136.7, 136.4, 130.7, 128.7, 128.4, 128.4, 127.9, 127.8, 127.4, 127.2, 126.7, 126.2, 124.1, 123.2, 74.7 (d, J_{CP} = 8.6 Hz), 60.6 (d, J_{CP} = 17.0 Hz), 35.5 (d, J_{CP} = 4.9 Hz), 31.8, 31.8, 26.2, 18.5, −4.3.

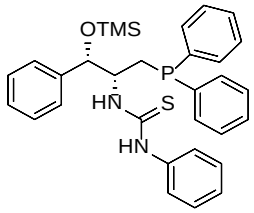
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −22.0.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3375 (w), 3183 (w), 2952 (s), 1588 (m), 1496 (s), 1361 (m), 1247 (s), 1093 (m), 1067 (m), 958 (w), 833 (s), 777 (s), 737 (m), 696 (s), 502 (w), 423 (w).

EA ($C_{50}H_{73}N_2OPSSi$) calc.: C 74.21, H 9.09, N 3.46; found: C 74.10, H 9.18, N 3.51.

$[\alpha]_D^{20}$ = +53.4 (*c* = 0.64, CH_2Cl_2).

1-((1*S*,2*R*)-3-(Diphenylphosphanyl)-1-phenyl-1-((trimethylsilyl)oxy)propan-2-yl)-3-phenylthiourea (49a)



According to general procedure **GP4**, 1-((1S,2R)-3-(diphenylphosphanyl)-1-hydroxy-1-phenyl-propan-2-yl)-3-phenylthiourea (**45a**) (30.0 mg, 63.8 µmol), DIPEA (24.7 mg, 31.6 µL, 191 µmol), TMS triflate (28.3 mg, 23.1 µL, 128 µmol), CH_2Cl_2 (0.5 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (100:0 to 10:1), d x h: 2 x 17 cm) to afford the product **49a** (28.0 mg, 52 µmol, 81%) as a white solid.

$C_{31}H_{35}N_2OPSSi$ (584.83 g/mol):

MP: 56.57 °C.

TLC: R_f = 0.10 (SiO_2, cyclohexane:ethyl acetate (10:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.63 (br s, 2H, ar-*H*), 7.54 (br s, 1H, N*H*), 7.47-7.42 (m, 2H, ar-*H*), 7.38-7.32 (m, 6H, ar-*H*), 7.30-7.23 (m, 3H, ar-*H*), 7.14-7.04 (m, 7H, ar-*H*), 6.36 (s, 1H, N*H*), 5.30 (s, 1H, Ph-C*H*), 4.53 (s, 1H, NC*H*), 2.56-2.47 (m, 1H, PCH_2), 2.37-2.29 (m, 1H, PCH_2), 0.01 (s, 9H, Si(CH_3)$_3$).

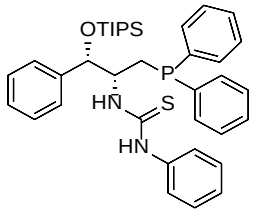
^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.8, 142.2, 137.9, 133.8 (d, J_{CP} = 19.6 Hz), 133.3 (d, J_{CP} = 18.8 Hz), 132.6, 129.6, 129.2, 129.1, 129.0, 128.9, 128.5, 128.0, 126.6, 126.4, 117.2 (d, J_{CP} = 22.4 Hz), 74.1, 59.9 (d, J_{CP} = 16.7 Hz), 31.0, 0.3.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −24.5.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3368 (w), 3171 (w), 2954 (w), 2901 (w), 1504 (s), 1305 (m), 1250 (m), 1214 (s), 1186 (w), 1152 (w), 1090 (m), 1066 (m), 957 (w), 834 (s), 734 (m), 694 (m), 632 (m), 505 (m).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +6.4 (*c* = 0.59, MeOH).

1-((1*S*,2*R*)-3-(Diphenylphosphanyl)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)-3-phenylthiourea (49b)



According to general procedure **GP4**, 1-((1S,2R)-3-(diphenylphosphanyl)-1-hydroxy-1-phenyl-propan-2-yl)-3-phenylthiourea (**45a**) (35.0 mg, 74.4 µmol), DIPEA (28.8 mg, 36.9 µL, 223 µmol), TIPS triflate (47.0 mg, 41.2 µL, 149 µmol), CH_2Cl_2 (0.5 mL) were stirred for six hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (100:0 to 10:1), d x h: 2 x 17 cm) to afford the product **49b** (42.0 mg, 67 µmol, 90%) as a white solid.

$C_{37}H_{47}N_2OPSSi$ (626.91 g/mol):

MP: 63-64 °C.

TLC: R_f = 0.14 (SiO_2, cyclohexane:ethyl acetate (10:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = δ 7.86 (s, 1H, N*H*), 7.51-7.44 (m, 4H, ar-*H*), 7.38-7.31 (m, 8H, ar-*H*), 7.30-7.20 (m, 4H, ar-*H*), 7.17-7.14 (m, 2H, ar-*H*), 7.09 (d, $^3J_{HH}$ = 7.6 Hz, 2H, ar-*H*), 6.03 (d, $^3J_{HH}$ = 8.7 Hz, 1H, N*H*), 5.36 (d, $^3J_{HH}$ = 3.4 Hz, 1H, Ph-C*H*), 4.72 (br s, 1H, NC*H*), 2.65 (dd, $^2J_{HP}$ = 13.9 Hz, $^3J_{HH}$ = 5.6 Hz, 1H, PCH_2), 2.09 (dd, $^2J_{HP}$ = 13.9 Hz, $^3J_{HH}$ = 9.5 Hz, 1H, PCH_2), 1.03-0.88 (m, 21H, TIPS).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.6, 141.6, 139.1 (d, J_{CP} = 13.5 Hz), 138.8 (d, J_{CP} = 12.5 Hz), 136.4, 133.6 (d, J_{CP} = 8.4 Hz), 133.4 (d, J_{CP} = 8.6 Hz), 130.6, 129.3, 129.1, 129.0, 128.3, 128.1, 127.8, 127.3, 126.1, 74.7, 59.3 (d, J_{CP} = 16.4 Hz), 29.9 (d, J_{CP} = 13.9 Hz), 18.4, 18.3, 12.9.

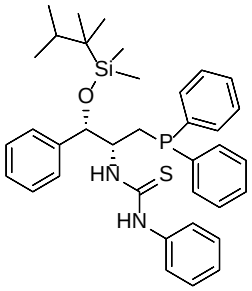
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −23.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3371 (w), 3187 (w), 3053 (w), 2941 (m), 2863 (m), 1522 (s), 1495 (s), 1316 (w), 1242 (m), 1096 (s), 1063 (s), 1025 (m), 881 (m), 840 (w), 734 (s), 692 (s), 574 (w), 496 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{37}H_{47}N_2OPSSi^+$: 627.2989 $[M+H]^+$; found: 627.2988.

$[\alpha]_D^{20}$ = −14.3 (*c* = 0.69, MeOH).

1-((1*S*,2*R*)-1-(((2,3-Dimethylbutan-2-yl)dimethylsilyl)oxy)-3-(diphenylphosphanyl)-1-phenylpropan-2-yl)-3-phenylthiourea (49c)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with 1-((1*S*,2*R*)-3-(diphenylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenylthiourea (**45a**) (100 mg, 213 µmol) and THF (1.5 mL). The corresponding solution was cooled in an ice bath and at 0 °C sodium hydride (60% in mineral oil, 20.4 mg, 850 µmol) was added in one portion. The reaction mixture was stirred for 30 minutes at 0 °C and then chloro(dimethyl)thexylsilane (57.3 mg, 63.0 µL, 320 µmol) was added drowise over 5 minutes. The corresponding reaction mixture was stirred for 16 hours at room temperature and then quenched by water (5 mL). The biphasic mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1), d x h: 2 x 13 cm) to afford the product **49c** (69.9 mg, 114 µmol, 54%) as a white solid.

$C_{36}H_{45}N_2OPSSi$ (612.89 g/mol):

MP: 59-60 °C.

TLC: R_f = 0.40 (SiO_2, cyclohexane:ethyl acetate (10:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.68-7.61 (m, 2H, ar-*H*), 7.52-7.23 (m, 14H, ar-*H*), 7.17-7.06 (m, 4H, ar-*H*), 6.46 (s, 1H, N*H*), 5.28 (s, 1H, Ph-C*H*), 4.59 (s, 1H, nC*H*), 2.56-2.48 (m, 1H, PCH_2), 2.44-2.37 (m, 1H, PCH_2), 1.51 (p, $^3J_{HH}$ = 6.9 Hz, 1H, C*H*$(CH_3)_2$), 0.79-0.72 (m, 11H, TDS-CH_3), 0.11 (s, 4H, TDS-CH_3), −0.21 (s, 3H, TDS-CH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.6, 142.2, 138.0 (d, J_{CP} = 12.8 Hz), 136.4, 133.9 (d, J_{CP} = 19.8 Hz), 133.2 (d, J_{CP} = 18.8 Hz), 130.7, 129.5, 129.1, 129.1, 129.0, 128.9, 128.4, 127.9, 126.8, 126.4, 74.6, 60.1 (d, J_{CP} = 16.9 Hz), 34.4, 31.1 (d, J_{CP} = 15.1 Hz), 25.5, 20.7, 20.5, 19.0, 18.8, −1.2, −2.1.

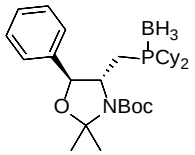
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −24.4.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3369 (w), 3157 (w), 2955 (m), 2864 (w), 1494 (m), 1433 (m), 1376 (w), 1315 (w), 1249 (m), 1087 (m), 1064 (m), 956 (w), 825 (s), 775 (m), 733 (s), 692 (s), 492 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{36}H_{45}N_2OPSSi^+$: 613.2832 $[M+H]^+$; found: 613.2833.

$[\alpha]_D^{20}$ = +1.7 (*c* = 0.57, MeOH).

tert-Butyl (4*R*,5*S*)-4-((dicyclohexylphosphanyl)methyl)-2,2-dimethyl-5-phenyloxazolidine-3-carboxylate·BH_3 (50)



Under argon atmosphere, a heat gun dried two-necked flask was charged with borane dicyclohexylphosphine complex (165 mg, 778 µmol), potassium hydride (95%, 32.9 mg, 778 µmol) and THF (2 mL). The corresponding mixture was stirred for two hours at 0 °C and afterwards *tert*-butyl (4*S*,5*S*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carboxylate (**34**) (200 mg, 519 µmol) was added in one portion at 0 °C. The reaction mixture was stirred for 30 minutes at 0 °C and additional 16 hours at room temperature. Then, water (20 mL) was added dropwise to the reaction mixture and the resulting biphasic solution was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (50:1), d x h: 3.5 x 13 cm) to afford the product **50** (187.0 mg, 372 µmol, 72%) as a white solid.

$C_{29}H_{49}BNO_3$ (501.50 g/mol):

MP: 150-151 °C.

TLC: R_f = 0.25 (SiO_2, cyclohexane:ethyl acetate (50:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = δ 7.45 (d, $^3J_{HH}$ = 7.0 Hz, 2H, ar-*H*), 7.34 (t, $^3J_{HH}$ = 7.4 Hz, 2H, ar-*H*), 7.28 (t, $^3J_{HH}$ = 7.2 Hz, 1H, ar-*H*), 5.19 (br s, 1H, Ph-C*H*), 4.76-4.69 (m, 1H, NC*H*), 2.24-1.66 (m, 16H, cy-CH_2, cy-C*H*, PCH_2), 1.58 (s, 3H, C(CH_3)$_2$), 1.53-1.44 (m, 10H, cy-CH_2, cy-C*H*, C(CH_3)$_2$), 1.37-1.24 (m, 10. cy-CH_2, cy-C*H*, C(CH_3)$_3$), 0.63-−0.15 (br m, 3H, BH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 152.1, 140.9, 128.7, 128.2, 127.8, 81.8, 80.9, 58.1, 33.8-33.1 (m), 32.7-31.9 (m), 29.3-28.4 (m), 27.9-26.4 (m), 24.5-23.6 (m).

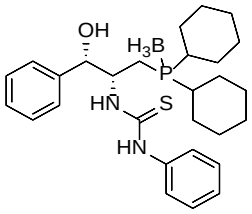
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = 20.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2930 (m), 2853 (w), 2366 (w), 2337 (w), 1683 (s), 1449 (m), 1364 (s), 1250 (m), 1170 (m), 1135 (m), 1101 (m), 1061 (m), 1015 (m), 849 (w), 735 (m), 697 (m), 621 (w), 536 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{29}H_{49}BNO_3^+$: 524.3440 $[M+Na]^+$; found: 524.3449.

$[\alpha]_D^{20}$ = −17.0 (*c* = 0.13, CH_2Cl_2).

1-((1*S*,2*R*)-3-(Dicyclohexylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenyl-thiourea·BH_3 (51)



Under argon atmosphere, a heat gun dried two-necked flasked was charged with *tert*-butyl (4*R*,5*S*)-4-((dicyclohexylphosphanyl)methyl)-2,2-dimethyl-5-phenyloxazolidine-3-carboxylate BH_3 (**50**) (259 mg, 516 µmol) and THF (2 mL). Afterwards the reaction mixture was cooled to 0 °C in an ice-bath and then at 0 °C concentrated HCl solution (37%, 1.02 g, 0.88 mL, 10.3 mmol) was added dropwise to the reaction mixture. After addition, the mixture was stirred for 16 hours at room temperature. Then, the crude product was concentrated under vacuum to yield the corresponding hydrochloride amino phosphine adduct which was directly used for the next step.

The crude amino phosphine from the previous step was dissolved in water (3 mL) and CH_2Cl_2 (5 mL) followed by phenyl isothiocyanate addition (109 mg, 96.3 µL, 789 µmol). Then, potassium carbonate (713 mg, 5.16 mmol) was added over 15 mintues at 0 °C. After addition, the reaction mixture was stirred at room temperature for 16 hours. Afterwards the crude product was diluted with water (10 mL) and the biphasic mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (4:1), d x h: 3.5 x 23 cm) to afford the product **51** (210 mg, 423 µmol, 82%) as a white solid. ^{31}P-NMR analysis of the purified product showed that a mixture of borane-protected and free phosphine of 1:3 was isolated. The different products were not separated because of similarl R_f value.

$C_{28}H_{42}N_2BN_2OPS$ (496.51 g/mol):

MP: 81-82 °C.

TLC: R_f = 0.30 (SiO_2, cyclohexane:ethyl acetate (4:1)).

^{1}H NMR (400 MHz, $CDCl_3$) of borane-phosphine: δ/ppm = 7.79-7.57 (br m, 1H, N*H*), 7.40-7.15 (m, 8H, ar-*H*), 6.85 (d, $^3J_{HH}$ = 7.7 Hz, 2H, ar-*H*), 6.39 (d, $^3J_{HH}$ = 7.5 Hz, 1H, N*H*), 5.38 (s, 1H, Ph-C*H*), 4.78 (s, 1H, NC*H*), 2.86-2.68 (br m, 1H, O*H*), 2.34-2.18 (m, 1H, PCH_2), 2.06-1.88 (m, 1H, PCH_2), 1.85-1.39 (m, 10H, cy-CH_2, cy-C*H*), 1.31-0.94 (m, 12H, cy-CH_2), 0.78-0.16 (br m, 3H, BH_3).

^{1}H NMR (400 MHz, $CDCl_3$) of free phosphine δ/ppm = 7.79-7.57 (br m, 1H, N*H*), 7.40-7.15 (m, 8H, ar-*H*), 7.01 (d, $^3J_{HH}$ = 7.7 Hz, 2H, ar-*H*), 6.45 (d, $^3J_{HH}$ = 8.1 Hz, 1H, N*H*), 5.09 (s, 1H, Ph-C*H*), 4.65 (s, 1H, NC*H*), 3.19-3.04 (br m, 1H, O*H*), 2.06-1.88 (m, 1H, PCH_2), 1.85-1.39 (m, 11H, PCH_2, cy-CH_2, cy-C*H*), 1.31-0.94 (m, 12H, cy-CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) of the mixture: δ/ppm = 180.2, 179.9, 141.8, 141.2, 136.0, 135.8, 130.1, 128.5, 128.5, 127.8, 127.5, 127.3, 126.1, 125.7, 125.5, 125.5, 74.7, 72.5, 60.2 (d, J_{CP} = 19.1 Hz), 57.8, 33.4 (d, J_{CP} = 10.7 Hz), 33.0 (d, J_{CP} = 11.0 Hz), 32.9, 32.6, 32.3, 30.2 (d, J_{CP} = 10.2 Hz), 30.1 (d, J_{CP} = 9.9 Hz), 29.0 (d, J_{CP} = 8.2 Hz), 28.7 (d, J_{CP} = 7.4 Hz), 27.5, 27.5, 27.4, 27.3, 27.3, 27.2, 27.1, 27.0, 27.0, 26.9, 26.8, 26.7, 26.6, 26.5, 26.1 (d, J_{CP} = 10.7 Hz), 24.2, 24.0, 21.8, 21.6.

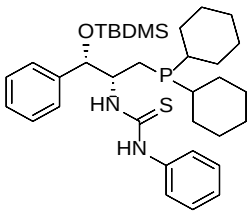
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = 19.6 (borane-protected phosphine), −13.5 (free phosphine).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3364 (w), 2920 (m), 2848 (m), 1595 (w), 1517 (s), 1495 (s), 1446 (m), 1235 (m), 1180 (m), 1060 (m), 739 (s), 695 (s), 603 (w), 493 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{28}H_{42}N_2BN_2OPS^+$: 519.2746 [M+Na]$^+$; found: 519.2738.

$[\boldsymbol{\alpha}]_D^{20}$ = +21.3 (*c* = 0.81, MeOH).

1-((1*S*,2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(dicyclohexylphosphanyl)-1-phenylpropan-2-yl)-3-phenylthiourea (52)



Under argon atmosphere, a heat-gun dried Schlenk flask was charged with 1-((1*S*,2*R*)-3-(dicyclohexylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)-3-phenyl-thiourea·BH_3 (**51**) (144 mg, 290 µmol) and diethylamine (1.42 g, 2.00 mL, 19.4 mmol). Then, the reaction mixture was degassed three-times by freeze-pump-thaw method. After degassing, the reaction solution was stirred for five days at 55 °C and afterwards the mixture was concentrated under vacuum. The corresponding white solid was dissolved in ether (40 mL) and the organic layer was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude phosphine was directly used for the next step without any further purification step.

Under argon atmosphere, a heat-gun dried two-neckeded flask was charged with the crude phosphine (140 mg, 290 µmol), CH_2Cl_2 (2 mL) and the reaction mixture was cooled in an ice-bath. At 0 °C, DIPEA (112 mg, 144 µL, 870 µmol) was added followed by dropwise addition of TBDMS triflate (81.3 mg, 70.7 µL, 307 µmol) over 10 minutes. After completed addition, the reaction mixture was stirred for two hours at 0 °C and 16 hours at room temperature. Then, the mixture was concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (7:1), d x h: 2.5 x 14 cm) to afford the product **52** (87.0 mg, 146 µmol, 50%) as a white solid.

$C_{34}H_{53}N_2OPSSi$ (596.93 g/mol):

MP: 79-80 °C.

TLC: R_f = 0.26 (SiO_2, cyclohexane:ethyl acetate (7:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.71 (s, 1H, N*H*), 7.44 (t, $^3J_{HH}$ = 7.6 Hz, 2H, ar-*H*), 7.33-7.23 (m, 6H, ar-*H*), 7.16 (d, $^3J_{HH}$ = 7.2 Hz, 2H, ar-*H*), 6.39 (s, 1H, N*H*), 5.26 (s, 1H, Ph-C*H*), 4.52 (s, 1H, NC*H*), 1.82-1.53 (m, 13H, PCH_2, cy-CH_2, cy-*H*), 1.33-1.15 (m, 3H, cy-CH_2, cy-*H*), 0.78 (s, 9H, SiC(CH_3)$_3$), 0.07 (s, 3H, SiCH_3), −0.25 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.5, 142.6, 136.7, 130.7, 128.4, 127.9, 126.9, 126.4, 74.3 (d, $^3J_{CP}$ = 10.1 Hz), 61.0 (d, $^2J_{CP}$ = 19.7 Hz), 34.2 (d, J_{CP} = 12.6 Hz), 33.8 (d, J_{CP} = 13.4 Hz), 30.9 (d, J_{CP} = 14.2 Hz), 30.7 (d, J_{CP} = 13.0 Hz), 30.2 (d, J_{CP} = 9.9 Hz), 29.8 (d, J_{CP} = 8.8 Hz), 28.2, 28.0, 28.0, 27.9, 27.8 (d, J_{CP} = 3.2 Hz), 27.1, 26.2, 18.4, −4.2, −4.4.

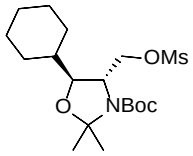
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −14.5.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3371 (w), 3169 (w), 2922 (m), 2849 (w), 1496 (s), 1446 (m), 1248 (m), 1183 (w), 1089 (m), 1064 (m), 958 (w), 835 (s), 776 (s), 744 (m), 696 (s), 557 (w), 504 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{34}H_{53}N_2OPSSi^+$: 597.3458 $[M+H]^+$; found: 597.3460.

$[\alpha]_D^{20}$ = +37.3 (*c* = 0.60, MeOH).

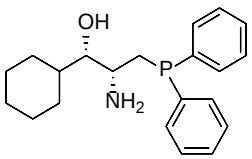
tert-Butyl (4*S*,5*S*)-5-cyclohexyl-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)oxazolidine-3-carboxylate (53)



An autoclave inlet was charged with *tert*-butyl (4*S*,5*S*)-4-(hydroxymethyl)-2,2-dimethyl-5-phenyloxazolidine-3-carboxylate (**34**) (300 mg, 778 µmol), rhodium on activated carbon (5% Rh basis, 87 mg) and MeOH (3 mL). Then, the autoclave was pressurized to 5 bar with H_2 and the reaction mixture stirred for 16 hours at room temperature. Afterwards, the crude mixture was filtrated over Celite and concentrated under vacuum. The crude product was purified by flash column chromatography (SiO_2, cyclohexane:ethyl acetate (3:1), 3.5 x 12 cm) to afford the product **53** (290 mg, 741 µmol, 95%) as a white solid.

$C_{18}H_{33}NO_6S$ (391.52 g/mol):
MP: 85-86 °C.
TLC: R_f = 0.56 (SiO_2, cyclohexane:ethyl acetate (2:1))
^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = δ 4.40-4.31 (br m, 1H, NC*H*), 4.19 (s, 1H, OCH_2), 3.89 (d, $^3J_{HH}$ = 15.9 Hz, 1H, cy-C*H*), 3.70 (dd, $^3J_{HH}$ = 8.1 Hz, $^2J_{HH}$ = 4.3 Hz, 1H, OCH_2), 3.20 (s, 3H, SCH_3), 1.85 (d, $^3J_{HH}$ = 12.9 Hz, 1H, cy-C*H*), 1.74-1.67 (m, 2H, cy-CH_2), 1.65-1.58 (m, 2H, cy-CH_2), 1.49 (s, 3H, CH_3), 1.43 (s, 9H, C(CH_3)$_3$), 1.41 (s, 3H, CH_3), 1.28-1.06 (m, 4H, cy-CH_2), 1.04-0.88 (m, 2H, cy-CH_2).
^{13}C{^{1}H} NMR (DMSO-d_6): δ/ppm = 151.1/150.6*, 93.7/93.3*, 81.2/80.3*, 79.9, 68.1/67.2*, 58.2, 54.9, 40.6, 36.7, 29.0, 27.9, 26.9, 26.3, 25.9, 25.2, 25.1. [* refers to signal of rotamers]
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2928 (m), 2851 (w), 1698 (s), 1385 (m), 1361 (s), 1255 (m), 1171 (s), 1115 (m), 1075 (m), 973 (m), 957 (m), 852 (m), 818 (w), 771 (m), 719 (w), 526 (m).
EA ($C_{18}H_{27}NO_6$) calc.: C 55.22, H 8.50, N 3.58; found: C 55.23, H 8.24, N 3.71.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +13.6 (*c* = 0.54, MeOH).

(1*S*,2*R*)-2-Amino-1-cyclohexyl-3-(diphenylphosphanyl)propan-1-ol (54)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl (4*S*,5*S*)-5-cyclohexyl-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)oxazolidine-3-carboxylate (**53**) (250 mg, 639 µmol) and THF (1.7 mL). Then, the reaction mixture was degassed three-times by freeze-pump-thaw method. At 0 °C potassium diphenylphosphide solution (0.5 M in THF, 1.66 g, 1.8 mL, 0.9 mmol) was added dropwise over five minutes and afterwards the mixture was stirred two hours at 0 °C and two hours at room temperature. At ambient temperature, aqueous HCl (37%, 1.1 mL, 12.8 mmol) was added and then the mixture was stirred at room temperature for 16 hours. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed aqueous NaOH (2 M) and then the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by flash column chromatography (SiO_2, cyclohexane:ethyl acetate (1:5) + 5% NEt_3, 2.5 x 11 cm) to afford the product **54** (210 mg, 615 µmol, 96%) as a white solid.

$C_{21}H_{28}NOP$ (341.19 g/mol):

MP: 83-84 °C.

TLC: R_f = 0.33 (SiO_2, cyclohexane:ethyl acetate (1:5) + 5% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.53-7.29 (m, 10H, ar-*H*), 3.13 (t, $^3J_{HH}$ = 5.3 Hz, 1H, NC*H*), 2.91-2.83 (m, 1H, cy-C*H*), 2.36 (ddd, $^2J_{HP}$ = 13.8 Hz, $^3J_{HH}$ = 4.2 Hz, $^4J_{HH}$ = 2.7 Hz, 1H, PCH_2), 2.09 (ddd, $^2J_{HP}$ = 13.8 Hz, $^3J_{HH}$ = 9.4 Hz, $^4J_{HH}$ = 2.7 Hz, 1H, PCH_2), 1.99 (br s, 2H, NH_2), 1.73-1.59 (m, 4H, cy-CH_2), 1.49 (d, $^3J_{HH}$ = 12.8 Hz, 1H, cy-C*H*), 1.40-1.28 (m, 1H, cy-CH_2), 1.23-0.93 (m, 5H, cy-CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 138.8 (d, J_{CP} = 11.5 Hz), 137.9 (d, J_{CP} = 12.3 Hz), 133.2 (d, J_{CP} = 19.2 Hz), 132.6 (d, J_{CP} = 18.3 Hz), 130.8 (d, J_{CP} = 11.4 Hz), 129.1, 129.1, 129.0, 128.7, 128.7, 128.7, 128.6, 78.7 (d, J_{CP} = 8.3 Hz), 49.4 (d, J_{CP} = 13.7 Hz), 40.5, 35.4 (d, J_{CP} = 11.9 Hz), 30.0, 27.8, 26.5, 26.5, 26.2.

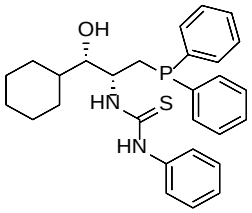
^{31}P NMR (162 MHz, $CDCl_3$) δ/ppm: −22.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3215 (w), 2922 (m), 2856 (m), 1595 (m), 1429 (m), 1180 (w), 1095 (w), 942 (m), 815 (w), 733 (s), 691 (s), 514 (m), 472 (s).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{21}H_{28}NOP^+$: 342.1981 $[M+H]^+$; found: 342.1984.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −20.6 (*c* = 0.60, MeOH).

1-((1*S*,2*R*)-3-(Diphenylphosphanyl)-1-hydroxy-1-cyclohexylpropan-2-yl)-3-phenylthiourea (55)



According to general procedure **GP1**, ((1*S*,2*R*)-2-amino-1-cyclohexyl-3-(diphenylphosphanyl)-propan-1-ol (**54**) (70.0 mg, 205 µmol), phenyl isothiocyanate (33.9 mg, 30.0 µL, 246 µmol), CH_2Cl_2 (1 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (4:1), d x h: 2.5 x 11 cm) to afford the product **55** (75.0 mg, 157 µmol, 77%) as a white solid.

$C_{28}H_{33}N2OPS$ (476.62 g/mol):

MP: 80-81 °C.

TLC: R_f = 0.22 (SiO_2, cyclohexane:ethyl acetate (4:1)).

^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm = 7.61-7.53 (m, 3H, N*H,* ar-*H*), 7.47-7.42 (m, 2H, ar-*H*), 7.42-7.24 (m, 8H, ar-*H*), 7.28-7.20 (m, 1H, ar-*H*), 7.07-7.03 (m, 2H, ar-*H*), 6.64 (d, $^3J_{HH}$ = 8.3 Hz, 1H, N*H*), 4.78 (br s, 1H, NC*H*), 3.69 (d, $^3J_{HH}$ = 8.3 Hz, 1H, cy-C*H*), 2.63 (ddd, $^2J_{HP}$ = 13.8 Hz, $^3J_{HH}$ = 5.2 Hz, $^2J_{HH}$ = 2.6 Hz, 1H, PCH_2), 2.46 (dd, $^2J_{HP}$ = 13.8, $^3J_{HH}$ = 8.9 Hz, 1H, PCH_2), 2.06 (br s, 1H, O*H*), 1.80-1.59 (m, 5H, cy-CH_2, cy-C*H*), 1.28-1.06 (m, 4H, cy-CH_2), 0.96-0.77 (m, 2H, cy-CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 179.5, 138.5 (d, J_{CP} = 10.7 Hz), 137.0 (d, J_{CP} = 10.5 Hz), 136.2, 133.2 (d, J_{CP} = 19.2 Hz), 132.8 (d, J_{CP} = 19.1 Hz), 130.2, 129.1, 128.9, 128.7 (d, J_{CP} = 4.5 Hz), 128.6 (d, J_{CP} = 4.4 Hz), 127.0, 124.7, 123.8, 76.8, 54.4 (d, J_{CP} = 15.4 Hz), 40.9, 31.8 (d, J_{CP} = 14.8 Hz), 29.0, 28.9, 26.4, 26.0, 25.9.

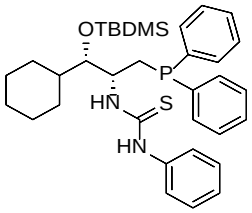
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −24.5.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3234 (w), 2919 (m), 2848 (w), 1594 (w), 1517 (m), 1447 (m), 1316 (w), 1295 (m), 1238 (m), 1162 (m), 1134 (m), 1076 (w), 1007 (m), 930 (m), 736 (m), 692 (s), 603 (m), 491 (m), 407 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{28}H_{33}N2OPS^+$: 477.2124 $[M+H]^+$; found: 477.2131.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −4.0 (*c* = 0.28, MeOH).

1-((1*S*,2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-cyclohexyl-3-(diphenylphosphanyl)propan-2-yl)-3-phenylthiourea (56)



According to general procedure **GP4**, 1-((1*S*,2*R*)-3-(diphenylphosphanyl)-1-hydroxy-1-cyclohexylpropan-2-yl)-3-phenylthiourea (**55**) (62.0 mg, 130 µmol), DIPEA (33.6 mg, 43.0 µL, 260 µmol), TBDMS triflate (41.2 mg, 35.9 µL, 156 µmol), CH_2Cl_2 (1.4 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 2.5 x 11 cm) to afford the product **56** (8.0 mg, 14 µmol, 10%) as a white solid.

$C_{34}H_{47}N_2OPSSi$ (590.88 g/mol):

MP: 65-66 °C.

TLC: R_f = 0.49 (SiO_2, cyclohexane:ethyl acetate (4:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.73-7.64 (m, 2H, ar-*H*), 7.54 (s, 1H, N*H*), 7.42-7.34 (m, 7H, ar-*H*), 7.32-7.23 (m, 4H, ar-*H*), 7.15-7.11 (m, 2H, ar-*H*), 6.71 (d, $^3J_{HH}$ = 8.3 Hz, 1H, N*H*), 4.63-4.51 (m, 1H, OC*H*), 4.06 (dd, $^3J_{HH}$ = 5.3 Hz, $^4J_{HH}$ = 3.2 Hz, 1H, NC*H*), 2.70 (dt, $^2J_{HP}$ = 13.4 Hz, $^3J_{HH}$ = 4.7 Hz, 1H, PCH_2), 2.04 (ddd, $^2J_{HP}$ = 13.6 Hz, $^3J_{HH}$ = 10.5 Hz, $^4J_{HH}$ = 4.5 Hz, 1H, PCH_2), 1.73-1.65 (m, 2H, cy-CH_2), 1.64-1.56 (m, 1H, cy-C*H*), 1.18-1.04 (m, 4H, cy-CH_2), 0.93-0.80 (m, 4H, cy-CH_2), 0.66 (s, 9H, SiC(CH_3)$_3$), 0.03 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −24.3.

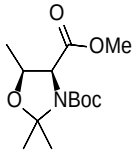
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3373 (w), 2953 (m), 2926 (m), 2853 (m), 1486 (s), 1344 (m), 1315 (s), 1249 (s), 1069 (m), 973 (w), 885 (w), 834 (s), 775 (s), 736 (s), 697 (s), 573 (w), 526 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{34}H_{47}N_2OPSSi^+$: 591.2989 $[M+H]^+$; found: 591.2989.

$[\alpha]_D^{20}$ = −13.7 (*c* = 1.00, MeOH).

5.2.4 Synthesis of 4th Generation Catalysts

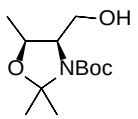
3-(*tert*-Butyl) 4-methyl (4*S*,5*S*)-2,2,5-trimethyloxazolidine-3,4-dicarboxylate (59)



Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with *N-Boc-L-allo*-threonine methyl ester (**58**) (1.40 g, 6.00 mmol), 2,2-dimethoxypropane (2.55 g, 3.00 mL, 24.0 mmol), *p*-toluenesulfonic acid monohydrate (15.4 mg, 0.08 mmol) and toluene (30 mL). Then, a Dean-Stark apparatus was attached and the reaction was refluxed for 16 hours. Afterwards the reaction mixture was concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 3.5 x 13 cm) to afford the product **59** (1.38 g, 5.06 mmol, 84%) as a yellow oil.

$C_{13}H_{23}NO_5$ (273.33 g/mol):
TLC: R_f = 0.38 (SiO_2, cyclohexane:ethyl acetate (5:1)).
^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 4.45-4.38 (m, 1H, OC*H*), 4.31-4.29 (m, 1H, NC*H*), 3.68/3.65* (s, 3H, OCH_3), 1.59/1.58* (s, 3H, CH_3), 1.45/1.42* (s, 3H, CH_3), 1.41/1.33* (s, 9H, C(CH_3)$_3$), 1.09 (d, $^3J_{HH}$ = 6.3 Hz, 3H, CH_3) [* refers to signal of rotamers].
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 170.4/170.1*, 151.2/150.4*, 93.3/93.1*, 79.9/79.3*, 71.0/70.7*, 62.8/62.7*, 51.7/51.6*, 27.9/27.8*, 26.4/25.4*, 24.9/24.1*, 15.2/15.1*.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 1751 (m), 1702 (s), 1454 (w), 1367 (s), 1265 (s), 1168 (m), 1123 (s), 1053 (w), 979 (w), 737 (s), 704 (w).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{13}H_{23}NO_5^+$: 296.1468 $[M+Na]^+$; found: 296.1472.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −6.6 (*c* = 0.95, CH_2Cl_2).

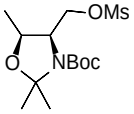
***tert*-Butyl (4*R*,5*S*)-4-(hydroxymethyl)-2,2,5-trimethyloxazolidine-3-carboxylate (60)**



Under argon atmosphere, a heat-gun dried two-necked flask was charged with $LiAlH_4$ (1M in THF, 271 mg, 7.14 mL, 7.14 mmol) and then the solution was cooled in an ice-bath. At 0 °C, a solution of 3-(*tert*-butyl) 4-methyl (4*S*,5*S*)-2,2,5-trimethyloxazolidine-3,4-dicarboxylate (**59**) (1.30 g, 4.76 mmol) in THF (6 mL) was added dropwise over 15 minutes to the $LiAlH_4$ solution *via* dropping funnel. The corresponding mixture was stirred for two hours at 0 °C and then the reaction was quenched by slow addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), then the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (3:1), d x h: 3.5 x 15 cm) to afford the product **60** (1.02 g, 4.16 mmol, 87%) as a pale yellow oil.

$C_{12}H_{23}NO_4$ (245.32 g/mol):
TLC: R_f = 0.35 (SiO_2, cyclohexane:ethyl acetate (2:1)).
^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 4.63 (dd, $^3J_{HH}$ = 5.8, $^3J_{HH}$ = 4.4 Hz, 1H, O*H*), 4.21 (quint, $^3J_{HH}$ = 6.0 Hz, 1H, OC*H*), 3.74-3.57 (m, 1H, NCH_2), 3.51-3.35 (m, 2H, CH_2), 1.43-1.37 (m, 15H, CH_3, C(CH_3)$_3$), 1.22 (d, $^3J_{HH}$ = 6.4 Hz, 3H, CH_3).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 151.3/151.0*, 91.4/91.3*, 79.1/78.6*, 71.4/71.0*, 60.6/60.5*, 58.7/58.0*, 28.1/28.0*, 27.7/26.9*, 24.5/23.2*, 14.3. [* refers to signal of rotamers].
IR (ATR): $\tilde{\nu}$/cm^{-1} = 1688 (s), 1473 (w), 1363 (s), 1257 (m), 1174 (s), 1129 (m), 1065 (m), 963 (m), 859 (w), 799 (w), 716 (w), 528 (m).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{12}H_{23}NO_4^+$: 268.1519 $[M+Na]^+$; found: 268.1522.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −11.9 (*c* = 1.0, CH_2Cl_2).

tert-Butyl (4*R*,5*S*)-2,2,5-trimethyl-4-(((methylsulfonyl)oxy)methyl)oxazolidine-3-carboxylate (61)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl (4*R*,5*S*)-4-(hydroxymethyl)-2,2,5-trimethyloxazolidine-3-carboxylate (**60**) (819 mg, 3.34 mmol), CH_2Cl_2 (11 mL) and this mixture was cooled in an ice-bath to 0 °C. Then, triethylamine (845 mg, 1.17 mL, 8.35 mmol) was added, followed by dropwise addition of methanesulfonyl chloride (497 mg,

0.34 mL, 4.34 mmol) over 10 minutes at 0 °C. After addition the mixture was stirred for four hours at 0 °C and 16 hours at room temperature. Water (10 mL) was added and the biphasic mixture was extracted with CH2CL2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (3:1), d x h: 3.5 x 14 cm) to afford the product **61** (991 mg, 3.06 mmol, 92%) as a colorless oil.

$C_{13}H_{25}NO_6S$ (245.32 g/mol):

TLC: R_f = 0.38 (SiO_2, cyclohexane:ethyl acetate (2:1)).

^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 4.33-4.21 (m, 2H, OC*H,* CH_2), 4.17-4.07 (m, 1H, CH_2), 4.02-3.93 (m, 1H, NC*H*), 3.20 (s, 3H, SCH_3), 1.49-1.40 (m, 15H, CH_3,C(CH_3)$_3$), 1.22 (d, $^3J_{HH}$ = 6.5 Hz, 3H, CH_3).

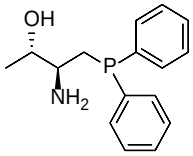
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 151.2/150.7*, 92.1/92.0*, 79.8/79.4*, 70.9/70.5*, 66.1/65.2*, 57.6/57.5*, 36.6/36.5*, 27.9, 27.2/26.4*, 24.3/23.1*, 13.9. [* refers to signal of rotamers].

IR (ATR): $\tilde{\nu}$/cm^{-1} = 1688 (w), 1421 (m), 1391 (m), 1366 (m), 1264 (s), 1176 (m), 1130 (w), 1066 (w), 960 (w), 736 (w), 705 (s).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{13}H_{25}NO_6S^+$: 346.1295 [M+Na]$^+$; found: 346.1301.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −21.0 (*c* = 1.16 CH_2Cl_2).

(2*S*,3*S*)-3-Amino-4-(diphenylphosphanyl)butan-2-ol (62)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl (4*R*,5*S*)-2,2,5-trimethyl-4-(((methylsulfonyl)oxy)methyl)oxazolidine-3-carboxylate (**61**) (401 mg, 1.24 mmol) and THF (4 mL). Then the reaction mixture was degassed by three freeze-pump-thaw cycles. At 0 °C, potassium diphenylphosphide solution (0.5 M in THF, 3.02 g, 3.25 mL, 1.62 mmol) was added dropwise over five minutes and afterwards the mixture was stirred two hours at 0 °C and two hours at room temperature. At ambient temperature aqueous HCl (37%, 2.58 g, 2.22 mL, 36.5 mmol) was added and then the mixture was stirred at room temperature for 16 hours. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed aqueous NaOH

(2 M) and then the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (1:5) + 3% NEt_3, d x h: 2.5 x 12 cm) to afford the product **62** (173 mg, 0.63 mmol, 51%) as a pale yellow gum.

$C_{16}H_{20}NOP$ (273.32 g/mol):

TLC: R_f = 0.14 (SiO_2, cyclohexane:ethyl acetate (1:5) + 5% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.50-7.39 (m, 4H, ar-*H*), 7.37-7.29 (m, 6H, ar-*H*), 3.78-3.67 (m, 1H, OC*H*), 2.86-2.75 (m, 1H, NC*H*), 2.32 (dd, $^2J_{HP}$ = 13.8 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, PCH_2), 2.02-1.88 (m, 3H, PCH_2^*, NH_2^*), 1.12 (d, $^3J_{HH}$ = 6.4 Hz, 3H, CH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 133.3 (d, J_{CP} = 19.5 Hz), 132.6 (d, J_{CP} = 18.4 Hz), 129.2, 128.8 (d, J_{CP} = 7.3 Hz), 128.7 (d, J_{CP} = 6.6 Hz), 71.2 (d, J_{CP} = 8.4 Hz), 54.9 (d, J_{CP} = 12.8 Hz), 34.9 (d, J_{CP} = 12.1 Hz), 20.1.

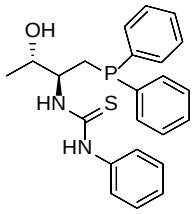
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −23.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3289 (w), 3203 (w), 1584 (m), 1480 (m), 1433 (s), 1372 (w), 1305 (w), 1095 (m), 1067 (m), 1026 (w), 922 (w), 740 (s), 697 (s), 508 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{16}H_{20}NOP^+$: 274.1356 $[M+H]^+$; found: 274.1355.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +44.7 (*c* = 1.00, $CHCl_3$).

1-((2*S*,3*S*)-1-(Diphenylphosphanyl)-3-hydroxybutan-2-yl)-3-phenylthiourea (63)



According to general procedure **GP1**, (2*S*,3*S*)-3-amino-4-(diphenylphosphanyl)butan-2-ol (**62**) (145 mg, 531 µmol), phenyl isothiocyanate (80.6 mg, 71.3 µL, 584 µmol), CH_2Cl_2 (2.0 mL) were stirred for 16 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (3:1), d x h: 2.5 x 14 cm) to afford the product **63** (171 mg, 418 µmol, 79%) as a white solid.

$C_{23}H_{25}N_2OPS$ (408.50 g/mol):

MP: 64-65 °C.

TLC: R_f = 0.25 (SiO_2, cyclohexane:ethyl acetate (2:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm: 7.98 (s, 1H, N*H*), 7.49-7.38 (m, 4H, ar-*H*), 7.37-7.28 (m, 8H, ar-*H*), 7.25-7.20 (m, 1H, ar-*H*), 7.11 (d, $^3J_{HH}$ = 7.8 Hz, 2H, ar-*H*), 6.40 (d, $^3J_{HH}$ = 8.4 Hz, 1H, N*H*), 4.70 (s, 1H, OC*H*), 4.20-3.99 (m, 1H, NC*H*), 2.57-2.45 (m, 2H, PCH_2, O*H*), 2.30-2.21 (m, 1H, PCH_2), 1.16 (d, $^3J_{HH}$ = 6.5 Hz, 3H, CH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 180.2, 138.2, 137.3, 136.1, 133.2 (d, J_{CP} = 19.6 Hz), 132.6 (d, J_{CP} = 18.8 Hz), 130.1, 129.3, 128.9, 128.8 (d, J_{CP} = 5.6 Hz), 128.7 (d, J_{CP} = 5.1 Hz), 127.0, 124.9, 70.5 (d, J_{CP} = 6.6 Hz), 58.0 (d, J_{CP} = 12.3 Hz), 28.8, 19.2.

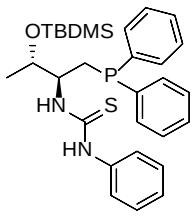
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −23.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3357 (w), 3240 (w), 1594 (w), 1520 (s), 1494 (s), 1432 (w), 1314 (m), 1296 (m), 1237 (m), 1095 (w), 1024 (w), 871 (w), 736 (s), 692 (s), 503 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{23}H_{25}N_2OPS^+$: 409.1498 $[M+H]^+$; found: 409.1503.

$[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = +118.8 (*c* = 0.94, $CHCl_3$).

1-((2*S*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-(diphenylphosphanyl)butan-2-yl)-3-phenyl thiourea (64)



According to general procedure **GP4**, 1-((2*S*,3*S*)-1-(diphenylphosphanyl)-3-hydroxybutan-2-yl)-3-phenylthiourea (**63**) (100 mg, 245 µmol), DIPEA (96.3 mg, 123 µL, 745 µmol), TBDMS triflate (68.0 mg, 59.0 µL, 257 µmol), CH_2Cl_2 (2 mL) were stirred for 6 hours and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1), d x h: 2.5 x 14 cm) to afford the product **63** (98.0 mg, 187 µmol, 77%) as a white solid.

$C_{29}H_{39}N_2OPSSi$ (522.76 g/mol):

MP: 50-52 °C.

TLC: R_f = 0.28 (SiO_2, cyclohexane:ethyl acetate (10:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.96 (s, 1H, N*H*), 7.53-7.42 (m, 4H, ar-*H*), 7.39-7.31 (m, 8H, ar-*H*), 7.26-7.21 (m, 1H, ar-*H*), 7.12 (d, $^{3}J_{HH}$ = 7.8 Hz, 2H, ar-*H*), 6.31 (d, $^{3}J_{HH}$ = 8.9 Hz, 1H, N*H*), 4.54 (s, 1H, OC*H*), 4.18-4.07 (m, 1H, NC*H*), 2.46-2.30 (m, 2H, PCH_2), 1.11 (d, $^{3}J_{HH}$ = 6.4 Hz, 3H, CH_3), 0.71 (s, 9H, SiC(CH_3)$_3$), −0.01 (s, 3H, SiCH_3), −0.19 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 180.1, 139.6, 139.0, 136.7, 133.7 (d, J_{CP} = 19.5 Hz), 133.1 (d, J_{CP} = 18.9 Hz), 130.5, 129.4, 129.2 (d, J_{CP} = 4.3 Hz), 129.1, 129.0, 127.2, 125.4, 70.5, 59.2 (d, J_{CP} = 13.3 Hz), 27.8, 26.0, 20.7, 18.3, −5.0, −4.9.

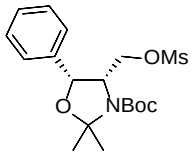
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −23.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3380 (w), 3052 (w), 2926 (w), 2892 (w), 2854 (w), 1590 (s), 1520 (s), 1495 (m), 1378 (w), 1248 (s), 1138 (m), 1072 (s), 954 (m), 833 (s), 775 (m), 735 (s), 693 (s), 502 (m), 475 (m).

EA ($C_{29}H_{39}N_2OPSSi$) calc.: C 66.63, H 7.52, N 5.36; found: C 66.62, H 7.64, N 5.38.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +139.9 (*c* = 0.63, CH_2Cl_2).

tert-Butyl (4*S*,5*R*)-2,2-dimethyl-4-(((methylsulfonyl)oxy)methyl)-5-phenyloxazolidine-3-carboxylate (72)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl (4*S*,5*R*)-4-(hydroxymethyl)-2,2-dimethyl-5-phenyloxazolidine-3-carboxylate (**71**) (750 mg, 2.44 mmol), CH_2Cl_2 (7.8 mL) and this mixture was cooled in an ice-bath to 0 °C. Then, triethylamine (543 mg, 0.75 mL, 5.37 mmol) was added, followed by dropwise addition of methanesulfonyl chloride (363 mg, 0.25 mL, 3.17 mmol) over 10 minutes at 0 °C. After addition, the mixture was stirred for four hours at 0 °C and 16 hours at room temperature. Water (10 mL) was added and the biphasic mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (7:1), d x h: 3.5 x 19 cm) to afford the product **72** (775 mg, 2.01 mmol, 82%) as a colorless gum.

$C_{18}H_{27}NO_6S$ (385.48 g/mol):

TLC: R_f = 0.35 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.47-7.29 (m, 5H, ar-*H*), 5.41 (d, $^3J_{HH}$ = 5.6 Hz, 1H, Ph-C*H*), 4.44-4.33 (m, 1H, CH_2), 4.08-3.94 (m, 1H, NC*H*), 3.76-3.67 (m, 1H, CH_2), 2.71/2.66* (s, 3H, SCH_3), 1.64 (s, 3H, CH_3), 1.59/1.58* (s, 3H, CH_3), 1.46/1.43* (s, 9H, C(CH_3)$_3$).

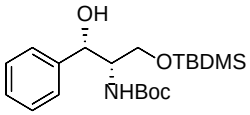
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 151.3/150.7*, 135.0/128.1*, 127.9/126.4*, 92.7/92.5*, 80.1/79.6*, 76.0/75.5*, 66.2/65.3*, 58.3/58.1*, 35.84/35.7*, 27.9, 27.1/26.3*, 24.5/23.3*.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2979 (w), 2936 (w), 1688 (s), 1456 (m), 1359 (s), 1256 (w), 1172 (s), 960 (m), 811 (w), 768 (w), 701 (m), 526 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{18}H_{27}NO_6S^+$: 408.1451 [M+Na]$^+$; found: 408.1452.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −5.4 (*c* = 0.45, MeOH).

tert-butyl ((1*S*,2*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-1-phenylpropan-2-yl) carbamate (69)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (**32**) (3.60 g, 21.5 mmol), MeOH (10 mL) and this mixture was cooled in an ice-bath to 0 °C. Then, di-*tert*-butyldicarbonat (5.16 g, 5.06 mL, 23.7 mmol) was added and the corresponding clear reaction solution was stirred for one hour at 0 °C. Afterwards the solvent was removed under vacuum and the yellow oil was directly used for the next step. The crude was dissolved in DMF (172 mL) and then imidazole (3.22 g, 47.3 mmol) and TBSCl (3.93 g, 25.8 mmol) was added. After 16 hours the crude was quenched by slow addition of saturated aquous $NaHCO_3$ solution (100 mL). The biphasic mixture was extracted with ether (3 x 100 mL) and the combined organic layers were washed with brine (3 x 100 mL), dried over Na_2SO_4, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), d x h: 5 x 19 cm) to afford the product **69** (7.20 g, 18.88 mmol, 88%) as a colorless oil.

$C_{20}H_{35}NO_4Si$ (381.59 g/mol):

TLC: R_f = 0.50 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.39-7.30 (m, 4H, ar-*H*), 7.29-7.24 (m, 1H, ar-*H*), 5.17 (d, $^3J_{HH}$ = 8.4 Hz, 1H, N*H*), 5.01 (d, $^3J_{HH}$ = 3.6 Hz, 1H, Ph-C*H*), 3.86-3.73 (m, 3H, CH_2, NC*H*), 1.37 (s, 9H, C(CH_3)$_3$), 0.93 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 6H, SiCH_3).

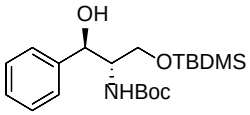
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 156.4, 141.4, 128.4, 127.7, 126.2, 79.7, 75.0, 65.1, 56.6, 28.4, 26.0, 18.3, −5.4.

IR (ATR): $\tilde{\nu}$/cm^{-1} 3436 (m), 2953 (w), 2928 (m), 2883 (w), 2856 (m), 1689 (s), 1495 (s), 1471 (m), 1390 (m), 1365 (m), 1321 (w), 1252 (s), 1168 (s), 1115 (m), 1069 (m), 1045 (m), 1024 (m), 836 (s), 777 (s), 738 (w), 699 (w), 669 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{20}H_{35}NO_4Si^+$: 504.2228 $[M+Na]^+$; found: 504.2232.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +13.2 (*c* = 1.02, MeOH).

tert-Butyl ((1*R*,2*S*)-3-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-1-phenylpropan-2-yl) carbamate (73)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl ((1*S*,2*S*)-3-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-1-phenylpropan-2-yl)carbamate (**69**) (7.10 g, 18.6 mmol) and THF (180 mL) and this mixture was cooled in an ice-bath to 0 °C. Then, 4-nitrobenzoic acid (3.72 g, 22.3 mmol) and triphenylphosphine (5.85 g, 22.3 mmol) was added, followed by dropwise addition of diisopropyl azodicarboxylate (4.51 g, 4.38 mL, 22.3 mmol) over 10 minutes at 0 °C. After addition the mixture was stirred for four hours at 0 °C and 16 hours at room temperature. Afterwards the reaction mixture was concentrated under vacuum and treated with an ether-hexane mixture (1:3, 100 mL). The precipitate was filtered off and the filtrate was concentrated under vacuum. The yellow oil was dissolved in MeOH (71 mL) and potassium carbonate (5.14 g, 37.2 mmol) was added in one portion. Then, the reaction mixture was stirred at room temperature for 80 minutes and then quenched with water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic layers were washed with brine (100 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under vacuum and the crude was triturated with hexane (100 mL) to remove the byproduct 4-nitrobenzoic methyl ester. After filtration and concentration of the filtrate the crude product was purified by column

chromatography (SiO_2, cyclohexane:ethyl acetate (7:1), d x h: 8 x 16 cm) to afford the product **73** (6.60 g, 17.30 mmol, 93%) as a pale yellow oil.

$C_{20}H_{35}NO_4Si$ (381.59 g/mol):

TLC: R_f = 0.36 (SiO_2, cyclohexane:ethyl acetate (5:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm =7.38-7.33 (m, 4H, ar-*H*), 7.30-7.24 (m, 1H, ar-*H*), 5.36 (d, $^3J_{HH}$ = 8.7 Hz, 1H, N*H*), 4.94 (dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 3.9 Hz, 1H, Ph-C*H*), 4.16 (d, $^3J_{HH}$ = 8.4 Hz, 1H, O*H*), 3.87-3.78 (m, 1H, NC*H*), 3.69-3.63 (m, 2H, CH_2), 1.44 (s, 9H, C(CH_3)$_3$), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.05 (s, 3H, SiCH_3), 0.04 (s, 3H, SiCH_3).

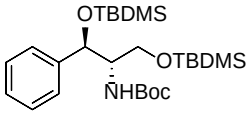
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ/ppm = 155.8, 141.7, 128.4, 127.5, 125.8, 79.7, 76.5, 63.2, 55.4, 28.5, 26.0, 18.3, −5.5.

IR (ATR): $\tilde{\nu}$/cm^{-1} 3448 (m), 2953 (m), 2929 (m), 2884 (w), 2856 (w), 1692 (s), 1495 (s), 1365 (m), 1251 (s), 1167 (s), 1062 (m), 834 (s), 776 (s), 699 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{20}H_{35}NO_4Si^+$: 504.2228 $[M+Na]^+$; found: 504.2234-

$[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = +11.5 (*c* = 0.95, MeOH).

tert-Butyl ((5*R*,6*S*)-2,2,3,3,9,9,10,10-octamethyl-5-phenyl-4,8-dioxa-3,9-disilaundecan-6-yl) carbamate (76)



Under argon atmosphere, a heat-gun dried two-necked flask was charged *tert*-butyl ((1*R*,2*S*)-3-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-1-phenylpropan-2-yl)carbamate (**73**) (1.20 g, 3.14 mmol) and DMF (4 mL). Then DMAP (269 mg, 2.20 mmol), imidazole (428 mg, 6.28 mmol) and TBSCl (669 mg, 4.40 mmol) was added to the reaction mixture. After stirring for 18 hours at room temperature the reaction solution was quenched by addition of water (10 mL) and the corresponding aqueous mixture was extracted with MTBE (3 x 30 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (20:1), d x h: 5 x 16 cm) to afford the product **76** (1.40 g, 2.83 mmol, 90%) as a colorless oil.

$C_{26}H_{49}NO_4Si_2$ (495.85 g/mol):

TLC: R_f = 0.38 (SiO_2, cyclohexane:ethyl acetate (4:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.35-7.27 (m, 4H, ar-*H*), 7.25-7.19 (m, 1H, ar-*H*), 4.87 (d, $^3J_{HH}$ = 5.1 Hz, 1H, Ph-C*H*), 4.59 (d, $^3J_{HH}$ = 8.4 Hz, 1H, NC*H*), 3.89-3.74 (m, 2H, CH_2), 3.54-3.44 (m, 1H, N*H*), 1.33 (s, 9H, C(CH_3)$_3$), 0.88 (s, 18H, SiC(CH_3)$_3$), 0.06-0.02 (m, 9H, SiCH_3), −0.19 (s, 3H, SiCH_3).

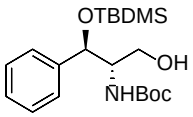
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 155.5, 141.7, 128.0, 127.4, 126.9, 79.0, 74.0, 61.2, 58.2, 28.5, 26.1, 26.0, 18.4, 18.3, −4.6, −5.0, −5.2, −5.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2953 (w), 2928 (s), 2884 (w), 2856 (m), 1716 (s), 1493 (s), 1471 (m), 1389 (m), 1364 (s), 1252 (s), 1170 (s), 1094 (s), 1053 (s), 1027 (m), 1005 (w), 966 (m), 835 (s), 777 (s), 700 (w), 671 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{26}H_{49}NO_4Si_2^+$: 518.3092 $[M+Na]^+$; found: 518.3095.

$[\boldsymbol{\alpha}]_D^{20}$ = −14.9 (*c* = 0.98, MeOH).

tert-Butyl ((1*R*,2*S*)-1-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-1-phenylpropan-2-yl) carbamate (77)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl ((5*R*,6*S*)-2,2,3,3,9,9,10,10-octamethyl-5-phenyl-4,8-dioxa-3,9-disilaundecan-6-yl)carbamate (**76**) (2.70 g, 5.45 mmol), pyridine (4.01 g, 4.1 mL, 50.7 mmol), THF (65 mL) and this mixture was cooled in an ice-bath to 0 °C. Then HF-Pyridine (70%, 4.51 g, 4.1 mL, 158 mmol) was added dropwise over 10 minutes at 0 °C and after addition the mixture was stirred for 30 minutes at 0 °C and 3 h at room temperature. At 0 °C the reaction mixture was quenched by slow addition of saturated aqueous $NaHCO_3$ solution and then the biphasic mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (6:1), 3.5 x 23 cm) to afford the product **77** (1.62 g, 4.25 mmol, 78%) as a colorless oil.

$C_{20}H_{35}NO_4Si$ (381.59 g/mol):

TLC: R_f = 0.52 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.33-7.24 (m, 4H, ar-*H*), 7.21-7.15 (m, 1H, ar-*H*), 5.41 (d, $^3J_{HH}$ = 8.0 Hz, 1H, N*H*), 5.16-5.10 (m, 1H, Ph-C*H*), 3.76 (dt, $^3J_{HH}$ = 11.7 Hz, $^4J_{HH}$ = 2.2 Hz, 1H, CH_2), 3.54-3.49 (m, 1H, NC*H*), 3.34 (td, $^3J_{HH}$ = 10.9 Hz, $^4J_{HH}$ = 3.7 Hz, 1H, CH_2), 2.92 (d, $^3J_{HH}$ = 10.1 Hz, 1H, O*H*), 1.39 (s, 9H, C(CH_3)$_3$), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.00 (s, 3H, SiCH_3), −0.18 (s, 3H, SiCH_3).

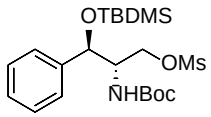
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 155.8, 141.2, 128.5, 127.6, 126.0, 79.7, 77.8, 61.4, 56.7, 28.6, 26.0, 18.2, −4.8, −5.2.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2953 (m), 2928 (m), 2856 (w), 1705 (s), 1490 (s), 1451 (m), 1364 (m), 1249 (s), 1166 (s), 1102 (m), 1069 (w), 940 (w), 833 (s), 775 (m), 742 (s), 700 (m), 450 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{20}H_{35}NO_4Si^+$: 504.2228 $[M+Na]^+$; found: 504.2232.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −32.1 (*c* = 0.91, MeOH).

(2*S*,3*R*)-2-((*tert*-Butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-3-phenylpropyl methanesulfonate (78)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl ((1*R*,2*S*)-1-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-1-phenylpropan-2-yl) carbamate (**77**) (599 mg, 1.57 mmol), CH_2Cl_2 (5 mL) and this solution was cooled in an ice-bath to 0 °C. Then, triethylamine (318 mg, 0.44 mL, 3.14 mmol) was added followed by dropwise addition of methansulfonyl chloride (216 mg, 0.15 mL, 1.88 mmol) over 10 minutes at 0 °C. After addition the mixture was stirred for 30 minutes at 0 °C and 6 h at room temperature. Afterwards the reaction mixture was quenched with water (10 mL) and then the biphasic mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1), 3.5 x 19 cm) to afford the product **78** (518 mg, 1.13 mmol, 72%) as a colorless gum.

$C_{21}H_{37}NO_6SSi$ (459.67 g/mol):

TLC: R_f = 0.52 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.39-7.25 (m, 5H, ar-*H*), 4.89-4.80 (m, 2H, CH_2), 4.42-4.36 (m, 1H, PH-C*H*), 4.19 (dd, $^3J_{HH}$ = 10.5 Hz, $^2J_{HH}$ = 3.6 Hz, 1H, NC*H*), 4.03 (br s, 1H, N*H*), 2.95 (s, 3H, SCH_3), 1.37 (s, 9H, C(CH_3)$_3$), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.06 (s, 3H, SiCH_3), −0.18 (s, 3H, SiCH_3).

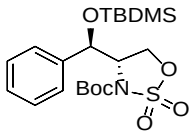
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 155.3, 140.6, 128.5, 128.0, 126.5, 80.0, 74.5, 67.8, 56.2, 37.6, 28.4, 25.9, 18.3, −4.6, −5.1.

IR (ATR): $\tilde{\nu}$/cm^{-1} 3385 (w), 2954 (m), 2930 (m), 2888 (w), 2857 (m), 1704 (s), 1496 (m), 1455 (m), 1351 (s), 1251 (s), 1169 (s), 1094 (m), 1048 (m), 966 (m), 927 (m), 835 (s), 776 (s), 700 (s), 672 (m), 528 (s).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{21}H_{37}NO_6SSi^+$: 482.2003 $[M+Na]^+$; found: 482.2010.

$[\boldsymbol{\alpha}]_D^{20}$ = −24.0 (*c* = 0.14, MeOH).

tert-Butyl (*S*)-4-((*R*)-((*tert*-butyldimethylsilyl)oxy)(phenyl)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (80)

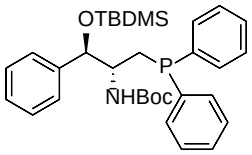


Under argon atmosphere, a heat-gun dried two-necked flask was charged with MeCN (7.6 mL), CH_2Cl_2 (7.6 mL), thionyl chloride (755 mg, 460 µL, 6.35 mmol) and the resulting solution was cooled in a dry-ice acetone bath. At −78 °C *tert*-butyl ((1*R*,2*S*)-1-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-1-phenylpropan-2-yl)carbamate (**77**) (969 mg, 2.54 mmol) in MeCN/CH_2Cl_2/THF (13 mL/13 mL/2.5 mL) was added dropwise to the reaction mixture over 45 minutes. After addition the mixture was stirred for 10 minutes at −78 °C and then pyridine (1.11 g, 1.13 mL, 14.0 mmol) was added over 10 minutes at −78 °C. The reaction solution was slow warmed to room temperature and stirred at ambient temperature overnight. Then the reaction mixture was concentrated under vacuum and the residue was dissolved in EtOAc (100 mL). The organic layer was washed with brine (2 x 50 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was directly used for the next step. The crude product was dissolved in MeCN (5 mL) and then at 0 °C sodium periodate (1.10 g, 5.14 mmol) and ruthenium chloride hydrate (7.69 mg, 0.037 mmol) were added. After water addition (5 mL) the resulting blue solution was

stirred for one hour at room temperature. Then brine (20 mL) was added and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (20:1), d x h: 3.5 x 15 cm) to afford the product **80** (883 mg, 1.99 mmol, 78%) as a white solid.

$C_{20}H_{33}NO_6SSi$ (443.60 g/mol):
TLC: R_f = 0.41 (SiO_2, cyclohexane:ethyl acetate (10:1)).
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.43-7.34 (m, 4H, ar-*H*), 7.33-7.27 (m, 1H, ar-*H*), 5.25 (d, $^3J_{HH}$ = 2.9 Hz, 1H, Ph-C*H*), 4.69-4.61 (m, 1H, NC*H*), 4.34-4.25 (m, 2H, CH_2), 1.54 (s, 9H, C(CH_3)$_3$), 0.93 (s, 9H, SiC(CH_3)$_3$), 0.12 (s, 3H, SiCH_3), −0.11 (s, 3H, SiCH_3).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 149.2, 139.4, 128.8, 128.3, 126.2, 85.6, 71.9, 65.1, 62.7, 28.1, 26.0, 18.3, −4.9, −5.1.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2963 (w), 2934 (m), 2896 (w), 2860 (m), 1723 (s), 1384 (s), 1315 (s), 1252 (m), 1192 (s), 1141 (s), 1052 (m), 1026 (m), 968 (m), 832 (s), 792 (m), 744 (m), 705 (s), 654 (m), 622 (m), 569 (w), 542 (w), 514 (w).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{20}H_{33}NO_6SSi^+$: 466.1690 $[M+Na]^+$; found: 466.1696.
$[\alpha]_D^{20}$ = −19.5 (*c* = 0.85, CH_2Cl_2).

tert-Butyl ((1*R*,2*R*)-1-((_tert_-butyldimethylsilyl)oxy)-3-(diphenylphosphanyl)-1-phenylpropan-2-yl)carbamate (79a)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl (*S*)-4-((*R*)-((*tert*-butyldimethylsilyl)oxy)(phenyl)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (**80**) (250 mg, 0.54 mmol) and THF (3 mL). Then, the reaction mixture was degassed by three freeze-pump-thaw cycles. At −78 °C, potassium diphenylphosphide solution (0.5 M, 158 mg, 1.41 mL, 0.71 mmol) was added dropwise over five minutes and afterwards the mixture was stirred one hour at −78 °C and overnight room temperature. At ambient temperature, a mixture of degassed H_2SO_4 (1 M, 3.6 mL) and brine (50%, 11 mL) was added and then the reaction mixture was stirred at room temperature for two hours. Then the reaction mixture was adjusted to an

alkaline pH (>10) by addition of degassed saturated aqueous Na_2CO_3 solution and the resulting biphasic mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (20:1), d x h: 2.5 x 13 cm) to afford the product **79a** (172 mg, 0.31 mmol, 58%) as a colorless gum.

$C_{32}H_{44}NO_3PSi$ (550.29 g/mol):

TLC: R_f = 0.32 (SiO_2, cyclohexane:ethyl acetate (10:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.33-7.21 (m, 11H, ar-*H*), 7.17 (t, $^3J_{HH}$ = 7.4 Hz, 2H, ar-*H*), 7.07 (d, $^3J_{HH}$ = 7.2 Hz, 2H, ar-*H*), 5.03 (br s, 1H, Ph-C*H*), 4.63 (d, $^3J_{HH}$ = 8.5 Hz, 1H, N*H*), 3.77-3.64 (m, 1H, NC*H*), 2.18-2.01 (m, 2H, PCH_2), 1.43 (s, 9H, C(CH_3)$_3$), 0.94 (s, 9H, SiC(CH_3)$_3$), 0.04 (s, 3H, SiCH_3), −0.10 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 155.1, 141.7, 139.4 (d, J_{CP} = 12.4 Hz), 137.2 (d, J_{CP} = 12.5 Hz), 133.0 (d, J_{CP} = 19.3 Hz), 132.6 (d, J_{CP} = 18.6 Hz), 128.8, 128.6, 128.5, 128.4, 128.2, 127.2, 126.3, 79.3, 76.2 (d, J_{CP} = 7.0 Hz), 55.4 (d, J_{CP} = 12.7 Hz), 28.6, 26.3 (d, J_{CP} = 12.5 Hz), 26.1, 18.4, −4.6, −5.0.

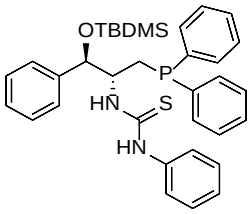
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −22.0.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2954 (m), 2928 (m), 2856 (w), 1704 (s), 1492 (m), 1363 (m), 1251 (m), 1168 (m), 1100 (m), 1068 (w), 1006 (w), 940 (w), 833 (s), 775 (s), 737 (s), 694 (s), 496 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{32}H_{44}NO_3PSi^+$: 550.2901 $[M+H]^+$; found: 550.2908.

$[\alpha]_D^{20}$ = −70.8 (*c* = 0.91, MeOH).

1-((1*R*,2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(diphenylphosphanyl)-1-phenylpropan-2-yl)-3-phenylthiourea (81a)

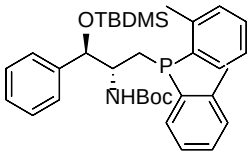


Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with *tert*-butyl ((1*R*,2*R*)-3-(diphenyl)-1-hydroxy-1-phenylpropan-2-yl)carbamate (**79a**) (87.4 mg, 0.16 mmol) and CH_2Cl_2 (1.6 mL). The resulting solution was cooled in an ice-water bath. At 0 °C, TFA (1.60 g, 1.04 mL, 14.0 mmol) was added dropwise and the mixture stirred for four hours at 0 °C and

overnight at room temperature. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the resulting crude product was directly used for the next step. The crude product was dissolved in CH_2Cl_2 (1.5 mL) and then phenyl isothiocyanate (24.1 mg, 21.3 µL, 0.18 mmol) was added. The reaction solution was stirred at room temperature overnight and afterwards concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (8:1), d x h: 2.5 x 17 cm) to afford the product **81a** (81.7 mg, 0.14 mmol, 88%) as a white solid.

$C_{34}H_{41}N_2OPSSi$ (584.83 g/mol):
MP: 64-65 °C.
TLC: R_f = 0.44 (SiO_2, cyclohexane:ethyl acetate (5:1)).
^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 8.15 (br s, 1H, N*H*), 7.43-7.36 (m, 4H, ar-*H*), 7.35-7.25 (m, 10H, ar-*H*), 7.23-7.17 (m, 4H, ar-*H*), 7.09 (t, $^3J_{HH}$ = 7.5 Hz, 2H, ar-*H*), 6.39 (br s, 1H, N*H*), 5.31 (s, 1H, Ph-C*H*), 4.72-4.62 (m, 1H, NC*H*), 2.26-2.12 (m, 2H, PCH_2), 0.78 (s, 9H, SiC(CH_3)$_3$), −0.15 (s, 1H, SiCH_3), −0.18 (s, 1H, SiCH_3).
^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.3, 141.9, 136.6, 133.4 (d, J_{CP} = 19.3 Hz), 132.8 (d, J_{CP} = 18.6 Hz), 130.6, 129.5, 129.2, 129.1 (d, J_{CP} = 2.8 Hz), 129.0 (d, J_{CP} = 3.6 Hz), 128.7, 127.8, 127.3, 126.5, 125.4, 75.4, 60.2 (d, J_{CP} = 13.0 Hz), 26.4, 26.0, 18.5, −4.4, −5.2.
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −23.4.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2950 (m), 2926 (m), 2854 (w), 1522 (s), 1494 (s), 1301 (m), 1248 (m), 1098 (m), 1066 (m), 936 (m), 832 (m), 776 (s), 735 (s), 693 (s), 499 (s).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{34}H_{41}N_2OPSSi^+$: 585.2519 $[M+H]^+$; found: 585.2517.
$[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = −156.4 (*c* = 0.90, CH_2Cl_2).

tert-butyl ((1*R*,2*R*)-1-((_tert_-butyldimethylsilyl)oxy)-3-(di-_o_-tolylphosphanyl)-1-phenylpropan-2-yl)carbamate (79b)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl (*S*)-4-((*R*)-((*tert*-butyldimethylsilyl)oxy)(phenyl)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (**80**) (230 mg, 520 µmol) and THF (2.1 mL). Then, the reaction mixture was degassed by three freeze-pump-thaw cycles. At −78 °C, potassium di(*o*-tolyl)phosphide solution (freshly prepared from di(*o*-tolyl)phosphine (**44a**) [189 mg, 880 µmol] and potassium hydride [35.4 mg, 880 µmol] in THF [1.8 mL]) was added dropwise over five minutes and afterwards the mixture was stirred one hour at −78 °C and overnight room temperature. At ambient temperature, a mixture of degassed H_2SO_4 (1 M, 3.5 mL) and brine (50%, 10 mL) was added and then the reaction mixture was stirred at room temperature for two hours. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed saturated aqueous Na_2CO_3 solution and the resulting biphasic mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (30:1), d x h: 2.5 x 14 cm) to afford the product **79b** (238 mg, 0.41 mmol, 80%) as a white gum.

$C_{34}H_{48}NO_3PSi$ (577.81 g/mol):

TLC: R_f = 0.34 (SiO_2, cyclohexane:ethyl acetate (20:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.35-7.02 (m, 11H, ar-*H*), 6.93-6.87 (m, 1H, ar-*H*), 6.65 (dd, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 3.8 Hz, 1H, ar-*H*), 5.05 (t, $^3J_{HH}$ = 2.4 Hz, 1H, Ph-C*H*), 4.55 (d, $^3J_{HH}$ = 8.2 Hz, 1H, N*H*), 3.74-3.60 (m, 1H, NC*H*), 2.41 (s, 3H, ar-CH_3), 2.32 (s, 3H, ar-CH_3), 2.12-1.96 (m, 2H, PCH_2), 1.44 (s, 9H, C(CH_3)$_3$), 0.95 (s, 9H, SiC(CH_3)$_3$), 0.04 (s, 3H, SiCH_3), −0.10 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 155.2, 142.9 (d, J_{CP} = 26.3 Hz), 142.3 (d, J_{CP} = 25.9 Hz), 141.8, 137.6 (d, J_{CP} = 13.4 Hz), 135.6 (d, J_{CP} = 13.3 Hz), 131.2, 131.1, 130.2 (d, J_{CP} = 4.8 Hz), 130.1 (d, J_{CP} = 5.1 Hz), 128.5, 128.4, 128.1, 127.1, 126.2, 126.1, 79.3, 76.0 (d, J_{CP} = 7.5 Hz), 55.7 (d, J_{CP} = 13.9 Hz), 28.6, 26.1, 24.7 (d, J_{CP} = 12.4 Hz), 21.4 (d, J_{CP} = 21.6 Hz), 21.2 (d, J_{CP} = 21.9 Hz), 18.4, −4.6, −5.0.

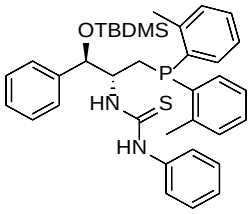
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −44.1.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2953 (m), 2928 (m), 2856 (w), 1705 (s), 1490 (m), 1451 (m), 1364 (m), 1249 (m), 1166 (s), 1102 (m), 1069 (m), 940 (w), 833 (s), 775 (s), 742 (s), 700 (m), 450 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{34}H_{48}NO_3PSi^+$: 578.3214 $[M+H]^+$; found: 578.3221.

$[\alpha]_D^{20}$ = −105.3 (*c* = 0.82, $CHCl_3$).

1-((1*R*,2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(di-*o*-tolylphosphanyl)-1-phenylpropan-2-yl)-3-phenylthiourea (81b)



Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with *tert*-butyl ((1*R*,2*R*)-3-(di-*o*-tolylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)carbamate (**79b)** (145 mg, 250 µmol) and CH_2Cl_2 (2.5 mL). The resulting solution was cooled in an ice-water bath. At 0 °C, TFA (2.77 g, 1.80 mL, 24.3 mmol) was added dropwise and the mixture stirred for four hours at 0 °C and overnight at room temperature. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the resulting crude product was directly used for the next step. The crude product was dissolved in CH_2Cl_2 (1.5 mL) and then phenyl isothiocyanate (38.1 mg, 33.7 µL, 280 µmol) was added. The reaction solution was stirred at room temperature overnight and afterwards concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (25:1), d x h: 2.5 x 15 cm) to afford the product **81b** (238 mg, 410 µmol, 80%) as a white solid.

$C_{36}H_{45}N_2OPSSi$ (612.89 g/mol):

MP: 75-76 °C.

TLC: R_f = 0.29 (SiO_2, cyclohexane:ethyl acetate (10:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 9.80 (br s, 1H, N*H*), 7.47 (d, $^3J_{HH}$ = 7.4 Hz, 2H, ar-*H*), 7.41-7.33 (m, 7H, ar-*H*), 7.32-7.26 (m, 1H, ar-*H*), 7.24-7.04 (m, 6H, ar-*H*), 6.84-6.73 (m, 2H, ar-*H*), 6.30-6.23 (br m, 1H, N*H*), 5.46 (s, 1H, Ph-C*H*), 4.43-4.36 (m, 1H, NC*H*), 2.37 (s, 3H, ar-CH_3), 2.23 (s, 3H, ar-CH_3), 2.07-1.88 (m, 2H, PCH_2), 0.86 (s, 9H, SiC(CH_3)$_3$), 0.00 (s, 3H, SiCH_3), −0.15 (s, 3H, SiCH_3).

$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_2Cl_2): δ/ppm = 179.9, 142.1 (d, J_{CP} = 26.0 Hz), 141.6, 140.9 (d, J_{CP} = 25.6 Hz), 138.8, 137.0 (d, J_{CP} = 13.1 Hz), 134.7 (d, J_{CP} = 14.4 Hz), 130.3, 130.2-129.8 (m), 128.7, 128.5, 128.4, 128.0, 127.1, 126.1 (d, J_{CP} = 17.0 Hz), 125.3, 124.5, 123.2, 74.1 (d, J_{CP} = 6.8 Hz), 57.8 (d, J_{CP} = 14.1 Hz), 25.8, 24.0 (d, J_{CP} = 11.9 Hz), 20.8 (d, J_{CP} = 16.1 Hz), 20.6 (d, J_{CP} = 16.8 Hz), 17.9, −5.2, −5.3.

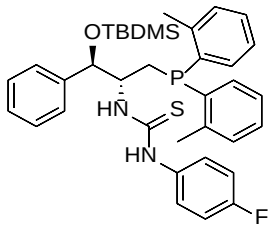
$^{31}P\{^{1}H\}$ NMR (162 MHz, CD_2Cl_2): δ/ppm = −44.5.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2950 (m), 2926 (m), 2854 (m), 1589 (w), 1516 (s), 1494 (m), 1449 (m), 1376 (m), 1248 (s), 1101 (s), 1066 (s), 938 (m), 832 (s), 776 (m), 741 (s), 698 (s), 501 (m), 455 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{36}H_{45}N_2OPSSi^+$: 613.2832 $[M+H]^+$; found: 613.2842

$[\alpha]_D^{20}$ = −186.0 (*c* = 0.70, CH_2Cl_2).

1-((1*R*,2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(di-*o*-tolylphosphanyl)-1-phenylpropan-2-yl)-3-(4-fluorophenyl)thiourea (81c)



Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with *tert*-butyl ((1*R*,2*R*)-3-(di-*o*-tolylphosphanyl)-1-hydroxy-1-phenylpropan-2-yl)carbamate (**79b**) (60.0 mg, 100 µmol) and CH_2Cl_2 (1 mL). The resulting solution was cooled in an ice-water bath. At 0 °C, TFA (1.02 g, 0.66 mL, 8.90 mmol) was added dropwise and the mixture stirred for four hours at 0 °C and overnight at room temperature. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the resulting crude product was directly used for the next step. The crude product was dissolved in CH_2Cl_2 (1 mL) and then 4-fluorophenyl isothiocyanate (17.7 mg, 110 µmol) was added. The reaction solution was stirred at room temperature overnight and afterwards concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (20:1), d x h: 2.5 x 12 cm) to afford the product **81c** (55.8 mg, 88.0 µmol, 86%) as a white solid.

$C_{36}H_{44}FN_2OPSSi$ (630.88 g/mol):

MP: 77-78 °C.

TLC: R_f = 0.20 (SiO_2, cyclohexane:ethyl acetate (20:1)).

^{1}H NMR (400 MHz CD_2Cl_2): δ/ppm = 8.08 (br s, 1H, N*H*), 7.42 (d, $^3J_{HH}$ = 7.0 Hz, 2H, ar-*H*), 7.38-7.02 (m, 12H, ar-*H*), 6.91 (t, $^3J_{HH}$ = 7.4 Hz, 2H, ar-*H*), 6.53 (s, 1H, ar-*H*), 6.14 (d, $^3J_{HH}$ = 8.3 Hz, 1H, N*H*), 5.41 (s, 1H, Ph-C*H*), 4.61 (br s, 1H, NC*H*), 2.42 (s, 3H, ar-CH_3), 2.30 (s, 3H, ar-CH_3), 2.12-1.98 (m, 2H, PCH_2), 0.80 (s, 9H, SiC(CH_3)$_3$), -0.10 (s, 3H, SiCH_3), −0.15 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.6, 163.0, 160.5, 143.4 (d, J_{CP} = 26.1 Hz), 142.4 (d, J_{CP} = 26.1 Hz), 142.0, 137.5 (d, J_{CP} = 12.7 Hz), 135.5 (d, J_{CP} = 12.9 Hz), 132.4, 131.7, 131.1, 130.7 (d, J_{CP} = 3.2 Hz), 130.6 (d, J_{CP} = 3.4 Hz), 129.1, 129.1, 128.7, 128.0 (d, J_{CP} = 2.5 Hz), 127.9 (d, J_{CP} = 2.6 Hz), 127.8, 126.7, 126.6, 126.5, 117.4 (d, J_{CP} = 22.8 Hz), 75.2, 60.5 (d, J_{CP} = 14.2 Hz), 26.0, 24.7, 21.6 (d, J_{CP} = 14.1 Hz), 21.4 (d, J_{CP} = 14.1 Hz), 18.5, −4.4, −5.1.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −45.4.

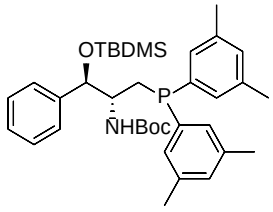
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ/ppm = −114.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2951 (m), 2926 (m), 2855 (w), 1505 (s), 1469 (m), 1450 (m), 1375 (m), 1217 (s), 1101 (m), 1066 (s), 938 (m), 832 (s), 776 (s), 743 (s), 700 (m), 509 (m), 454 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{36}H_{45}N_2OPSSi^+$: 613.2832 $[M+H]^+$; found: 613.2842.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −169.8 (*c* = 0.96, CH_2Cl_3).

tert-Butyl ((1*R*,2*R*)-3-(bis(3,5-dimethylphenyl)phosphanyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)carbamate (79c)

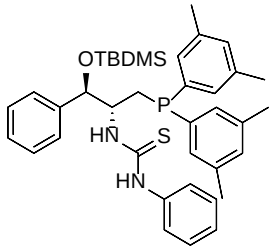


Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl (*S*)-4-((*R*)-((*tert*-butyldimethylsilyl)oxy)(phenyl)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (**80**) (200 mg, 520 µmol) and THF (2 mL). Then the reaction mixture was degassed by three freeze-pump-thaw cycles. At −78 °C, potassium bis(3,5-dimethylphenylphosphide solution (freshly prepared from bis(3,5-dimethylphenylphosphine (**44g**) [186 mg, 770 µmol] and potassium hydride [30.8 mg, 770 µmol] in THF [2 mL]) was added dropwise over five minutes and afterwards the

mixture was stirred one hour at −78 °C and overnight room temperature. At ambient temperature, a mixture of degassed H_2SO_4 (1 M, 4 mL) and brine (50%, 12 mL) was added and then the reaction mixture was stirred at room temperature for two hours. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed saturated aqueous Na_2CO_3 solution and the resulting biphasic mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (30:1), d x h: 2.5 x 13 cm) to afford the product **79c** (180 mg, 300 µmol, 66%) as a white gum.

$C_{36}H_{52}NO_3PSi$ (605.87 g/mol):
TLC: R_f = 0.53 (SiO_2, cyclohexane:ethyl acetate (10:1)).
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.35-7.21 (m, 5H, ar-*H*), 6.94-6.87 (m, 4H, ar-*H*), 6.70 (d, $^3J_{HH}$ = 8.0 Hz, 2H, ar-*H*), 5.06 (s, 1H, Ph-C*H*), 4.68 (d, $^3J_{HH}$ = 8.1 Hz, 1H, N*H*), 3.73-3.60 (m, 1H, NC*H*), 2.25 (s, 6H, ar-CH_3), 2.16 (s, 6H, ar-CH_3), 2.13-2.03 (m, 2H, PCH_2), 1.43 (s, 9H, C(CH_3)$_3$), 0.94 (s, 9H, SiC(CH_3)$_3$), 0.05 (s, 3H, SiCH_3), −0.11 (s, 3H, SiCH_3).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 155.0, 141.7, 139.1 (d, J_{CP} = 10.8 Hz), 137.8, 137.7, 137.6, 136.4 (d, J_{CP} = 11.8 Hz), 130.6, 130.4, 130.2, 130.2, 130.0, 127.9, 127.0, 126.2, 79.0, 75.8 (d, J_{CP} = 6.7 Hz), 55.5 (d, J_{CP} = 12.5 Hz), 28.5, 26.0, 21.3, 21.2, 18.3, −4.7, −5.1.
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −22.5.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2947 (m), 2934 (m), 2860 (w), 1711 (s), 1468 (m), 1460 (m), 1370 (m), 1244 (m), 1109 (s), 1089 (m), 1059 (m), 932 (w), 745 (m).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{34}H_{48}NO_3PSi^+$: 606.3527 $[M+H]^+$; found: 606.3524.
$[\alpha]_D^{20}$ = −96.1 (*c* = 0.92, $CHCl_3$).

1-((1*R*,2*R*)-3-(bis(3,5-dimethylphenyl)phosphanyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-3-phenylthiourea (81d)



Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with *tert*-butyl ((1*R*,2*R*)-3-(bis(3,5-dimethylphenyl)phosphanyl)-1-hydroxy-1-phenylpropan-2-yl)carbamate (**79c**) (135.0 mg, 0.22 mmol) and CH_2Cl_2 (3 mL). The resulting solution was cooled in an ice-water bath. At 0 °C, TFA (2.46 g, 1.59 mL, 21.6 mmol) was added dropwise and stirred for four hours at 0 °C and overnight at room temperature. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the resulting crude product was directly used for the next step. The crude product was dissolved in CH_2Cl_2 (2 mL) and then phenyl isothiocyanate (33.8 mg, 250 µmol) was added. The reaction solution was stirred at room temperature overnight and afterwards concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (20:1), d x h: 2.5 x 14 cm) to afford the product **81d** (127 mg, 198 µmol, 89%) as a white solid.

$C_{38}H_{49}N_2OPSSi$ (640.94 g/mol):

MP: 72-73 °C.

TLC: R_f = 0.47 (SiO_2, cyclohexane:ethyl acetate (5:1)).

^{1}H NMR (400 MHz CD_2Cl_2): 8.05 (s, 1H, N*H*), 7.42-7.23 (m, 8H, ar-*H*), 7.20-7.13 (m, 2H, ar-*H*), 6.93 (t, $^3J_{HH}$ = 7.7 Hz, 4H, ar-*H*), 6.73 (d, $^3J_{HH}$ = 8.0 Hz, 2H, ar-*H*), 6.30 (s, 1H, N*H*), 5.30 (s, 1H, Ph-C*H*), 4.65 (s, 1H, NC*H*), 2.25 (s, 6H, ar-CH_3), 2.18 (s, 6H, ar-CH_3), 2.17-2.12 (m, 2H, PCH_2), 0.77 (s, 9H, SiC(CH_3)$_3$), −0.15 (s, 3H, SiCH_3), −0.18 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.2, 142.0, 138.5 (t, J_{CP} = 7.2 Hz), 136.6, 131.1, 130.9, 130.7, 130.6, 130.5, 130.4, 128.6, 127.7, 127.3, 126.5, 125.4, 75.4, 60.6 (d, J_{CP} = 13.8 Hz), 26.0, 21.5 (d, J_{CP} = 7.0 Hz), 18.5, −4.4, −5.1.

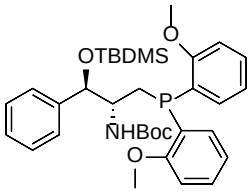
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −24.2.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2950 (m), 2920 (m), 2840 (w), 1500 (s), 1487 (m), 1379 (m), 1216 (s), 1104 (m), 1062 (s), 936 (m), 837 (s), 771 (s), 747 (s), 710 (m), 511 (m), 436 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{38}H_{50}N_2OPSSi^+$: 641.3145 $[M+H]^+$; found: 641.3153.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −178.8 (*c* = 0.86, CH_2Cl_2).

tert-Butyl ((1*R*,2*R*)-3-(bis(2-methoxyphenyl)phosphanyl)-1-((_tert_-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)carbamate (79d)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with *tert*-butyl (*S*)-4-((*R*)-((*tert*-butyldimethylsilyl)oxy)(phenyl)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (**80**) (212 mg, 478 µmol) and THF (2 mL). Then, the reaction mixture was degassed three-times by freeze-pump-thaw method. At −78 °C, potassium bis(2-methoxyphenyl)phosphide solution (freshly prepared from bis(2-methoxyphenyl)phosphine [200 mg, 812 µmol] and potassium hydride [32.6 mg, 813 µmol] in THF [2 mL]) was added dropwise over five minutes and afterwards the mixture was stirred one hour at −78 °C and overnight room temperature. At ambient temperature, a mixture of degassed H_2SO_4 (1 M, 4 mL) and brine (50%, 12 mL) was added and then the reaction mixture was stirred at room temperature for two hours. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed saturated aqueous Na_2CO_3 solution and then the biphasic mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (10:1), d x h: 2.5 x 14 cm) to afford the product **79d** (158 mg, 259 µmol, 54%) as a white gum.

$C_{34}H_{48}NO_5PSi$ (609.82 g/mol):

TLC: R_f = 0.51 (SiO_2, cyclohexane:ethyl acetate (3:1)).

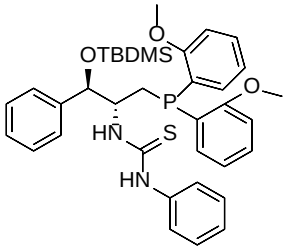
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.36 (d, $^3J_{HH}$ = 7.5 Hz, 2H, ar-*H*), 7.30 (d, $^3J_{HH}$ = 6.8 Hz, 2H, ar-*H*), 7.27 (d, $^3J_{HH}$ = 3.0 Hz, 1H, ar-*H*), 7.30-7.21 (m, 2H, ar-*H*), 6.84 (dd, $^3J_{HH}$ = 8.2, 4.2 Hz, 1H, ar-*H*), 6.80-6.74 (m, 3H, ar-*H*), 6.67 (t, $^3J_{HH}$ = 7.4 Hz, 1H, ar-*H*), 6.54 (t, $^3J_{HH}$ = 6.9 Hz, 1H, ar-*H*), 5.17 (br s, 1H, N*H*), 4.92 (br s, 1H, Ph-C*H*), 3.83 (s, 3H, OCH_3), 3.68-3.59 (m, 1H, NC*H*), 3.54 (s, 3H, OCH_3), 2.23-2.09 (m, 2H, PCH_2), 1.42 (s, 9H, C(CH_3)$_3$), 0.94 (s, 9H, SiC(CH_3)$_3$), 0.06 (s, 3H, SiCH_3), −0.10 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 161.9 (d, J_{CP} = 11.5 Hz), 160.8 (d, J_{CP} = 12.9 Hz), 155.4, 142.2, 133.3 (d, J_{CP} = 10.3 Hz), 132.9 (d, J_{CP} = 6.3 Hz), 130.4, 129.8, 128.0, 126.9, 126.4, 121.1 (d, J_{CP} = 3.5 Hz), 120.9 (d, J_{CP} = 2.6 Hz), 110.2 (d, J_{CP} = 20.1 Hz), 79.0, 75.5 (d, J_{CP} = 7.1 Hz), 56.3 (d, J_{CP} = 14.0 Hz), 55.5, 55.4, 28.6, 26.1, 21.8 (d, J_{CP} = 11.3 Hz), 18.5, −4.6, −5.0.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −38.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3003 (w), 2929 (w), 2855 (w), 1709 (s), 1584 (w), 1472 (m), 1429 (m), 1365 (w), 1238 (s), 1164 (s), 1103 (w), 1069 (m), 1023 (m), 942 (m), 834 (m), 749 (s), 701 (w), 496 (w).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{34}H_{48}NO_5PSi^+$: 610.3112 $[M+H]^+$; found: 610.3117.
$[\alpha]_D^{20}$ = −55.1 (*c* = 0.61, $CHCl_3$).

1-((1*R*,2*R*)-3-(bis(2-Methoxyphenyl)phosphanyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-3-phenylthiourea (81e)



Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with *tert*-butyl ((1*R*,2*R*)-3-(bis(2-methoxyphenyl)phosphanyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)carbamate (**79d**) (115.0 mg, 189 µmol), CH_2Cl_2 (2 mL) and this solution was cooled in an ice-water bath. At 0 °C, TFA (2.01 g, 1.30 mL, 17.6 mmol) was added dropwise to the reaction mixture and then the mixture was stirred for four hours at 0 °C and overnight at room temperature. The reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed saturated aqueous Na_2CO_3 and then the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the corresponding crude was directly used for the next step. The crude mixture was dissolved in CH_2Cl_2 (2 mL) and then phenyl isothiocyanate (28.7 mg, 25.4 µL, 208 µmol) was added. The reaction solution was stirred at room temperature overnight and afterwards concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (20:1), d x h: 2.5 x 14 cm) to afford the product **81e** (105 mg, 163 µmol, 86%) as a white solid.

$C_{36}H_{45}N_2O_3PSSi$ (644.89 g/mol):
MP: 97-98 °C.
TLC: R_f = 0.47 (SiO_2, cyclohexane:ethyl acetate (5:1)).
^{1}H NMR (400 MHz CD_2Cl_2): 8.02 (s, 1H, N*H*), 7.49-7.41 (m, 4H, ar-*H*), 7.39-7.22 (m, 8H, ar-*H*), 6.90-6.70 (m, 5H, ar-*H*), 6.59-6.54 (m, 1H, ar-*H*), 6.50 (d, $^3J_{HH}$ = 7.3 Hz, 1H, N*H*), 5.46 (s, 1H, Ph-C*H*), 4.60-4.45 (m, 1H, NC*H*), 3.71 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 2.34 (ddd, $^2J_{HP}$ = 15.0 Hz,

$^{2}J_{HH}$ = 12.4 Hz, $^{3}J_{HH}$ = 5.6 Hz, 1H, PCH_2), 2.14-2.07 (m, 1H, PCH_2), 0.78 (s, 9H, SiC(CH_3)$_3$), −0.11 (s, 3H, SiCH_3), −0.17 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 180.0, 162.4 (d, J_{CP} = 11.6 Hz), 161.1 (d, J_{CP} = 13.3 Hz), 142.4, 136.8, 133.6 (d, J_{CP} = 11.2 Hz), 133.1 (d, J_{CP} = 6.2 Hz), 130.9, 130.6, 130.2, 128.5, 127.6, 127.1, 126.5, 125.3, 123.55 (d, J_{CP} = 16.3 Hz), 121.4 (d, J_{CP} = 18.8 Hz), 110.8 (d, J_{CP} = 25.6 Hz), 74.9, 61.0 (d, J_{CP} = 15.5 Hz), 55.9, 55.8, 26.0, 22.2 (d, J_{CP} = 9.2 Hz), 18.4, −4.4, −5.2.

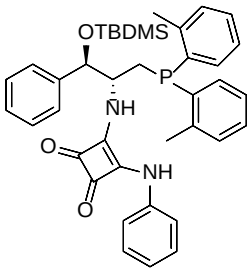
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −37.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3382 (w), 3167 (w), 2951 (w), 2927 (w), 1521 (m), 1460 (m), 1428 (m), 1379 (m), 1236 (s), 1177 (w), 1102 (w), 1067 (m), 1023 (m), 940 (w), 832 (m), 748 (s), 699 (s), 501 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{36}H_{45}N_2O_3PSSi^+$: 645.2731 $[M+H]^+$; found: 645.2742.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −157.4 (*c* = 0.52, MeOH).

3-(((1R,2R)-1-((tert-butyldimethylsilyl)oxy)-3-(di-o-tolylphosphanyl)-1-phenylpropan-2-yl)-amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione (83)



According to general procedure **GP3**, (1R,2R)-1-((tert-butyldimethylsilyl)oxy)-3-(di-*o*-tolyl-phosphanyl)-1-phenylpropan-2-amine (**82**) (43.3 mg, 209 µmol) in MeOH (5 mL) and 3-(methoxy)-4-(phenylamino)-3-cyclobutene-1,2-dione (**24a**) (99.8 mg, 209 µmol) were stirred for four days to give the product **83** (75.0 mg, 116 µmol, 55%) as a white solid.

$C_{39}H_{45}N_2O_3PSi$ (648.85 g/mol):

MP: >250 °C.

^{1}H NMR (400 MHz DMSO-d_6): δ/ppm = 9.54 (s, 1H, N*H*), 7.57 (d, $^{3}J_{HH}$ = 8.9 Hz, 1H, N*H*), 7.41-6.98 (m, 19H, ar-*H*), 6.85 (dd, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 3.9 Hz, 1H, ar-*H*), 4.94 (d, $^{3}J_{HH}$ = 4.7 Hz, 1H, Ph-C*H*), 4.20-4.05 (m, 1H, NC*H*), 2.27 (s, 3H, ar-CH_3), 2.25 (s, 3H, ar-CH_3), 2.48-2.42 (m, 1H,

PCH_2), 2.13-2.02 (m, 1H, PCH_2), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.03 (s, 3H, SiCH_3), −0.20 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): 183.3, 180.4, 168.8, 163.5, 142.0 (d, J_{CP} = 26.1 Hz), 141.2 (d, J_{CP} = 25.7 Hz), 140.6, 138.8, 136.5 (d, J_{CP} = 13.2 Hz), 135.0 (d, J_{CP} = 14.0 Hz), 130.6 (d, J_{CP} = 7.2 Hz), 130.0 (d, J_{CP} = 4.8 Hz), 129.4, 128.6 (d, J_{CP} = 21.8 Hz), 128.1, 127.6, 126.4, 126.2 (d, J_{CP} = 3.7 Hz), 122.7, 118.0, 77.5 (d, J_{CP} = 7.4 Hz), 58.1 (d, J_{CP} = 14.0 Hz), 27.3 (d, J = 12.9 Hz), 25.7, 20.8 (d, J_{CP} = 14.7 Hz), 20.6 (d, J_{CP} = 15.3 Hz), 17.8, −5.2, −5.1.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −44.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2853 (w), 1653 (m), 1561 (s), 1535 (s), 1470 (m), 1434 (w), 1251 (w), 1036 (w), 898 (w), 862 (s), 780 (s), 716 (m), 670 (m), 568 (s), 452 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{39}H_{45}N_2O_3PSi^+$: 649.3010 $[M+H]^+$; found: 6439.3002.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −58.2 (*c* = 0.39, DMSO).

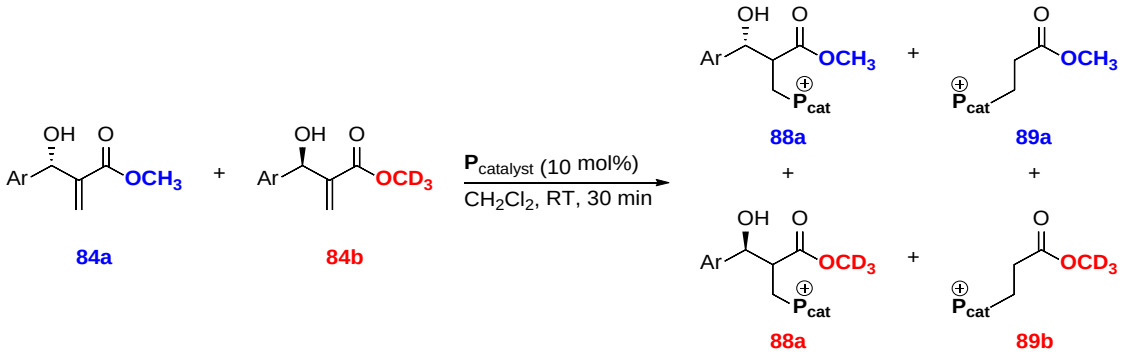
5.2.5 Catalyst Evaluation by ESI-MS Back Reaction Screening

General Procedure for ESI-MS Back Reaction Screening

A GC-vial was charged with an equimolar mixture of **84a** (1186 µg, 5.0 µmol), **84b** (1201 µg, 5.0 µmol) and the organocatalyst (1.0 µmol; 10 mol% based on the total amount of quasi-enantiomeric substrates **84a** and **84b**). The mixture was dissolved in CH_2Cl_2 (0.1 mL) and the corresponding solution was stirred for 30 minutes at room temperature. Then, the reaction mixture was diluted with CH_2Cl_2 (1 mL), treated with acetic acid (10 µL) and directly injected into the ESI-MS spectrometer.

Overview of Single Catalyst Screening

Table 50: ESI-MS screening of bifunctional organocatalysts.



Entry	catalyst	ESI-MS screening 88a/88b	ESI-MS screening 89a/89b	preparative reaction e.r.
1	**19a**	48:52	39:61	38:62
2	**19b**	31:69	23:77	22:78
3	**19c**	32:68	26:74	28:72
4	**19d**	40:60	23:77	23:77
5	**19e**	40:60	26:74	25:75
6	**19f**	35:65	21:79	20:80

7	**20a**	46:54	23:77	23:77
8	**20b**	47:53	23:77	23:77
9	**20c**	48:52	22:78	24:76
10	**20d**	40:60	16:84	17:83
11	**20e**	50:50	16:84	14:86
12	**20f**	50:50	16:84	16:84
13	**20g**	46:54	20:60	21:79
14	**25a**	18:82	14:86	12:88
15	**25b**	35:65	18:82	19:81
16	**25c**	31:69	18:82	18:82
17	**25d**	37:63	15:85	14:86
18	**25e**	40:60	18:82	19:81
19	**25f**	40:60	17:83	15:85
20	**26a**	37:63	16:84	17:83
21	**26b**	35:65	14:86	14:86
22	**26c**	38:62	15:85	11:89
23	**26j**	33:67	23:77	25:75
24	**26k**	37:63	24:76	25:75
25	**26l**	25:75	16:84	16:84
26	**26d**	40:60	20:80	20:80
27	**26e**	32:68	15:85	15:85
28	**26f**	49:51	19:81	18:82
29	**26h**	47:53	16:84	16:84

30	**26m**	33:67	18:82	15:85
31	**26g**	26:74	16:84	16:84
32	**26l**	27:73	12:88	15:85
33	**37**	28:72	23:77	24:76
34	**46a**	53:47	91:9	90:10
35	**56**	60:40	70:30	80:20
36	**45a**	51:49	52:48	50:50
37	**49a**	72:28	85:15	83:17
38	**49b**	50:50	82:18	81:19
39	**49c**	70:30	83:17	84:16
40	**46b**	66:34	88:12	87:13
41	**46c**	81:19	91:9	90:10
42	**46d**	60:40	89:11	87:13
42	**46e**	65:35	87:13	87:13
44	**46f**	60:40	83:17	80:20
45	**48a**	73:27	94:6	94:6
46	**48b**	72:28	93:7	94:6
47	**48c**	60:40	94:6	93:7
48	**48d**	85:15	96:4	95:5
49	**48e**	86:14	95:5	95:5
50	**48g**	75:25	79:21	79:21
51	**48h**	73:27	80:20	81:19
52	**52**	47:53	50:50	49:51

53	**64**	43:57	13:87	13:87
54	**81a**	58:42	93:7	94:6
55	**81b**	86:14	95:5	95:5
56	**81c**	80:20	95:5	95:5
57	**81d**	50:50	71.29	71:29
58	**81e**	77:23	89.11	89:11
59	**83**	76:24	93:7	92:7

Synthesis of crude catalyst mixture for the first catalyst generation

Under argon atmosphere a heat-gun dried two-necked flask was charged with (S)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (**18d**) (11.0 mg, 34.4 µmol) and CH_2Cl_2 (200 µL). Then, a mixture of phenyl isothiocyanate (1.58 mg, 1.40 µL, 11.7 µmol), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (3.18 mg, 2.14 µL, 11.7 µmol) and 4-trifluoromethylphenyl isothiocyanate (2.38 mg, 11.7 µmol) in CH_2Cl_2 (100 µL) was added dropwise to the amino phosphine solution. The reaction solution was stirred at room temperature overnight and concentrated under vacuum. The resulting crude catalyst mixture (524 µg, equal to 10mol% based on the average molecular mass of the catalyst mixture) was directly used for ESI-MS back reaction screening following the standard protocol for single catalyst screening.

Synthesis of crude catalyst mixture for the second catalyst generation

Under argon atmosphere a heat-gun dried two-necked flask was charged with (S)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (3.53 mg, 11.1 µmol), (S)-1-(diphenylphosphanyl)-4-methylpentan-2-amine (3.16 mg, 11.1 µmol), (S)-1-(diphenylphosphanyl)-3-methylbutan-2-amine (3.0 mg, 11.1 µmol) and MeOH (500 µL). Then, 3-(methoxy)-4-(phenylamino)-3-cyclobutene-1,2-dione (6.74 mg, 33.2 µmol) was added to the reaction mixture and stirred for 48 hours at room temperature. The resulting precipitate was filtered off and washed with MeOH to afford the pure

catalyst mixture after drying under vacuum. The resulting crude catalyst mixture (463 µg, equal to 10mol% based on the average molecular mass of the catalyst mixture) was directly used for ESI-MS back reaction screening following the standard protocol for single catalyst screening.

Synthesis of crude catalyst mixture for the third catalyst generation

Step A: Under argon atmosphere a heat-gun dried two-necked flask was charged with (1*S*,2*R*)-2-amino-3-(diphenylphosphanyl)-1-phenylpropan-1-ol (7.71 mg, 23.0 µmol), (1*S*,2*R*)-2-amino-3-(di-*o*-tolylphosphanyl)-1-phenylpropan-1-ol (8.36 mg, 23.0 µmol), (1*S*,2*R*)-2-amino-3-(bis(3,5-dimethylphenyl)phosphanyl)-1-phenylpropan-1-ol (9.00 mg, 23.0 µmol) and CH_2Cl_2 (500 µL). Then, a mixture of phenyl isothiocyanate (4.76 mg, 4.21 µL, 34.5 µmol) and 4-fluorophenyl isothiocyanate (5.28 mg, 34.5 µmol) in CH_2Cl_2 (100 µL) was added. The reaction solution was stirred at room temperature overnight and concentrated under vacuum. The remaining residue was directly used for the next step.

Step B: Under argon atmosphere a heat-gun dried round bottomed flask was charged with the crude product mixture from step A, CH_2Cl_2 (500 µL) and triethylamine (14.0 mg, 19.4 µL, 138 µmol. Then, TBDMS triflate (18.2 mg, 15.9 µL, 69.0 µmol) was added dropwise over 5 minutes to the reaction mixture at 0 °C. After stirring for two hours at 0 °C and additional four hours at room temperature, the mixture was concentrated under vacuum. The crude reaction mixture was dissolved in ether (10 mL) and the corresponding organic layer was washed with saturated NH_4Cl solution (10 mL), saturated $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic layers was then dried over Na_2SO_4, filtered and concentrated under vacuum. The resulting crude catalyst mixture (1.86 mg, equal to 10mol% based on the average molecular mass of the catalyst mixture) was directly used for ESI-MS back reaction screening following the standard protocol for single catalyst screening.

Synthesis of crude catalyst mixture for the fourth catalyst generation

Step A: Under argon atmosphere a heat-gun dried two-necked flask was charged with *tert*-butyl (*S*)-4-((*R*)-((*tert*-butyldimethylsilyl)oxy)(phenyl)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (50 mg, 110 µmol) and THF (1 mL). Then, the reaction mixture was degassed by three freeze-pump-thaw cycles. At −78 °C potassium phosphide solution (freshly prepared from a mixture di(*o*-tolyl)phosphine [12.1 mg, 56.5 µmol], diphenylphosphine [12.1 mg, 56.5 µmol],

bis(3,5-dimethylphenyl)chlorophosphine [6.9 mg, 28.3 µmol] and potassium hydride [6.8 mg, 169 µmol] in THF [1.0 mL]) was added dropwise over five minutes and afterwards the mixture was stirred for one hour at −78 °C and overnight at room temperature. At ambient temperature, a mixture of degassed H_2SO_4 (1M, 3.6 mL) and brine (50%, 11 mL) was added and the resulting mixture was stirred at room temperature for two hours. Then, the reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The remaining residue was directly used for the next step.

Step B: Under argon atmosphere a heat-gun dried round bottomed flask was charged with the crude product mixture from step A, CH_2Cl_2 (1 mL) and the resulting solution was cooled in an ice-water bath. At 0 °C, TFA (1.02 g, 0.66 mL, 8.90 mmol) was added dropwise. After stirring for four hours at 0 °C and overnight at room temperature, the reaction mixture was adjusted to an alkaline pH (>10) by addition of degassed saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the residue was directly used for the next step.

Step C: The crude product mixture from step B was dissolved in CH_2Cl_2 (1 mL) and then a mixture of phenyl isothiocyanate (8.57 mg, 7.6 µL, 62.2 µmol) and 4-fluorophenyl isothiocyanate (9.71 mg, 62.2 µmol) in CH_2Cl_2 (200 µL) was added. The reaction solution was stirred at room temperature overnight and concentrated under vacuum. The resulting crude catalyst mixture (1.86 mg, equal to 10mol% based on the average molecular mass of the catalyst mixture) was directly used for ESI-MS back reaction screening following the standard protocol for single catalyst screening.

5.2.6 Kinetic Measurements

Reaction Order in Aldehyde

A stock solution was prepared by dissolving methyl acrylate (25.8 mg, 27.0 µL, 300 µmol), catalyst (1*R*,2*R*)-**81b** (18.4 mg, 30.0 µmol) and mesitylene as internal standard (36.1 mg, 41.5 µL, 300 µmol) in CD_2Cl_2 (3.53 mL).

Under argon atmosphere four different NMR tubes were charged with different amounts of 4-nitrobenzaldehyde (25 µmol, 0.5 eq. / 50 µmol, 1.0 eq. / 100 µmol, 2.0 eq. / 150 µmol, 3 eq.). Then, 0.6 mL of the stock solution (containing 50 µmol methyl acrylate, 1.0 eq.) was added into each NMR tube and after shaking the tubes were put into the autosampler of the NMR spectrometer. The reaction process at room temperature was tracked by ^{1}H-NMR analysis (every 30 minutes one ^{1}H-NMR measurement) based on the signals of the methyl ester group of acrylate **104a** (3.73 ppm) and MBH adduct **84a** (3.71 ppm).

Logarithmic plot of the dependence of [acrylate] on the reaction time between 0 to 720 min.

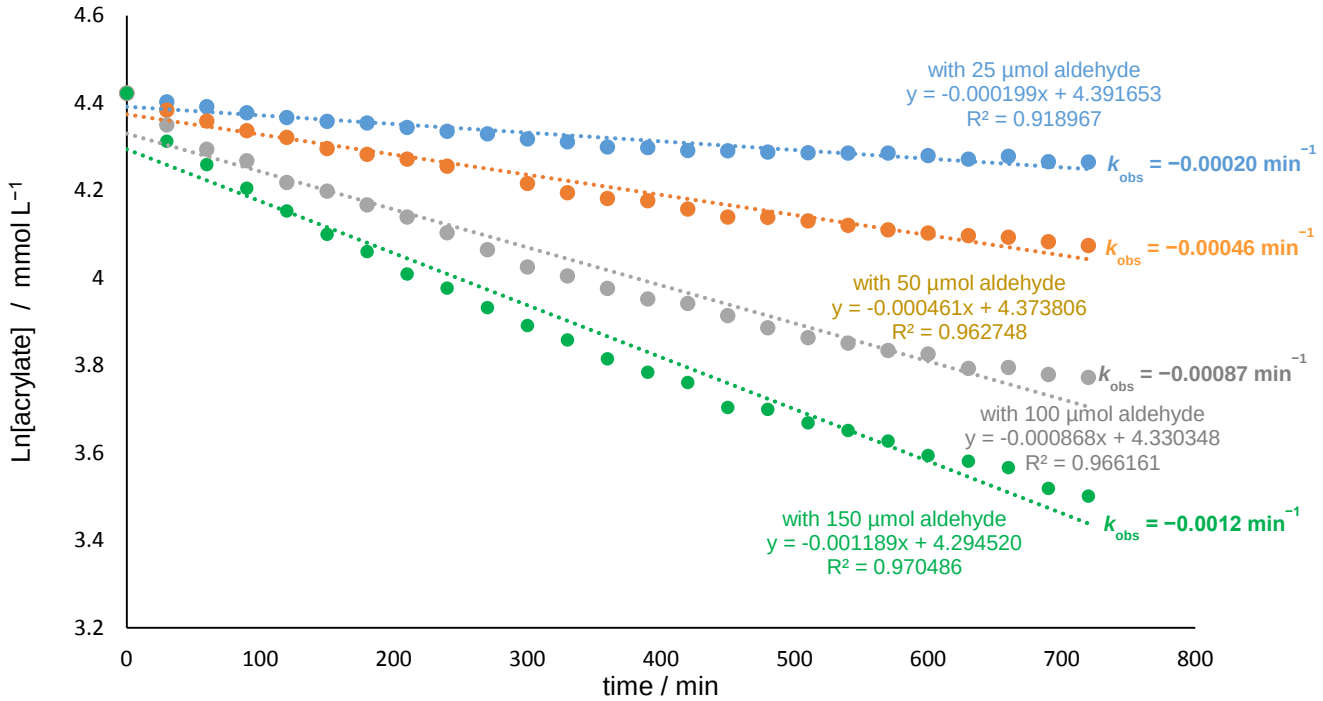


Figure 47: Kinetic analysis of the MBH reaction of methyl acrylate with 4-nitrobenzaldehyde.

Logarithmic plot of the dependence of [acrylate] on the reaction time between 0 to 60 min.

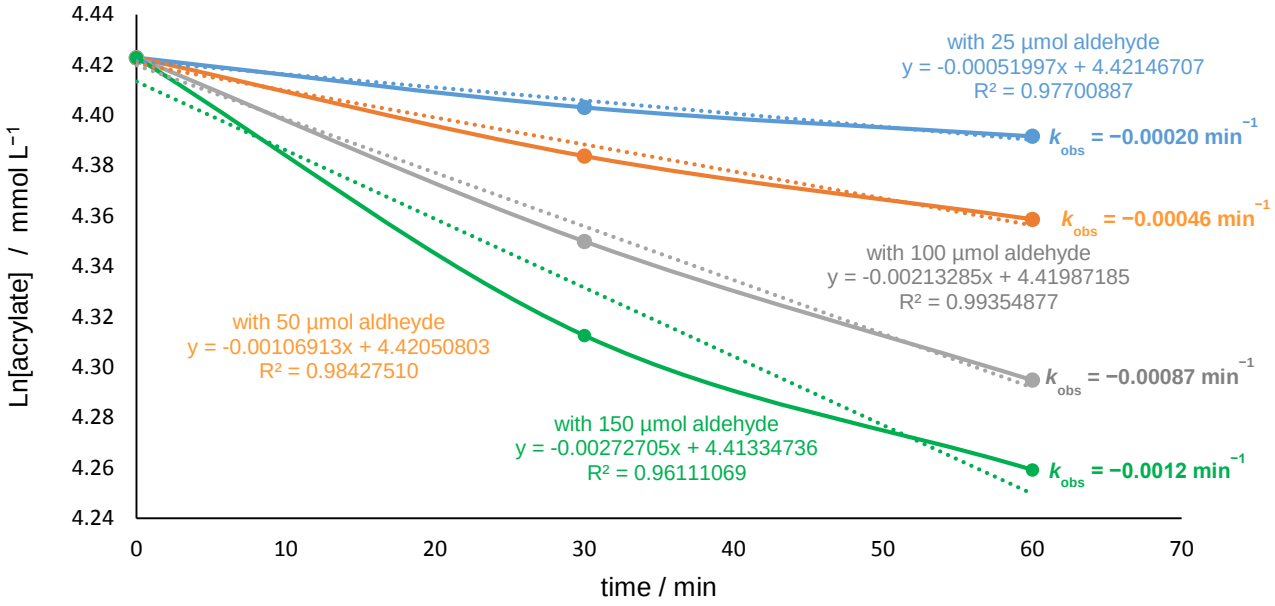


Figure 48: Kinetic analysis of the MBH reaction of methyl acrylate with 4-nitrobenzaldehyde.

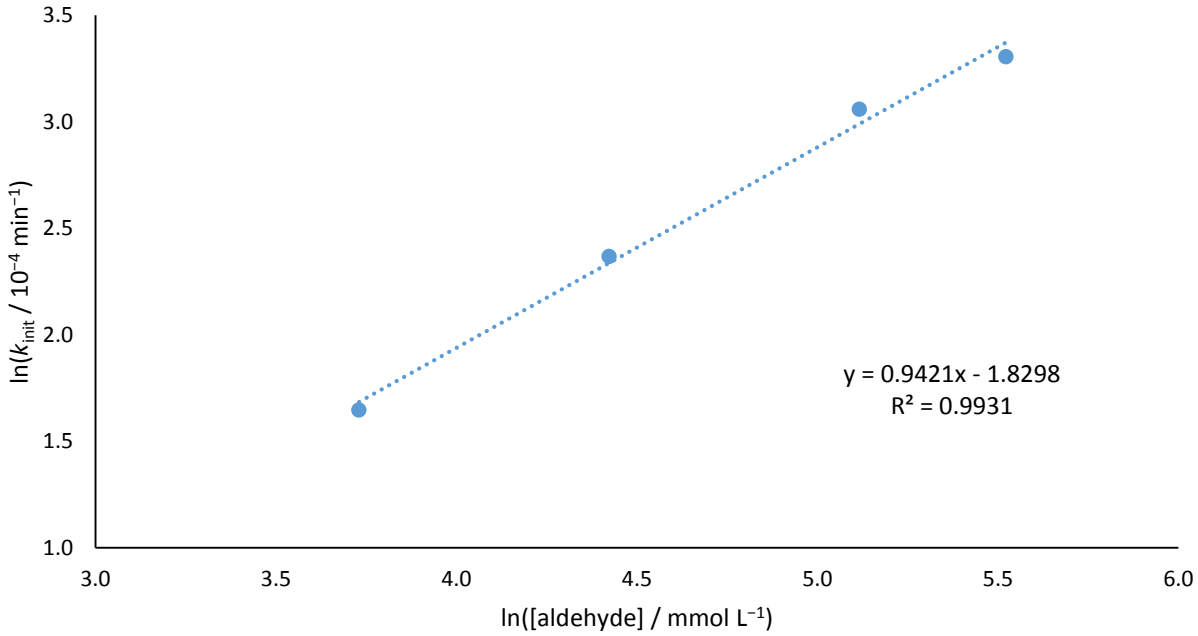


Figure 49: Kinetic analysis of the MBH reaction of methyl acrylate with 4-nitrobenzaldehyde between 0 and 60 minutes. Double logarithmic plot of the dependence of the reaction rate (k_{init}) on the initial aldehyde concentration. The data points correspond to aldehyde concentrations of 41.7, 83.3, 166.7, and 250.0 mmol/L and a constant acrylate concentration of 83.3 mmol/L. Linear fit for **105a**: y = 0.9421x –1.8298 (R^2 = 0.99), consistent with first order in **105a**.

Data from Kinetic Measurements

Table 51: Data from kinetic measurements.

	with 25 µmol 105a	**with 50 µmol 105a**	**with 100 µmol 105a**	**with 150 µmol 105a**
time (min)	[acrylate] / mmol L^{-1}	[acrylate] / mmol L^{-1}	[acrylate] / mmol L^{-1}	[acrylate] / mmol L^{-1}
0	83.333	83.3333	83.333	83.333
30	81.704	80.1382	77.473	74.629
60	80.774	78.1555	73.323	70.755
90	79.652	76.4884	71.406	67.037
120	78.800	75.3241	67.937	63.646
150	78.098	73.4337	66.607	60.327
180	77.826	72.4732	64.548	57.986
210	77.029	71.6556	62.786	55.120
240	76.362	70.4883	60.575	53.357
270	75.936		58.269	51.015
300	75.022	67.7942	56.000	48.998
330	74.561	66.3440	54.848	47.403
360	73.685	65.4724	53.301	45.396
390	73.552	65.1785	52.030	44.016
420	73.071	63.9079	51.513	43.007
450	73.057	62.7822	50.112	40.625
480	72.802	62.7345	48.738	40.423
510	72.720	62.2378	47.655	39.206
540	72.660	61.6006	47.032	38.525
570	72.686	60.9598	46.264	37.610

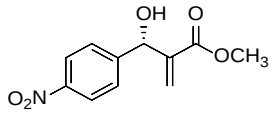
600	72.240	60.5299	45.896	36.396
630	71.663	60.1776	44.395	35.923
660	72.129	59.9266	44.493	35.388
690	71.238	59.3445	43.803	33.758
720	71.180	58.8217	43.508	33.168
750	70.974	58.4160	43.157	32.680
780	70.776	57.4776	42.319	32.538
810	70.605	56.9575	42.558	31.926
840	70.688	56.9505	42.555	
870	83.333	57.0109	42.526	
900	83.333	56.8463	42.656	31.022
930	70.454	56.9953	42.656	30.932
960	70.362	56.8463	42.630	30.941
990	70.112	56.9843	42.465	30.978
1020	70.171	56.9804	42.454	30.972
1050	70.079	56.9158	42.541	30.855
1080	70.023	56.8692	42.338	
1110		57.0339	42.413	

5.2.7 Reaction Scope

General Procedure for the Asymmetric MBH Reaction

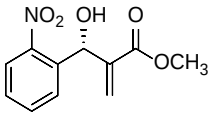
Under argon atmosphere a heat gun dried GC-vial was charged with activated molecular sieve (50 mg), aldehyde (100 µmol), methyl acrylate (200 µmol), phosphine catalyst (10-20 mol%) and THF (0.1 mL). The corresponding mixture was stirred at room temperature. The crude mixture was concentrated under vacuum and purified by preparative TLC.

Methyl 3-hydroxy-3-(4-nitrophenyl)-2-methylenepropanoate (106a)



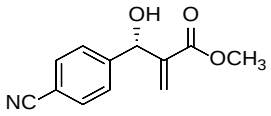
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 8.21 (d, $^{3}J_{HH}$ = 8.8 Hz, 2 H, ar-*H*), 7.58 (d, $^{3}J_{HH}$ = 8.8 Hz, 2 H, ar-*H*), 6.40 (s, 1 H, olefinic-*H*), 5.86 (s, 1 H, olefinic-*H*), 5.63 (s, 1 H, ar-C*H*), 3.25 (br s, 1H, O*H*), 3.75 (s, 3H, OCH_3).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 166.6, 148.7, 147.7, 141.1, 127.5, 123.8, 73.0, 52.4.
HPLC (Daicel Chiracel IC, heptane/*i*-PrOH = 90:10, 0.5 mL/min, 25 °C): t_R (major) = 22.3 min, t_R (minor) = 29.1 min, 94% *ee* (*S*).

Methyl 3-hydroxy-3-(2-nitrophenyl)-2-methylenepropanoate (106b)



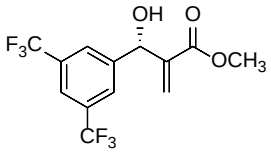
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.92 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, ar-*H*), 7.73 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, ar-*H*), 7.62 (t, $^{3}J_{HH}$ = 7.6 Hz, 1H, ar-*H*), 7.44 (t, $^{3}J_{HH}$ = 8.7 Hz, 1H, ar-*H*), 6.33 (s, 1H, olefinic-*H*), 6.18 (s, 1H, 1H, olefinic-*H*), 5.70 (s, 1H, ar-C*H*), 3.70 (s, 3H, OCH_3), 3.51 (br s, 1H, O*H*).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 166.5, 148.4, 140.9, 136.2, 133.5, 129.0, 128.8, 126.5, 124.6, 67.7, 52.2.
HPLC (Daicel Chiracel OD-H, heptane/*i*-PrOH = 90:10, 0.5 mL/min, 25 °C): t_R (major) = 29.3 min, t_R (minor) = 36.4 min, 80% *ee* (*S*).

Methyl 2-((4-cyanophenyl)(hydroxy)methyl)acrylate (106c)



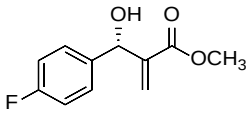
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.67-7.61 (m, 2H, ar-*H*), 7.53-7.49 (m, 2H, ar-*H*), 6.38 (s, 1H, olefinic-*H*), 5.85 (s, 1H, olefinic-*H*), 5.58 (s, 1H, ar-C*H*), 3.74 (s, 3H, OCH_3), 3.25 (br s, 1H, O*H*).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 166.6, 146.7, 141.2, 132.4, 127.4, 127.3, 118.8, 111.8, 73.1, 52.3.
HPLC (Daicel Chiracel IC, heptane/*i*-PrOH = 90:10, 0.5 mL/min, 25 °C): t_R (major) = 33.4 min, t_R (minor) = 46.4 min, 92% *ee* (*S*).

Methyl-2-((3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)acrylate (106d)



^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.86 (s, 2H, ar-*H*), 7.81 (s, 1H, ar-*H*), 6.43 (s, 1H, olefinic-*H*), 5.88 (s, 1H, olefinic-*H*), 5.65 (s, 1H, ar-C*H*), 3.76 (s, 3H, OCH_3), 3.30 (br s, 1H, O*H*).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 166.5, 144.2, 140.9, 131.9 (q, J_{CF} = 33.3 Hz), 126.9, 123.42 (q, J_{CF} = 272.6 Hz), 122.00-121.80 (m), 72.7, 52.4.
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ/ppm = −63.8.
HPLC (Daicel Chiracel OD-H, heptane/*i*-PrOH = 95:5, 0.5 mL/min, 25 °C): t_R (major) = 11.8 min, t_R (minor) = 10.0 min, 92% *ee* (*S*).

Methyl -2-((4-fluorophenyl)(hydroxy)methyl)acrylate (106e)

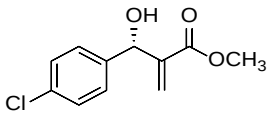


^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.30-7.24 (m, 2H, ar-*H*), 6.99-6.90 (m, 2H, ar-*H*), 6.26 (s, 1H, olefinic-*H*), 5.75 (s, 1H, olefinic-*H*), 5.46 (s, 1H, ar-C*H*), 3.65 (s, 3H, OCH_3), 2.94 (br s, 1H, O*H*).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 166.8, 163.7, 161.3, 142.0, 137.2 (d, J_{CF} = 3.1 Hz), 128.5 (d, J_{CF} = 8.3 Hz), 126.2, 115.4 (d, J_{CF} = 21.5 Hz), 72.8, 52.1,

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ/ppm = −114.7.

HPLC (Daicel Chiracel IC, heptane/*i*-PrOH = 90:10, 0.5 mL/min, 25 °C): t_R (major) = 14.0 min, t_R (minor) = 25.1 min, 90% *ee* (*S*).

Methyl-2-((4-chlorophenyl)(hydroxy)methyl)acrylate (106f)

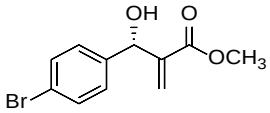


^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.31 (s, 4H, ar-*H*), 6.34 (s, 1H, olefinic-*H*), 5.83 (s, 1H, olefinic-*H*), 5.52 (s, 1H, ar-C*H*), 3.73 (s, 3H, OCH_3), 2.76 (br s, 1H, O*H*).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ/ppm = 166.8, 141.8, 139.9, 133.7, 128.7, 128.1, 126.5, 72.9, 52.2.

HPLC (Daicel Chiracel IC, heptane/*i*-PrOH = 90:10, 0.5 mL/min, 25 °C): t_R (major) = 15.6 min, t_R (minor) = 21.9 min, 90% *ee* (*S*).

Methyl-2-((4-bromophenyl)(hydroxy)methyl)acrylate (106g)

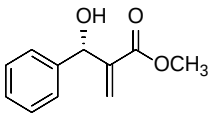


^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.45-7.34 (m, 2H, ar-*H*), 7.23-7.15 (m, 2H, ar-*H*), 6.27 (s, 1H, olefinic-*H*), 5.75 (s, 1H, olefinic-*H*), 5.44 (s, 1H, ar-C*H*), 3.66 (s, 3H, OCH_3), 2.74 (br s, 1H, O*H*).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ/ppm = 166.8, 141.7, 140.5, 131.7, 128.4, 126.6, 121.9, 72.9, 52.2.

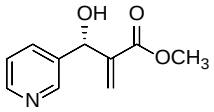
HPLC (Daicel Chiracel IC, heptane/*i*-PrOH = 90:10, 0.5 mL/min, 25 °C): t_R (major) = 14.0 min, t_R (minor) = 22.0 min, 92% *ee* (*S*).

Methyl-2-(hydroxy(phenyl)methyl)acrylate (106h)



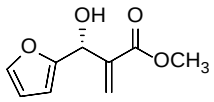
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.42-7.31 (m, 5H, ar-*H*), 6.34 (s, 1H, olefinic-*H*), 5.84 (s, 1H, olefinic-*H*), 5.57 (s, 1H, ar-C*H*), 3.72 (s, 3H, OCH_3), 3.04 (br s, 1H, O*H*).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 166.0, 142.1, 141.4, 128.6, 128.0, 126.7, 126.3, 73.4, 52.1.
HPLC (Daicel Chiracel IC, heptane/*i*-PrOH = 90:10, 0.5 mL/min, 25 °C): t_R (major) = 18.5 min, t_R (minor) = 34.4 min, 90% *ee* (*S*).

Methyl-2-(hydroxy(pyridin-3-yl)methyl)acrylate (106i)



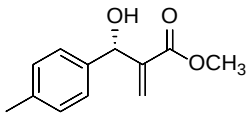
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 8.54 (d, $^{4}J_{HH}$ = 2.2 Hz, 1H, ar-*H*), 8.45 (dd, $^{3}J_{HH}$ = 4.9 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H, ar-*H*), 7.75-7.72 (m, 1H, ar-*H*), 7.29-7.25 (m, 1H, ar-*H*), 6.38 (s, 1H, olefinic-*H*), 5.94 (s, 1H, olefinic-*H*), 5.60 (s, 1H, ar-C*H*), 3.80 (br s, 1H, O*H*), 3.71 (s, 3H, OCH_3).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 166.5, 148.8, 148.3, 141.6, 137.5, 134.8, 126.6, 123.6, 71.1, 52.2.
HPLC (Daicel Chiracel IC, heptane/*i*-PrOH = 70:30, 0.5 mL/min, 25 °C): t_R (major) = 23.7 min, t_R (minor) = 39.7 min, 90% *ee* (*S*).

Methyl-2-(furan-2-yl(hydroxy)methyl)acrylate (106j)



^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.37 (dd, $^{3}J_{HH}$ = 1.8 Hz, $^{4}J_{HH}$ = 0.9 Hz, 1H, furyl-*H*), 6.39 (s, 1H, olefinic-*H*), 6.33 (dd, $^{3}J_{HH}$ = 3.3 Hz, $^{3}J_{HH}$ = 1.8 Hz, 1H), 6.27-6.26 (m, 1H, furyl-*H*), 5.94 (s, 1H, olefinic-*H*), 5.59 (d, $^{3}J_{HH}$ = 5.6 Hz, 1H, ar-C*H*), 3.76 (s, 3H, OCH_3), 3.10 (d, $^{3}J_{HH}$ = 6.5 Hz, 1H, O*H*).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 166.6, 154.3, 142.5, 139.6, 127.0, 110.6, 107.3, 67.6, 52.2.
HPLC (Daicel Chiracel OD-H, heptane/*i*-PrOH = 90:10, 0.5 mL/min, 40 °C): t_R (major) = 18.4 min, t_R (minor) = 19.3 min, 80% *ee* (*S*).

Methyl-2-(hydroxy(*p*-tolyl)methyl)acrylate (106k)

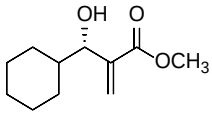


^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.26 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, ar-*H*), 7.15 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, ar-*H*), 6.33 (s, 1H, olefinic-*H*), 5.85 (s, 1H, olefinic-*H*), 5.53 (s, 1H, ar-C*H*), 3.71 (s, 3H, OCH_3), 2.85 (s, 3H, CH_3), 2.34 (br s, 1H, O*H*).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 166.9, 142.2, 138.5, 137.7, 129.3, 126.6, 126.0, 73.2, 52.0, 21.3.

HPLC (Daicel Chiracel IC, heptane/*i*-PrOH = 90:10, 0.5 mL/min, 25 °C): t_R (major) = 21.0 min, t_R (minor) = 36.3 min, 85% *ee* (*S*).

Methyl-2-(cyclohexyl(hydroxy)methyl)acrylate (106l)



^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 6.24 (s, 1H, olefinic-*H*), 5.72 (s, 1H, olefinic-*H*), 4.06 (d, $^{3}J_{HH}$ = 7.4 Hz, 1H, C*H*OH), 3.77 (s, 3H, OCH_3), 2.57 (s, 1H, O*H*), 2.01-1.90 (m, 1H, C*H*), 1.79-1.49 (m, 6H, CH_2), 1.28-1.08 (m, 2H, CH_2), 1.02-0.91 (m, 2H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 167.3, 141.1, 126.4, 52.0, 42.5, 30.1, 28.5, 26.5, 26.2, 26.1.

HPLC (Daicel Chiracel OD-H, heptane/*i*-PrOH = 97:3, 0.7 mL/min, 25 °C): t_R (minor) = 8.9 min, t_R (major) = 9.9 min, 30% *ee* (*S*).

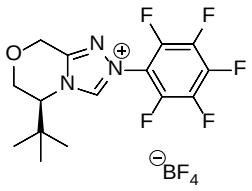
5.3 Asymmetric Cross-Benzoin Reaction

5.3.1 Synthesis of Morphopline-Based Triazolium Salts

General Procedure (GP8): Synthesis of triazolium salts

In the glovebox, a heat-gun dried round-bottomed flask was charged with the lactam (1.0 eq.) and CH_2Cl_2 (5 ml per mmol lactam). Then, trimethyloxonium tetrafluoroborate (1.1 eq. or 1.2 eq.) was added in one portion to the reaction mixture. The resulting solution was stirred for 16 hours at room temperature. Then, the hydrazine (1.1 eq.) was added in one portion and after stirring for four hours at room temperature the reaction flask was taken out of the glovebox and the crude mixture was concentrated under vacuum. The resulting solid was dissolved in trimethyl orthoformate (8.0 eq. or 50 eq.) and MeCN (only in some cases, 5 mL per mmol lactam) and refluxed at 80 °C for six to 48 hours. Afterwards, the crude product was concentrated under vacuum and purified by column chromatography. In some cases, an additional purification step (recrystallization or second column chromatography) was needed to get the pure product.

(*S*)-5-(*tert*-Butyl)-2-(perfluorophenyl)-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (113b)



According to general procedure **GP8**, (*S*)-5-(*tert*-butyl)morpholin-3-one (**112b**) (500 mg, 3.18 mmol) in CH_2Cl_2 (13 mL) and trimethyloxonium tetrafluoroborate (517 mg, 3.50 mmol) were stirred to give of the crude imidate. Then, pentafluorophenylhydrazine (693 mg, 3.50 mmol) was added and stirred for six hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (2.78 mL, 2.70 g, 25.4 mmol) and refluxed for 48 hours at 80 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH (70:1), d x h: 3.5 x 15 cm) and recrystallization in chloroform to afford the product **113b** (470 mg, 1.08 mmol, 34%) as a white solid.

$C_{15}H_{15}F_5N_3O \cdot BF_4$ (435.10 g/mol):

MP: 113-114 °C.

TLC: R_f = 0.47 (SiO_2, CH_2Cl_2:MeOH (10:1)).

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 10.95 (s, 1H, carbene-C*H*), 5.41 (d, $^2J_{HH}$ = 16.8 Hz, 1H, OCH_2), 5.04 (d, $^2J_{HH}$ = 16.8 Hz, 1H, OCH_2), 4.54-4.48 (m, 2H, CHCH_2), 4.01 (dd, $^3J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 3.9 Hz, 1H, C*H*CH_2), 1.07 (s, 9H, C(CH_3)$_3$).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ/ppm = 151.4, 146.8, 64.8, 64.1, 61.4, 35.3, 27.1.

^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ/ppm = −145.2-−145.3 (m), −147.5-−147.6 (m), −148.4, −159.9-−160.1 (m).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3124 (w), 2969 (w), 2879 (w), 1591 (m), 1539 (s), 1515 (s), 1477 (s), 1212 (w), 1075 (s), 1036 (s), 987 (s), 908 (m), 845 (m), 736 (m), 522 (w), 460 (w), 443 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{15}H_{15}F_5N_3O^+$: 348.1130 $[M]^+$; found: 348.1127.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +4.9 (*c* = 0.51, MeOH).

General Procedure (GP9): Synthesis of lactams derived from amino alcohols

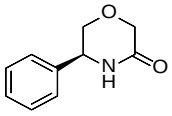
Step 1 (only for cases with a cbz-protected amino alcohol): Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with cbz-protected amine (1.0 eq). and MeOH (3.3 mL per mmol amine). Then, Pd/C (10% Pd basis, 78 mg per mmol amine) was added to the reaction mixture and afterwards the argon atmosphere was changed to a hydrogen atmosphere using a hydrogen filled balloon. After 16 hours reaction time under an hydrogen atmosphere (balloon), the hydrogen atmosphere was changed to a argon atmosphere by bubbling argon through the reaction solution. Afterwards, the reaction mixture was filtered over Celite, the Celite cake was washed with EtOAc (3 x 3 mL per mmol amine) and after concentration under vacuum the corresponding crude amine was isolated without any further purification steps and directly used for the next step.

Step 2: Under argon atmosphere, a heat-gun dried two-necked flask was charged with the crude amine (1.0 eq.) and CH_2Cl_2 (5 mL per mmol amine). The corresponding solution was cooled in an ice-bath and at 0 °C triethylamine (1.3 eq.) was added followed by dropwise addition of chloroacetyl chloride (1.1 eq.) over 15 minutes. After complete addition, the reaction was stirred for 30 minutes at 0 °C and for further six hours at room temperature. Afterwards saturated aqueous NH_4Cl solution (5 mL per mmol amine) was added and the biphasic mixture was extracted with CH_2Cl_2 (3 x 5 mL per mmol amine), the combined organic layers were washed with brine (5 mL

per mmol amine), dried over Na_2SO_4, filtered and concentrated under vacuum to yield the corresponding chloro acetamide which was directly used for the next step without any further purification steps.

Step 3: Under argon atmosphere a heat-gun dried two-neck flask was charged with the crude chloro acetamide (1.0 eq) and THF (5 mL pro chloro acetamide). The corresponding solution was cooled in an ice-bath and sodium hydride (60% in mineral oil, 1.5 eq.) was added over one hour at 0 °C. After completed addition the reaction was stirred for 30 minutes at 0 °C and further six hours at 75 °C. Afterwards, the reaction mixture was quenched by slowly addition of saturated aqueous NH_4Cl solution (5 mL per mmol chloro acetamide) and then the biphasic mixture was extracted with EtOAc (3 x 5 mL per mmol chloro acetamide). The combined organic layers were washed with brine (5 mL per mmol chloro acetamide), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by column chromatography to yield the corresponding lactam.

(*S*)-5-Phenylmorpholin-3-one (112c)



According to general procedure **GP9**, (*S*)-(+)-2-phenylglycinol (**111c**) (2.50 g, 18.2 mmol) in CH_2Cl_2 (90 mL), triethylamine (2.39 g, 3.33 mL, 23.7 mmol) and chloroacetyl chloride (2.26 g, 1.59 mL, 20.0 mmol) were stirred. In the next step the crude chloro acetamide was dissolved in THF (90 mL) and sodium hydride (60% in mineral oil, 1.09 g, 24.0 mmol) was added and stirred. The crude mixture was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (2:1), d x h: 3.5 x 19 cm) to afford the product **112c** (1.67 g, 9.41 mmol, 52%) as a pale yellow solid.

$C_{10}H_{11}NO_2$ (177.20 g/mol):

MP: 135-136 °C.

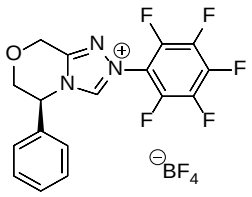
TLC: R_f = 0.32 (SiO_2, CH_2Cl_2:ethyl acetate (2:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.44-7.31 (m, 5H, ar-*H*), 6.24 (br s, 1H, N*H*), 4.75 (dd, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 4.2 Hz, 1H, NC*H*), 4.32 (d, $^2J_{HH}$ = 16.7 Hz, 1H, OCH_2), 4.23 (d, $^2J_{HH}$ = 16.7 Hz, 1H, OCH_2), 4.05 (dd, $^3J_{HH}$ = 11.8 Hz, $^3J_{HH}$ = 4.2 Hz, 1H, NCHCH_2), 3.56 (dd, $^3J_{HH}$ = 11.8 Hz, $^3J_{HH}$ = 8.4 Hz, 1H, NCHCH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 169.1, 137.7, 129.1, 128.8, 126.7, 70.3, 67.9, 56.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3180 (w), 3045 (w), 2890 (w), 2860 (w), 1668 (s), 1412 (m), 1341 (s), 1314 (m), 1286 (m), 1122 (s), 1067 (m), 966 (m), 945 (m), 799 (m), 762 (s), 701 (s), 527 (m), 475 (s), 439 (s).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{10}H_{11}NO_2^+$: 200.0682 $[M+Na]^+$; found: 200.0680.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +75.5 (*c* = 0.98, MeOH).

(*S*)-2-(Perfluorophenyl)-5-phenyl-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (113c)

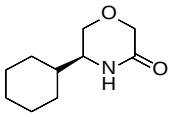


According to general procedure **GP8**, (*S*)-3-phenylmorpholine (**112c**) (571 mg, 3.22 mmol) in CH_2Cl_2 (16 mL) and trimethyloxonium tetrafluoroborate (524 mg, 3.54 mmol) were stirred to give of the crude imidate. Then, pentafluorophenylhydrazine (702 mg, 3.54 mmol) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (1.41 mL, 1.37 g, 12.9 mmol) and MeCN (16 mL) and refluxed for 18 hours at 80 °C. The crude product was purified by recrystallization from chloroform to afford the product **113c** (60 mg, 132 µmol, 4%) as a white solid.

$C_{17}H_{11}F_5N_3O \cdot BF_4$ (368.08 g/mol):
MP: 103-104 °C.
^{1}H NMR (400 MHz, acetone-d_6): δ/ppm = 10.37 (s, 1H, carbene-C*H*), 7.70-7.65 (m, 2H, ar-*H*), 7.56-7.46 (m, 3H, ar-*H*), 6.12 (dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, NC*H*), 5.47 (s, 2H, OCH_2), 4.60 (dd, $^3J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, CHCH_2), 4.40 (dd, $^3J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, CHCH_2).
^{13}C{^{1}H} NMR (101 MHz, acetone-d_6): δ/ppm = 153.1, 134.4, 131.0, 130.3, 129.1, 69.6, 62.6, 62.2.
^{19}F{^{1}H} NMR (376 MHz, acetone-d_6): δ/ppm = −146.5-−146.7 (m), −149.7-−150.0 (m), −153.5, −161.9-−162.1 (m).
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3114 (w), 1592 (w), 1526 (m), 1377 (w), 1022 (s), 1002 (s), 918 (m), 853 (m), 702 (w), 518 (w), 474 (m), 462 (w).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{17}H_{11}F_5N_3O^+$: 368.0817 $[M]^+$; found: 368.0822.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +58.1 (*c* = 0.58, MeOH).

(*S*)-5-Cyclohexylmorpholin-3-one (112d)



An autoclave inlet was charged with (*S*)-5-phenylmorpholin-3-one (**112c**) (400 mg, 2.26 mmol) and MeOH (5 mL). To the corresponding mixture Rhodium on alox (5 wt.%, 100 mg) was added and this mixture was put in an autoclave. After purging three times with hydrogen the reaction mixture was stirred for 16 hours at 10 bar hydrogen pressure. Then, the mixture was filtered through Celite and the Celite cake was washed with EtOAc (3 x 10 mL). The crude mixture was concentrated under vacuum to yield the product **112d** (410 mg, 2.24 mmol, 99%) as a beige solid.

$C_{10}H_{17}NO_2$ (183.25 g/mol):

MP: 89-90 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 6.22 (s, 1H, N*H*), 4.18 (d, $^2J_{HH}$ = 16.7 Hz, 1H, OCH_2), 4.09 (d, $^2J_{HH}$ = 16.6 Hz, 1H, OCH_2), 3.88 (dd, $^3J_{HH}$ = 11.8 Hz, $^3J_{HH}$ = 4.0 Hz, 1H, NCHCH_2), 3.62 (dd, $^3J_{HH}$ = 11.8 Hz, 7.0 Hz, 1H, NCHCH_2), 3.29 (tdd, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 4.0 Hz, $^3J_{HH}$ = 1.8 Hz, 1H, NC*H*), 1.83-1.75 (m, 3H, cy-C*H*, cy-CH_2), 1.72-1.67 (m, 2H, cy-CH_2), 1.51-1.41 (m, 1H, cy-CH_2), 1.30-1.14 (m, 3H, cy-CH_2), 1.08-0.93 (m, 2H, cy-CH_2).

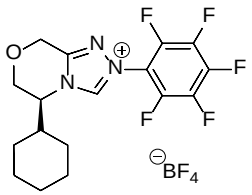
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 169.3, 67.8, 65.9, 56.4, 40.4, 28.8, 28.7, 26.1, 25.9, 25.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3231 (w), 2928 (m), 2851 (m), 1666 (s), 1635 (m), 1449 (w), 1414 (w), 1358 (m), 1329 (m), 1121 (m), 1099 (m), 959 (m), 753 (m), 700 (m), 469 (w), 454 (w), 428 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{10}H_{17}NO_2^+$: 206.1151 $[M+Na]^+$; found: 200.1153.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +3.1 (*c* = 0.89, MeOH).

(*S*)-5-Cyclohexyl-2-(perfluorophenyl)-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (113d)



According to general procedure **GP8**, (*S*)-3-cyclohexylmorpholine (**112d**) (420 mg, 2.29 mmol) in CH_2Cl_2 (12 mL) and trimethyloxonium tetrafluoroborate (406 mg, 2.75 mmol) were stirred to give of the crude imidate. Then, pentafluorophenylhydrazine (544 mg, 2.75 mmol) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (2.00 mL, 1.947 g, 18.3 mmol) and MeCN (12 mL) and refluxed for 18 hours at 80 °C. The crude product was purified by recrystallization from chloroform to afford the product **113d** (202 mg, 437 µmol, 19%) as a white solid.

$C_{17}H_{17}F_5N_3O \cdot BF_4$ (374.33 g/mol):

MP: 115-116 °C.

TLC: R_f = 0.43 (SiO_2, CH_2Cl_2:MeOH (20:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = δ 10.14 (s, 1H, carbene-C*H*), 5.12 (d, $^2J_{HH}$ = 16.5 Hz, 1H, OCH_2), 4.99 (d, $^2J_{HH}$ = 16.4 Hz, 1H, OCH_2), 4.55 (dd, $^3J_{HH}$ = 7.0 Hz, $^3J_{HH}$ = 3.2 Hz, 1H, NC*H*), 4.32 (d, $^3J_{HH}$ = 13.2 Hz, 1H, CHCH_2), 4.20 (dd, $^3J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, CHCH_2), 2.06-1.96 (m, 1H, cy-CH_2), 1.89-1.78 (m, 2H, cy-CH_2), 1.75-1.67 (m, 1H, cy-CH_2), 1.67-1.54 (m, 2H, cy-CH_2), 1.35-1.13 (m, 5H, cy-C*H*, cy-CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 151.1, 146.2, 144.9-143.9 (m), 143.1-142.7 (m), 142.3-141.6 (m), 139.9-138.9 (m), 64.1, 61.8, 61.5, 40.7, 29.3, 28.6, 25.8, 25.7.

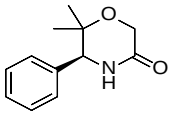
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ/ppm = −144.59-−144.77 (m), −146.17-−146.35 (m), −152.30, −158.87-−159.23 (m).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2932 (m), 2857 (w), 1592 (w), 1527 (s), 1451 (m), 1073 (s), 1030 (s), 986 (s), 881 (w), 852 (m), 731 (w), 678 (w), 522 (m), 460 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{17}H_{17}F_5N_3O^+$: 374.1286 $[M]^+$; found: 374.1289.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −16.3 (*c* = 0.49, MeOH).

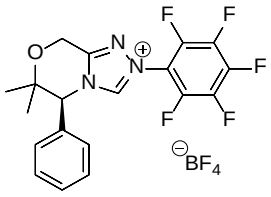
(*S*)-6,6-Dimethyl-5-phenylmorpholin-3-one (116a)



According to general procedure **GP9**, (*S*)-1-amino-2-methyl-1-phenylpropan-2-ol (**115a**) (1.85 g, 11.2 mmol) in CH_2Cl_2 (56 mL), triethylamine (1.47 g, 2.05 mL, 14.6 mmol) and chloroacetyl chloride (1.39 g, 980 µL, 12.3 mmol) were stirred. In the next step the crude chloro acetamide was dissolved in THF (56 mL) and sodium hydride (60% in mineral oil, 671 mg, 16.8 mmol) was added and stirred. The crude mixture was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (5:1), d x h: 3.5 x 19 cm) to afford the product **116a** (617 mg, 3.00 mmol, 27%) as a pale yellow oil.

$C_{12}H_{15}NO_2$ (205.26 g/mol):
TLC: R_f = 0.29 (SiO_2, CH_2Cl_2:ethyl acetate (5:1)).
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = δ 7.39-7.33 (m, 3H, ar-*H*), 7.30-7.26 (m, 2H, ar-*H*), 6.30 (br s, 1H, N*H*), 4.47 (s, 1H, NC*H*), 4.28 (s, 2H, OCH_2), 1.32 (s, 3H, C(CH_3)$_2$), 1.06 (s, 3H, C(CH_3)$_2$).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 169.3, 137.9, 128.7, 128.7, 127.9, 73.5, 64.9, 63.4, 25.6, 20.0.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3222 (w), 2979 (w), 2889 (w), 1660 (s), 1413 (w), 1347 (w), 1151 (w), 1099 (m), 1073 (m), 698 (s), 464 (m), 425 (s).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{12}H_{15}NO_2^+$: 228.1176 [M+Na]$^+$; found: 228.0995.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +2.0 (*c* = 0.50, MeOH).

(*S*)-6,6-Dimethyl-2-(perfluorophenyl)-5-phenyl-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]-oxazin-2-ium tetrafluoroborate (117a)

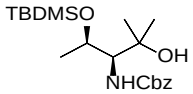


According to general procedure **GP8**, (*S*)-2,2-dimethyl-3-phenylmorpholine (**116a**) (571 mg, 2.78 mmol) in CH_2Cl_2 (14 mL) and trimethyloxonium tetrafluoroborate (452 mg, 3.06 mmol) were stirred to give of the crude imidate. Then, pentafluorophenylhydrazine (606 mg, 3.06 mmol) was

added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (2.43 mL, 2.36 g, 22.2 mmol) and MeCN (14 mL) and refluxed for 18 hours at 80 °C. The crude product was purified by two column chromatography (SiO_2, CH_2Cl_2:MeOH (100:1), d x h: 3.5 x 23 cm followed by SiO_2, cyclohexane:ethyl acetate (1:2), d x h: 2.5 x 14 cm)) to afford the product **117a** (139 mg, 286 µmol, 10%) as a white solid.

$C_{19}H_{15}F_5N_3O \cdot BF_4$ (396.34 g/mol):
MP: 90-91 °C.
TLC: R_f = 0.43 (SiO_2, CH_2Cl_2:MeOH (20:1)).
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 9.81 (s, 1H, carbene-C*H*), 7.45-7.37 (m, 3H, ar-*H*), 7.32-7.28 (m, 2H, ar-*H*), 5.78 (s, 1H, NC*H*), 5.31 (d, $^2J_{HH}$ = 17.5 Hz, 1H, OCH_2), 5.20 (d, $^2J_{HH}$ = 17.4 Hz, 1H, OCH_2), 1.55 (s, 3H, C(CH_3)$_2$), 1.16 (s, 3H, C(CH_3)$_2$).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 150.1, 146.9, 144.4-143.4 (m), 141.8-141.1 (m), 140.0-139.1 (m), 137.4-136.6 (m), 133.8, 130.4, 129.6, 128.2, 75.0, 67.5, 56.6, 24.2, 23.8.
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ/ppm = −144.4-−144.6 (m), −145.9-−146.2 (m), −152.3, −158.4-−158.7 (m).
IR (ATR): $\tilde{\nu}$/cm^{-1} = 1591 (w), 1514 (s), 1455 (w), 1392 (w), 1375 (w), 1229 (w), 1071 (s), 1004 (s), 987 (s), 858 (w), 837 (w), 701 (m), 520 (w).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{19}H_{15}F_5N_3O^+$: 396.1130 $[M]^+$; found: 396.1131.
$[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = +68.4 (*c* = 0.59, MeOH).

Benzyl ((3*S*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-methylpentan-3-yl)carbamate (120a)

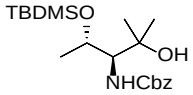


Under argon atmosphere, a heat-gun dried two-necked flask was charged with methylmagnesium bromide solution (3M in ether, 6.19 g, 5.95 mL, 17.8 mmol) and was cooled in an ice-bath. Then, at 0 °C a solution of methyl *N*-((benzyloxy)carbonyl)-*O*-(*tert*-butyldimethylsilyl)-L-threoninate (**119a**) (1.70 g, 4.46 mmol) in ether (17 mL) was added dropwise over 10 minutes to the Grignard solution. After addition the reaction was stirred for one hour at 0 °C and further 16 hours at room temperature. Afterwards the reaction mixture was quenched by slowly addition of aqueous saturated NH_4Cl solution (20 mL) at 0 °C. Then, the biphasic mixture was extracted with ether (3 x

50 mL), the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by column chromatography (SiO_2, ethyl acetate:cyclohexane (1:3), d x h: 3.5 x 16 cm) to afford the product **120a** (1.55 g, 4.05 mmol, 91%) as a colorless oil.

$C_{20}H_{35}NO_4Si$ (381.59 g/mol):
TLC: R_f = 0.44 (SiO_2, ethyl acetate:cyclohexane (1:3)).
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.40-7.29 (m, 5H, ar-*H*), 5.45 (d, $^3J_{HH}$ = 10.1 Hz, 1H, N*H*), 5.17 (d, $^2J_{HH}$ = 12.3 Hz, 1H, Ph-CH_2), 5.11 (d, $^2J_{HH}$ = 12.3 Hz, 1H, Ph-CH_2), 4.47 (qd, $^3J_{HH}$ = 6.2 Hz, $^3J_{HH}$ = 1.9 Hz, 1H, OC*H*), 3.54 (s, 1H, O*H*), 3.39 (dd, $^3J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 1.9 Hz, 1H, NC*H*), 1.34 (s, 3H, C(CH_3)$_2$), 1.21 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CHCH_3), 1.17 (s, 3H, C(CH_3)$_2$), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.14 (s, 3H, SiCH_3), 0.13 (s, 3H, SiCH_3).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 157.5, 136.8, 128.7, 128.2, 128.1, 73.4, 69.9, 67.0, 61.4, 27.7, 27.2, 26.0, 21.5, 18.0, −2.9, −4.6.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3494 (w), 3445 (w), 2930 (m), 2857 (w), 1723 (s), 1499 (s), 1374 (m), 1303 (m), 1214 (s), 1165 (m), 1123 (m), 1058 (s), 924 (s), 834 (s), 774 (s), 696 (m), 527 (m).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{20}H_{35}NO_4Si^+$: 404.2228 $[M+Na]^+$; found: 404.2301.
$[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = +11.1 (*c* = 0.38, MeOH).

Benzyl ((3*S*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-methylpentan-3-yl)carbamate (120b)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with methylmagnesium bromide solution (3M in ether, 7.63 g, 7.33 mL, 22.0 mmol) and was cooled in an ice-bath. Then, at 0 °C a solution of benzyl ((3*S*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-methylpentan-3-yl)carbamate (**119b**) (2.10 g, 5.50 mmol) in ether (16 mL) was added dropwise over 10 minutes to the Grignard solution. After addition the reaction was stirred for one hour at 0 °C and further 16 hours at room temperature. Afterwards the reaction mixture was quenched by slowly addition of aqueous saturated NH_4Cl solution (20 mL) at 0 °C. Then, the biphasic mixture was extracted with ether (3 x 50 mL), the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by column

chromatography (SiO_2, ethyl acetate:cyclohexane (1:3), d x h: 3.5 x 14 cm) to afford the product **120b** (2.09 g, 5.48 mmol, 99%) as a colorless oil.

$C_{20}H_{35}NO_4Si$ (381.59 g/mol):

TLC: R_f = 0.38 (SiO_2, ethyl acetate:cyclohexane (1:3)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.30-7.19 (m, 5H, ar-*H*), 5.16 (d, $^3J_{HH}$ = 9.5 Hz, 1H, N*H*), 5.04 (d, $^2J_{HH}$ = 12.2 Hz, 1H, Ph-CH_2), 4.99 (d, $^2J_{HH}$ = 12.3 Hz, 1H, Ph-CH_2), 4.04-3.97 (m, 1H, OC*H*), 3.75 (s, 1H, O*H*), 3.38 (dd, $^3J_{HH}$ = 9.4 Hz, $^3J_{HH}$ = 4.2 Hz, 1H, NC*H*), 1.27 (s, 3H, C(CH_3)$_2$), 1.24 (d, $^3J_{HH}$ = 6.7 Hz, 3H, CHCH_3), 1.09 (s, 3H, C(CH_3)$_2$), 0.79 (s, 9H, SiC(CH_3)$_3$), 0.00 (s, 3H, SiCH_3), −0.02 (s, 3H, SiCH_3).

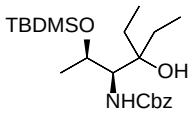
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 156.5, 136.7, 128.7, 128.2, 128.1, 73.8, 73.3, 66.9, 62.0, 28.7, 27.1, 25.9, 22.6, 18.0, −4.0, −4.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3442 (w), 2930 (m), 2857 (w), 1698 (s), 1509 (m), 1376 (m), 1251 (s), 1090 (s), 1004 (s), 918 (w), 829 (s), 774 (s), 695 (s), 569 (w), 488 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{20}H_{35}NO_4Si^+$: 404.2228 $[M+Na]^+$; found: 404.2227.

$[\alpha]_D^{20}$ = +25.4 (*c* = 1.06, MeOH).

Benzyl ((2*R*,3*S*)-2-((*tert*-butyldimethylsilyl)oxy)-4-ethyl-4-hydroxyhexan-3-yl)carbamate (120c)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with ethylmagnesium bromide solution (3M in ether, 3.99 g, 10.1 mL, 30.4 mmol) and was cooled in an ice-bath. Then, at 0 °C a solution of methyl *N*-((benzyloxy)carbonyl)-*O*-(*tert*-butyldimethylsilyl)-L-threoninate (**119a**) (2.90 g, 7.60 mmol) in ether (20 mL) was added dropwise over 10 minutes to the Grignard solution. After addition the reaction was stirred for one hour at 0 °C and further 16 hours at room temperature. Afterwards the reaction mixture was quenched by slowly addition of aqueous saturated NH_4Cl solution (20 mL) at 0 °C. Then, the biphasic mixture was extracted with ether (3 x 50 mL), the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by column chromatography

(SiO_2, ethyl acetate:cyclohexane (1:4), d x h: 3.5 x 21 cm) to afford the product **120c** (2.48 g, 6.07 mmol, 80%) as a colorless oil.

$C_{22}H_{39}NO_4Si$ (409.64 g/mol):

TLC: R_f = 0.53 (SiO_2, ethyl acetate:cyclohexane (1:4)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.40-7.29 (m, 5H, ar-*H*), 5.43 (d, $^3J_{HH}$ = 10.1 Hz, 1H, N*H*), 5.16 (d, $^2J_{HH}$ = 12.4 Hz, 1H, Ph-CH_2), 5.11 (d, $^2J_{HH}$ = 12.3 Hz, 1H, Ph-CH_2), 4.43 (qd, $^3J_{HH}$ = 6.2 Hz, $^3J_{HH}$ = 1.9 Hz, 1H, OC*H*), 3.51 (dd, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 1.9 Hz, 1H, NC*H*), 3.43 (s, 1H, O*H*), 1.78-1.61 (m, 1H, CH_2CH$_3$), 1.61-1.36 (m, 3H, CH_2CH$_3$), 0.92-0.90 (m, 3H, CH$_2$CH_3), 0.91 (d, $^3J_{HH}$ = 7.5 Hz, 3H, CH$_2$CH_3), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.81 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CHCH_3), 0.14 (s, 3H, SiCH_3), 0.12 (s, 3H, SiCH_3).

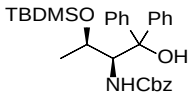
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 157.3, 136.9, 128.6, 128.2, 128.0, 77.8, 70.0, 66.9, 58.0, 28.2, 26.8, 26.0, 21.3, 18.0, 7.9, 7.7, −2.9, −4.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3499 (m), 2955 (m), 2858 (w), 1723 (s), 1498 (s), 1462 (m), 1314 (w), 1256 (m), 1215 (s), 1126 (w), 1058 (s), 936 (s), 883 (m), 835 (s), 775 (s), 735 (m), 695 (m), 497 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{22}H_{39}NO_4Si^+$: 432.2541 [M+Na]$^+$; found: 432.2542.

$[\alpha]_D^{20}$ = +20.1 (*c* = 0.70, MeOH).

Benzyl ((2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-1,1-diphenylbutan-2-yl)-carbamate (120d)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with phenylmagnesium bromide solution (3M in ether, 8.04 g, 8.04 mL, 24.1 mmol) and was cooled in an ice-bath. Then, at 0 °C a solution of methyl *N*-((benzyloxy)carbonyl)-*O*-(*tert*-butyldimethylsilyl)-L-threoninate (**119a**) (2.30 g, 6.03 mmol) in ether (17 mL) was added dropwise over 10 minutes to the Grignard solution. After addition the reaction was stirred for one hour at 0 °C and further 16 hours at room temperature. Afterwards the reaction mixture was quenched by slowly addition of aqueous saturated NH_4Cl solution (20 mL) at 0 °C. Then, the biphasic mixture was extracted with ether (3 x 50 mL), the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by column chromatography

(SiO_2, ethyl acetate:cyclohexane (1:6), d x h: 4.5 x 20 cm) to afford the product **120d** (2.48 g, 6.07 mmol, 80%) as a white solid.

$C_{30}H_{39}NO_4Si$ (505.73 g/mol):

MP: 99-100 °C.

TLC: R_f = 0.55 (SiO_2, ethyl acetate:cyclohexane (1:4)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.60-7.53 (m, 4H, ar-*H*), 7.35-7.19 (m, 8H, ar-*H*), 7.18-7.09 (m, 3H, ar-*H*), 5.57 (d, $^3J_{HH}$ = 9.9 Hz, 1H, N*H*), 5.23 (s, 1H, O*H*), 5.09 (d, $^2J_{HH}$ = 12.6 Hz, 1H, OCH_2), 4.92 (d, $^2J_{HH}$ = 12.6 Hz, 1H, OCH_2), 4.65 (dd, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 1.6 Hz, 1H, NC*H*), 4.25 (qd, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 1.6 Hz, 1H, C*H*CH_3), 1.23 (d, $^3J_{HH}$ = 6.3 Hz, 3H, CHCH_3), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.00 (s, 3H, SiCH_3), −0.17 (s, 3H, SiCH_3).

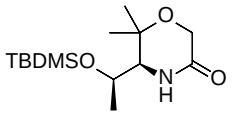
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 157.1, 145.8, 144.9, 136.8, 128.6, 128.5, 128.2, 127.9, 127.7, 127.0, 126.7, 125.4, 125.1, 81.5, 70.7, 66.6, 59.4, 26.1, 21.5, 18.0, −3.0, −4.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3369 (m), 3028 (w), 2952 (w), 2927 (w), 2858 (w), 1718 (s), 1499 (s), 1450 (m), 1307 (m), 1257 (m), 1211 (m), 1180 (s), 1069 (s), 939 (s), 870 (m), 836 (m), 749 (s), 696 (s), 597 (w), 489 (s).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{30}H_{39}NO_4Si^+$: 528.2541 $[M+Na]^+$; found: 528.2546.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +32.8 (*c* = 0.70, MeOH).

(*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6,6-dimethylmorpholin-3-one (121a)



According to general procedure **GP9**, benzyl ((3*S*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-methylpentan-3-yl)carbamate (**120a**) (1.70 g, 4.46 mmol) in MeOH (15 mL) and Pd/C (350 mg) were stirred to give of the crude amine as a colorless oil (1.09 g, 4.46 mmol, 98%).

Then, the crude amine (1.06 g, 4.28 mmol) in CH_2Cl_2 (22 mL), triethylamine (563 mg, 782 µL, 5.56 mmol) and chloroacetyl chloride (532 mg, 374 µL, 4.71 mmol) were stirred. In the next step the crude chloro acetamide was dissolved in THF (22 mL) and sodium hydride (60% in mineral oil, 257 mg, 6.42 mmol) was added and stirred. The crude mixture was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (1:1), d x h: 3.5 x 17 cm) to afford the product **121a** (895 mg, 3.11 mmol, 73%) as a pale yellow oil.

$C_{14}H_{29}NO_3Si$ (287.47 g/mol):

TLC: R_f = 0.40 (SiO_2, CH_2Cl_2:ethyl acetate (1:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 6.24 (s, 1H, N*H*), 4.16 (d, $^2J_{HH}$ = 17.3 Hz, 1H, OCH_2), 4.10 (d, $^2J_{HH}$ = 17.4 Hz, 1H, OCH_2), 3.78 (p, $^3J_{HH}$ = 5.9 Hz, 1H, OC*H*), 3.17-3.13 (m, 1H, NC*H*), 1.34 (s, 3H, C(CH_3)$_2$), 1.27-1.23 (m, 6H, C(CH_3)$_2$, CHCH_3), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.11 (s, 3H, SiCH_3), 0.10 (s, 3H, SiCH_3).

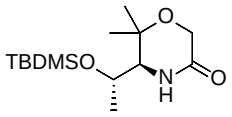
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 169.0, 72.1, 67.6, 65.0, 63.0, 27.0, 26.0, 22.8, 20.1, 18.1, −3.7, −4.6.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3207 (w), 2929 (m), 2889 (m), 2856 (w), 1674 (s), 1427 (w), 1253 (m), 1171 (m), 1085 (s), 1006 (w), 937 (w), 833 (s), 772 (s), 434 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{14}H_{29}NO_3Si^+$: 310.1809 [M+Na]$^+$; found: 310.1813.

$[\alpha]_D^{20}$ = −20.7 (*c* = 1.73, MeOH).

(*S*)-5-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6,6-dimethylmorpholin-3-one (121b)



According to general procedure **GP9**, benzyl ((3*S*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-methylpentan-3-yl)carbamate (**120b**) (1.80 g, 4.72 mmol) in MeOH (16 mL) and Pd/C (400 mg) were stirred to give of the crude amine as a colorless oil (1.16 g, 4.67 mmol, 99%).

Then, the crude amine (1.15 g, 4.65 mmol) in CH_2Cl_2 (24 mL), triethylamine (612 mg, 850 µL, 6.05 mmol) and chloroacetyl chloride (578 mg, 407 µL, 5.12 mmol) were stirred. In the next step the crude chloro acetamide was dissolved in THF (24 mL) and sodium hydride (60% in mineral oil, 279 mg, 6.98 mmol) was added and stirred. The crude mixture was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (1:1), d x h: 3.5 x 18 cm) to afford the product **121b** (969 mg, 3.37 mmol, 73%) as a white solid.

$C_{14}H_{29}NO_3Si$ (287.47 g/mol):

MP: 56-57 °C.

TLC: R_f = 0.52 (SiO_2, CH_2Cl_2:ethyl acetate (1:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 6.15 (s, 1H, N*H*), 4.19 (d, $^3J_{HH}$ = 17.4 Hz, 1H, OCH_2), 4.14 (d, $^3J_{HH}$ = 17.4 Hz, 1H, OCH_2), 4.05 (qd, $^3J_{HH}$ = 6.1 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, OC*H*), 3.19 (t, $^3J_{HH}$ = 3.1 Hz,

1H, NC*H*), 1.40 (s, 3H, C(C*H*$_3$)$_2$), 1.26 (s, 3H, C(C*H*$_3$)$_2$), 1.18 (d, $^3J_{HH}$ = 6.1 Hz, 3H, CHC*H*$_3$), 0.87 (s, 9H, SiC(C*H*$_3$)$_3$), 0.07 (s, 3H, SiC*H*$_3$), 0.06 (s, 3H, SiC*H*$_3$).

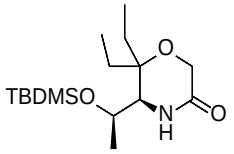
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 169.2, 70.6, 68.4, 64.0, 63.0, 25.9, 25.2, 24.3, 18.1, 17.6, −4.3, −4.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3357 (w), 2978 (w), 2935 (w), 1637 (s), 1350 (m), 1274 (m), 1164 (m), 1098 (s), 1077 (m), 1031 (w), 832 (w), 641 (w), 420 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{14}H_{29}NO_3Si^+$: 310.1809 [M+Na]$^+$; found: 310.1812.

$[\alpha]_D^{20}$ = −79.4 (*c* = 0.75, MeOH).

(*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6,6-diethylmorpholin-3-one (121c)



According to general procedure **GP9**, benzyl ((2*R*,3*S*)-2-((*tert*-butyldimethylsilyl)oxy)-4-ethyl-4-hydroxyhexan-3-yl)carbamate (**120c**) (2.40 g, 5.86 mmol) in MeOH (19 mL) and Pd/C (550 mg) were stirred to give of the crude amine as a colorless oil (1.60 g, 5.81 mmol, 99%).

Then the crude amine (1.60 g, 4.28 mmol) in CH_2Cl_2 (29 mL), triethylamine (764 mg, 1.06 mL, 7.55 mmol) and chloroacetyl chloride (722 mg, 508 µL, 6.39 mmol) were stirred. In the next step the crude chloro acetamide was dissolved in THF (29 mL) and sodium hydride (60% in mineral oil, 349 mg, 8.72 mmol) was added and stirred. The crude mixture was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (1:1), d x h: 3.5 x 21 cm) to afford the product **121c** (539 mg, 1.71 mmol, 29%) as a white solid.

$C_{16}H_{33}NO_3Si$ (315.53 g/mol):

MP: 83-84 °C.

TLC: R_f = 0.33 (SiO_2, CH_2Cl_2:ethyl acetate (1:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 6.56 (s, 1H, N*H*), 4.09 (d, $^2J_{HH}$ = 17.4 Hz, 1H, OC*H*$_2$), 4.02 (d, $^2J_{HH}$ = 17.4 Hz, 1H, OC*H*$_2$), 3.93 (qd, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 4.0 Hz, 1H, OC*H*), 3.20 (dd, $^3J_{HH}$ = 4.1 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, NC*H*), 1.87-1.76 (m, 1H, C*H*$_2$CH$_3$), 1.78-1.61 (m, 2H, C*H*$_2$CH$_3$), 1.41 (dq, $^2J_{HH}$ = 14.7 Hz, $^3J_{HH}$ = 7.4 Hz, 1H, C*H*$_2$CH$_3$), 1.22 (d, $^3J_{HH}$ = 6.3 Hz, 3H, CHC*H*$_3$), 0.92-0.84 (m, 15H, CH$_2$C*H*$_3$, SiC(C*H*$_3$)$_3$), 0.09 (s, 3H, SiC*H*$_3$), 0.08 (s, 3H, SiC*H*$_3$).

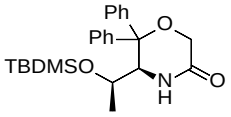
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 170.0, 75.6, 66.9, 62.6, 60.4, 25.9, 25.8, 24.1, 22.3, 18.1, 7.4, 7.3, −3.7, −4.5.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3195 (w), 3073 (w), 2927 (m), 2855 (m), 1673 (s), 1428 (w), 1353 (w), 1252 (m), 1146 (m), 1086 (s), 972 (m), 935 (w), 831 (s), 771 (s), 702 (w), 491 (w), 439 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{16}H_{33}NO_3Si^+$: 316.2302 $[M+H]^+$; found: 316.2303.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −20.5 (*c* = 0.82, MeOH).

(*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6,6-diphenylmorpholin-3-one (121d)



According to general procedure **GP9**, benzyl ((2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-1,1-diphenylbutan-2-yl)-carbamate (**120d**) (1.80 g, 3.56 mmol) in MeOH (12 mL) and Pd/C (278 mg) were stirred to give of the crude amine as a colorless oil (1.30 g, 3.50 mmol, 98%).

Then, the crude amine (1.28 g, 3.44 mmol) in CH_2Cl_2 (18 mL), triethylamine (453 mg, 629 µL, 4.47 mmol) and chloroacetyl chloride (427 mg, 301 µL, 3.78 mmol) were stirred. In the next step the crude chloro acetamide was dissolved in THF (18 mL) and sodium hydride (60% in mineral oil, 206 mg, 5.16 mmol) was added and stirred. The crude mixture was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (20:1), d x h: 3.5 x 20 cm) to afford the product **121d** (1.20 g, 2.90 mmol, 84%) as a white solid

$C_{24}H_{33}NO_3Si$ (411.61 g/mol):

MP: 196-197 °C.

TLC: R_f = 0.27 (SiO_2, CH_2Cl_2:ethyl acetate (20:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.48-7.40 (m, 2H, ar-*H*), 7.38-7.23 (m, 9H, ar-*H*, O*H*), 4.32 (d, $^{2}J_{HH}$ = 17.0 Hz, 1H, OCH_2), 4.04 (dd, $^{3}J_{HH}$ = 4.5 Hz, $^{3}J_{HH}$ = 3.1 Hz, 1H, NC*H*), 3.96 (d, $^{2}J_{HH}$ = 17.0 Hz, 1H, OCH_2), 3.85-3.78 (m, 1H, OC*H*), 0.96 (s, 9H, SiC(CH_3)$_3$), 0.94-0.87 (m, 3H, CHCH_3), 0.08 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3).

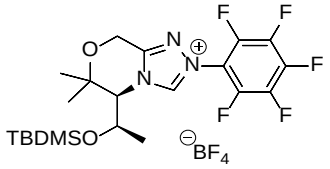
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 169.9, 143.1, 141.8, 128.8, 128.4, 127.7, 127.5, 127.3, 126.0, 79.8, 66.8, 63.9, 60.3, 26.0, 23.4, 18.1, −4.0, −4.5.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3191 (w), 3082 (w), 2926 (w), 2851 (w), 1681 (s), 1447 (w), 1366 (m), 1250 (m), 1125 (m), 1068 (m), 965 (m), 862 (s), 831 (m), 769 (s), 696 (s), 622 (w), 508 (w), 462 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{24}H_{33}NO_3Si^+$: 434.2122 $[M+Na]^+$; found: 434.2121.

$[\alpha]_D^{20}$ = −268.9 (*c* = 1.02, MeOH).

(*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6,6-dimethyl-2-(perfluorophenyl)-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (122a)



According to general procedure **GP8**, (*S*)-5-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-6,6-dimethyl-morpholin-3-one (**121a**) (650 mg, 2.26 mmol) in CH_2Cl_2 (11 mL) and trimethyloxonium tetrafluoroborate (368 mg, 2.49 mmol) were stirred to give of the crude imidate. Then, pentafluorophenylhydrazine (492 mg, 2.49 mmol] was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (2.40 g, 2.48 mL, 22.6 mmol) and refluxed for 20 hours at 80 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (2:3), d x h: 3.5 x 16 cm) to afford the product **122a** (300 mg, 531 µmol, 24%) as a beige solid.

$C_{21}H_{29}F_5N_3O_2Si\ BF_4$ (478.56 g/mol):

TLC: R_f = 0.38 (SiO_2, CH_2Cl_2:ethyl acetate (1:3)).

MP: 76-77 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 10.21 (s, 1H, carbene-C*H*), 5.06 (d, $^2J_{HH}$ = 17.4 Hz, 1H, OCH_2), 4.97 (d, $^2J_{HH}$ = 17.5 Hz, 1H, OCH_2), 4.68 (s, 1H, C*H*CH_3), 4.50 (qd, $^3J_{HH}$ = 6.4 Hz, $^3J_{HH}$ = 1.4 Hz, 1H, NC*H*), 1.53 (s, 3H, C(CH_3)$_2$), 1.41 (s, 3H, C(CH_3)$_2$), 1.36 (d, $^3J_{HH}$ = 6.7 Hz, 3H, CHCH_3), 0.75 (s, 9H, SiC(CH_3)$_3$), 0.06 (s, 6H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 151.2, 146.5, 145.0-144.2 (m), 142.6-140.7 (m), 140.3-138.4 (m), 137.4-135.9 (m), 73.7, 67.3, 65.3, 56.5, 25.5, 25.3, 23.4, 22.7, 17.8, −4.3, −4.5.

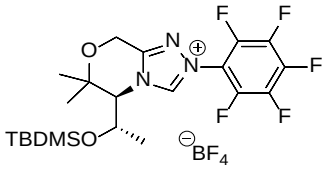
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ/ppm = −144.8-−145.2 (m), −146.0-−146.6 (m), −151.3, −158.6-−159.1 (m).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2952 (w), 2860 (w), 1663 (s), 1529 (s), 1257 (m), 1235 (w), 1054 (s), 983 (s), 836 (s), 776 (s), 704 (w), 521 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{21}H_{29}F_5N_3O_2Si^+$: 478.1944 $[M]^+$; found: 478.1943.

$[\alpha]_D^{20}$ = +15.0 (*c* = 0.70, MeOH).

(*S*)-5-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6,6-dimethyl-2-(perfluorophenyl)-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (122b)



According to general procedure **GP8**, (*S*)-5-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-6,6-dimethyl-morpholin-3-one (**121b**) (290 mg, 1.01 mmol) in CH_2Cl_2 (5 mL) and trimethyloxonium tetrafluoroborate (164 mg, 1.11 mmol) were stirred to give of the crude imidate. Then, pentafluorophenylhydrazine (240 mg, 1.21 mmol) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (536 mg, 0.55 mL, 5.05 mmol) and refluxed for 18 hours at 80 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (2:3), d x h: 3.5 x 20 cm) to afford the product **122b** (110 mg, 195 µmol, 19%) as a white solid.

$C_{21}H_{29}F_5N_3O_2Si$ BF_4 (478.56 g/mol):

TLC: R_f = 0.43 (SiO_2, CH_2Cl_2:ethyl acetate (1:3)).

MP: 171-172 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 9.75 (s, 1H, carbene-C*H*), 5.12 (d, $^2J_{HH}$ = 17.5 Hz, 1H, OCH_2), 5.04 (d, $^2J_{HH}$ = 17.2 Hz, 1H, OCH_2), 4.66 (d, $^3J_{HH}$ = 3.0 Hz, 1H, NC*H*), 4.42 (qd, $^3J_{HH}$ = 6.2 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, C*H*OTBDMS), 1.51 (s, 3H, C(CH_3)$_2$), 1.49 (s, 3H, C(CH_3)$_2$), 1.00 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CHCH_3), 0.93 (s, 9H, SiC(CH_3)$_3$), 0.21 (s, 3H, SiCH_3), 0.16 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 149.7, 146.9, 145.6-144.8 (m), 144.1-143.5 (m), 141.5-140.9 (m), 139.8-138.9 (m), 72.5, 67.6, 66.4, 56.2, 25.8, 24.8, 23.6, 18.1, 18.0, −4.9, −5.1.

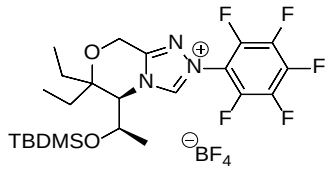
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ/ppm = −144.9–−145.1 (m), −145.8 (tt, J_{FF} = 21.5 Hz, J_{FF} = 4.0 Hz), −152.3, −157.6–−157.9 (m).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2953 (w), 2925 (w), 2857 (w), 1529 (s), 1513 (s), 1254 (w), 1227 (w), 1088 (s), 1072 (s), 1026 (s), 1001 (s), 981 (m), 843 (m), 811 (s), 777 (w), 522 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{21}H_{29}F_5N_3O_2Si^+$: 478.1944 $[M]^+$; found: 478.1947.

$[\alpha]_D^{20}$ = −17.9 (*c* = 0.40, MeOH).

(*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6,6-diethyl-2-(perfluorophenyl)-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-iumtetrafluoroborate (122c)



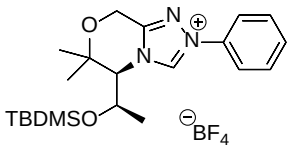
According to general procedure **GP8**, (*S*)-5-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-6,6-diethyl-morpholin-3-one (**121c**) (400 mg, 1.27 mmol) in CH_2Cl_2 (7 mL) and trimethyloxonium tetrafluoroborate (207 mg, 1.40 mmol) were stirred to give of the crude imidate. Then, pentafluorophenylhydrazine (277 mg, 1.40 mmol) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (4.85 g, 5.0 mL, 45.7 mmol) and refluxed for 36 hours at 80 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH (50:1), d x h: 3.5 x 21 cm) followed by recrystallization from CH_2Cl_2/pentane to afford the product **122c** (300 mg, 505 µmol, 40%) as a pink solid.

$C_{23}H_{33}F_5N_3O_2Si\ BF_4$ (593.42 g/mol):
MP: 82-83 °C.
TLC: R_f = 0.35 (SiO_2, CH_2Cl_2:MeOH (20:1)).
MP: 177-178 °C.
^{1}H NMR (400 MHz, CD_2Cl_2) δ/ppm = 10.27 (s, 1H, carbene-C*H*), 5.08 (d, $^2J_{HH}$ = 17.7 Hz, 1H, OCH_2), 4.91 (d, $^2J_{HH}$ = 17.7 Hz, 1H, OCH_2), 4.62 (s, 1H, NC*H*), 4.53 (q, $^3J_{HH}$ = 6.4 Hz, 1H, C*H*CH_3), 2.03-1.91 (m, 1H, C$H_2$$CH_3$), 1.81-1.54 (m, 3H, C$H_2$$CH_3$), 1.36 (d, $^3J_{HH}$ = 6.3 Hz, 3H, CHCH_3), 0.99-0.93 (m, 6H, CH_2CH_3), 0.75 (s, 9H, SiC(CH_3)$_3$), 0.09 (s, 3H, SiCH_3), 0.09 (s, 3H, SiCH_3).
^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2) δ/ppm = 152.7, 146.5, 145.2-144.6 (m), 142.6-142.0 (m), 140.5-139.4 (m), 138.0-137.4 (m), 78.8, 66.3, 65.2, 56.7, 26.1, 25.7, 23.7, 23.2, 18.0, 7.6, 7.0, −4.2, −4.3.
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2) δ/ppm = −145.2-−145.4 (m), −146.2-−146.4 (m), −151.0, −158.8-−159.1 (m).
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2949 (w), 2930 (w), 2860 (w), 1529 (m), 1472 (m), 1256 (w), 1061 (s), 1003 (s), 837 (s), 777 (s), 684 (w), 522 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{23}H_{33}F_5N_3O_2Si^+$: 506.2257 $[M]^+$; found: 506.2261.

$[\alpha]_D^{20}$ = +8.6 (*c* = 0.70, MeOH).

(*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6,6-dimethyl-2-phenyl-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (123a)



According to general procedure **GP8**, (*S*)-5-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-6,6-dimethyl-morpholin-3-one (**121a**) (290 mg, 1.01 mmol) in CH_2Cl_2 (5 mL) and trimethyloxonium tetrafluoroborate (164 mg, 1.11 mmol) were stirred to give of the crude imidate. Then, phenylhydrazine (120 mg, 110 µL, 1.11 mmol) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (2.35 g, 2.42 mL, 22.1 mmol) and refluxed for 16 hours at 80 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH (60:1), d x h: 3 x 23 cm)) to afford the product **123a** (280 mg, 589 µmol, 58%) as a pale yellow solid.

$C_{21}H_{34}N_3O_2Si\ BF_4$ (475.41 g/mol):

MP: 104-105 °C.

TLC: R_f = 0.29 (SiO_2, CH_2Cl_2:MeOH (20:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 10.17 (s, 1H, carbene-C*H*), 7.93-7.87 (m, 2H, ar-*H*), 7.65-7.55 (m, 3H, ar-*H*), 5.08 (d, $^2J_{HH}$ = 17.3 Hz, 1H, OCH_2), 4.99 (d, $^2J_{HH}$ = 17.3 Hz, 1H, OCH_2), 4.64 (d, $^3J_{HH}$ = 4.4 Hz, 1H, NC*H*), 4.29 (qd, $^3J_{HH}$ = 6.1 Hz, $^3J_{HH}$ = 4.3 Hz, 1H, C*H*OTBDMS), 1.50 (s, 3H, C(CH_3)$_2$), 1.45-1.41 (m, 6H, C(CH_3)$_2$, CHCH_3), 0.68 (s, 9H, SiC(CH_3)$_3$), 0.03 (s, 3H, SiCH_3), −0.10 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 149.7, 141.1, 134.8, 131.3, 130.6, 120.8, 73.5, 66.8, 65.3, 56.8, 25.6, 25.4, 23.9, 23.4, 17.7, −4.4, −4.8.

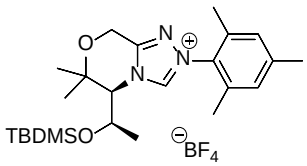
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ/ppm = −150.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2952 (w), 2857 (w), 1668 (w), 1577 (w), 1467 (w), 1405 (w), 1254 (w), 1047 (s), 983 (s), 915 (m), 835 (s), 772 (s), 682 (m), 518 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{21}H_{34}N_3O_2Si^+$: 388.2415 $[M]^+$; found: 388.2418.

$[\alpha]_D^{20}$ = +25.0 (*c* = 0.14, MeOH).

(*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-mesityl-6,6-dimethyl-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (123b)



According to general procedure **GP8**, (*S*)-5-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-6,6-dimethyl-morpholin-3-one (**121a**) (299 mg, 1.04 mmol) in CH_2Cl_2 (6 mL) and trimethyloxonium tetrafluoroborate (169 mg, 1.14 mmol) were stirred to give of the crude imidate. Then, mesitylhydrazine (freshly prepared from 1-mesitylhydrazine hydrochloride [214 mg, 1.14 mmol] in ether [5 mL] after extraction with saturated aqueous Na_2CO_3 solution [5 mL]) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (2.45 g, 2.49 mL, 22.8 mmol) and refluxed for 18 hours at 80 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH (50:1), d x h: 3.5 x 23 cm)) to afford the product **123b** (298 mg, 576 µmol, 55%) as a yellow solid.

$C_{24}H_{40}N_3O_4Si\ BF_4$ (517.49 g/mol):

MP: 72-73 °C.

TLC: R_f = 0.26 (SiO_2, CH_2Cl_2:MeOH (20:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 9.79 (s, 1H, carbene-C*H*), 7.04 (s, 2H, ar-*H*), 5.08 (d, $^2J_{HH}$ = 17.3 Hz, 1H, OCH_2), 4.97 (d, $^2J_{HH}$ = 17.3 Hz, 1H, OCH_2), 4.73 (s, 1H, NC*H*), 4.57 (q, $^3J_{HH}$ = 6.3 Hz, 1H, C*H*OTBDMS), 2.37 (s, 3H, ar-CH_3), 2.07 (s, 6H, ar-CH_3), 1.55 (s, 3H, C(CH_3)$_2$), 1.39 (s, 3H, C(CH_3)$_2$), 1.34 (d, J = 6.4 Hz, 3H, CHCH_3), 0.79 (s, 9H, SiC(CH_3)$_3$), 0.12 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 151.0, 143.8, 142.6, 135.0, 131.0, 130.0, 73.7, 66.2, 65.2, 56.7, 53.6, 25.7, 25.5, 23.6, 22.9, 21.4, 17.8, 17.3, −4.2, −4.4.

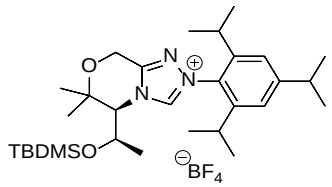
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ/ppm = −150.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2953 (w), 2928 (w), 2856 (w), 1576 (w), 1459 (w), 1447 (w), 1389 (w), 1254 (w), 1157 (w), 1053 (s), 1033 (s), 876 (m), 914 (m), 836 (s), 777 (s), 723 (m), 519 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{24}H_{40}N_3O_4Si^+$: 430.2884 $[M]^+$; found: 430.2888.

$[\alpha]_D^{20}$ = −9.0 (*c* = 0.27, MeOH).

(*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6,6-dimethyl-2-(2,4,6-triisopropylphenyl)-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (123c)



According to general procedure **GP8**, (*S*)-5-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-6,6-dimethyl-morpholin-3-one (**121a**) (500 mg, 1.74 mmol) in CH_2Cl_2 (8 mL) and trimethyloxonium tetrafluoroborate (283 mg, 1.91 mmol) were stirred to give of the crude imidate. Then, 1-(2,4,6-triisopropyl-phenyl)hydrazine (freshly prepared from *di-tert*-butyl 1-(2,4,6-triisopropylphenyl) hydrazine-1,2-dicarboxylate [907 mg, 2.09 mmol] and HCl in dioxane [4M, 4.4 mL, 5.05 g, 17.4 mmol] in ether [5 mL] after extraction with saturated aqueous Na_2CO_3 solution [10 mL]) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (1.29 g, 1.33 mL, 12.2 mmol) and refluxed for 18 hours at 80 °C. The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (1:1), d x h: 3.5 x 21 cm)) to afford the product **123c** (380 mg, 632 µmol, 36%) as a white solid.

$C_{30}H_{52}N_3O_2Si\ BF_4$ (514.85 g/mol):
TLC: R_f = 0.17 (SiO_2, cyclohexane:ethyl acetate (1:1)).
MP: 65-66 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 9.82 (s, 1H, carbene-C*H*), 7.18 (d, $^4J_{HH}$ = 1.9 Hz, 1H, ar-*H*), 7.13 (d, $^4J_{HH}$ = 2.0 Hz, 1H, ar-*H*), 5.08 (d, $^2J_{HH}$ = 17.3 Hz, 1H, OCH_2), 4.97 (d, $^2J_{HH}$ = 17.3 Hz, 1H, OCH_2), 4.80 (s, 1H NC*H*), 4.58 (q, $^3J_{HH}$ = 6.4 Hz, 1H, C*H*OTBDMS), 2.98 (hept, $^3J_{HH}$ = 7.0 Hz, 1H, C*H*$(CH_3)_2$), 2.37 (hept, $^3J_{HH}$ = 6.8 Hz, 1H, C*H*$(CH_3)_2$), 2.10 (hept, $^3J_{HH}$ = 6.9 Hz, 1H, C*H*$(CH_3)_2$), 1.56 (s, 3H, C(CH_3)$_2$), 1.40 (s, 3H, C(CH_3)$_2$), 1.35-1.27 (m, 12H, C(CH_3)$_2$, CHCH_3), 1.20 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH(CH_3)$_2$), 1.16 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(CH_3)$_2$), 1.14 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(CH_3)$_2$), 0.81 (s, 9H, SiC(CH_3)$_3$), 0.14 (s, 3H, SiCH_3), 0.09 (s, 3H, SiCH_3).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 153.9, 150.7, 146.4, 145.1, 144.2, 128.2, 123.1, 122.3, 73.6, 66.0, 65.2, 56.7, 34.7, 29.1, 29.0, 25.9, 25.6, 25.4, 24.7, 24.3, 24.2, 24.0, 23.9, 23.8, 23.4, 22.7, 17.8, −4.2, −4.4.

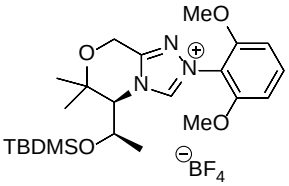
$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ/ppm = −151.0.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2960 (w), 2939 (w), 1574 (w), 1461 (w), 1253 (w), 1053 (s), 974 (m), 914 (w), 836 (m), 776 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{30}H_{52}N_3O_2Si^+$: 514.3823 $[M]^+$; found: 514.3826.

$[\alpha]_D^{20}$ = +15.8 (*c* = 0.55, MeOH).

(*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(2,6-dimethoxyphenyl)-6,6-dimethyl-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (123d)



According to general procedure **GP8**, (*S*)-5-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-6,6-dimethyl-morpholin-3-one (**121a**) (650 mg, 2.26 mmol) in CH_2Cl_2 (15 mL) and trimethyloxonium tetrafluoroborate (368 mg, 2.49 mmol) were stirred to give of the crude imidate. Then, 1-(2,6-dimethoxyphenyl)hydrazine (freshly prepared from di-*tert*-butyl 1-(2,6-dimethoxyphenyl)-hydrazine-1,2-dicarboxylate [831 mg, 2.26 mmol] and HCl in dioxane [4M, 4.7 mL, 5.59 g, 18.8 mmol] in ether [5 mL] after extraction with saturated aqueous Na_2CO_3 solution [10 mL]) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (4.0 mL, 3.88 g, 36.6 mmol) and refluxed for 6 hours at 80 °C. The crude product was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (5:1 to 0:1 after 300 mL), d x h: 3.5 x 23 cm)) to afford the product **123d** (538 mg, 1.01 mmol, 45%) as a white solid.

$C_{23}H_{38}N_3O_4Si\ BF_4$ (448.66 g/mol):

TLC: R_f = 0.28 (SiO_2, ethyl acetate).

MP: 83-84 °C.

^{1}H NMR (400 MHz, DMSO-*d*6) δ/ppm = 10.69 (s, 1H, carbene-C*H*), 7.65 (t, $^{3}J_{HH}$ = 8.6 Hz, 1H, ar-*H*), 6.98 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H, ar-*H*), 5.08 (s, 2H, OCH_2), 4.57 (d, $^{3}J_{HH}$ = 1.7 Hz, 1H NC*H*), 4.48 (qd, $^{3}J_{HH}$ = 6.3 Hz, $^{3}J_{HH}$ = 1.8 Hz, 1H, C*H*OTBDMS), 3.81 (s, 3H, OCH_3), 1.46 (s, 3H, C(CH_3)$_2$), 1.31 (s, 3H, C(CH_3)$_2$), 1.26 (d, $^{3}J_{HH}$ = 6.3 Hz, 3H, CHCH_3), 0.75 (s, 9H, SiC(CH_3)$_3$), 0.07 (s, 3H, SiCH_3), 0.04 (s, 3H, SiCH_3).

$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d*6) δ/ppm = 155.2, 149.7, 145.9, 133.7, 112.1, 104.9, 72.8, 65.8, 64.6, 56.6, 56.0, 25.3, 24.5, 23.6, 22.6, 17.3, −4.7, −4.8.

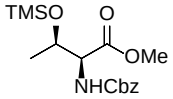
$^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-*d*6) δ/ppm = −148.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2952 (w), 2931 (w), 2855 (w), 1605 (w), 1580 (w), 1486 (s), 1263 (m), 1050 (s), 1006 (s), 836 (m), 778 (m), 734 (m), 519 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{23}H_{38}N_3O_4Si^+$: 448.2626 $[M]^+$; found: 448.2630.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +13.5 (*c* = 0.90, MeOH).

Methyl *N*-((benzyloxy)carbonyl)-*O*-(trimethylsilyl)-L-threoninate (125)



Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with *N*-cbz-L-threonine methyl ester (**124**) (2.50 g, 9.17 mmol) and DMF (6 mL). Then, imidazole (1.69 g, 24.8 mmol), TMS chloride (1.39 g, 1.63 mL, 12.8 mmol) and afterwards the reaction mixture was stirred for 48 hours at room temperature. After stirring for 48 hours aqueous HCl solution (1M, 30 mL) was added to the reaction solution and the corresponding aqueous mixture was extracted with ether (3 x 30 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered, concentrated under vacuum and the crude mixture was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (3:1), d x h: 5 x 13 cm) to afford the product **125** (2.96 g, 8.71 mmol, 95%) as a colorless oil.

$C_{16}H_{25}NO_5Si$ (339.46 g/mol):

TLC: R_f = 0.48 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.41-7.30 (m, 5H, ar-*H*), 5.53 (d, $^{3}J_{HH}$ = 9.7 Hz, 1H, N*H*), 5.14 (s, 2H, Ph-CH_2), 4.42 (qd, $^{3}J_{HH}$ = 6.3 Hz, $^{3}J_{HH}$ = 1.8 Hz, 1H, OC*H*), 4.26 (dd, $^{3}J_{HH}$ = 9.8 Hz, $^{3}J_{HH}$ = 1.8 Hz, 1H, NC*H*), 3.73 (s, 3H, OCH_3), 1.20 (d, $^{3}J_{HH}$ = 6.3 Hz, 3H, CHCH_3), 0.05 (s, 9H, Si(CH_3)$_3$).

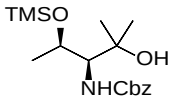
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ/ppm = 171.5, 156.9, 136.4, 128.7, 128.3, 128.3, 68.7, 67.2, 60.0, 52.4, 21.1, 0.1.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3443 (w), 2955 (w), 1724 (w), 1504 (m), 1250 (m), 1203 (m), 1067 (s), 961 (m), 839 (s), 735 (m), 695 (m), 546 (w), 458 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{16}H_{25}NO_5Si^+$: 362.1394 $[M+Na]^+$; found: 362.1397.

$[\alpha]_D^{20}$ = −30.4 (*c* = 0.36, MeOH).

Benzyl ((3*S*,4*R*)-2-hydroxy-2-methyl-4-((trimethylsilyl)oxy)pentan-3-yl)carbamate (126)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with ethylmagnesium bromide solution (3M in ether, 11.8 g, 11.4 mL, 34.2 mmol) and was cooled in an ice-bath. Then, at 0 °C a solution of methyl methyl *N*-((benzyloxy)carbonyl)-*O*-(trimethylsilyl)-L-threoninate (**125**) (2.90 g, 8.54 mmol) in ether (24 mL) was added dropwise over 10 minutes to the Grignard solution. After addition the reaction was stirred for one hour at 0 °C and further 16 hours at room temperature. Afterwards the reaction mixture was quenched by slowly addition of aqueous saturated NH_4Cl solution (20 mL) at 0 °C. Then, the biphasic mixture was extracted with ether (3 x 50 mL), the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by column chromatography (SiO_2, ethyl acetate:cyclohexane (1:4), d x h: 3.5 x 18 cm) to afford the product **126** (2.56 g, 7.54 mmol, 88%) as a colorless oil.

$C_{17}H_{29}NO_4Si$ (339.51 g/mol):

TLC: R_f = 0.31 (SiO_2, ethyl acetate:cyclohexane (1:3)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.39-7.29 (m, 5H, ar-*H*), 5.49 (d, $^3J_{HH}$ = 10.0 Hz, 1H, N*H*), 5.15 (d, $^2J_{HH}$ = 12.3 Hz, 1H, Ph-CH_2), 5.12 (d, $^2J_{HH}$ = 12.3 Hz, 1H, Ph-CH_2), 4.44 (qd, $^3J_{HH}$ = 6.2 Hz, $^3J_{HH}$ = 1.9 Hz, 1H, C*H*CH_3), 3.50 (s, 1H, O*H*), 3.37 (dd, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 1.9 Hz, 1H, NC*H*), 1.32 (s, 3H, C(CH_3)$_2$), 1.19 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CHCH_3), 1.17 (s, 3H, C(CH_3)$_2$), 0.16 (s, 9H, Si(CH_3)$_3$).

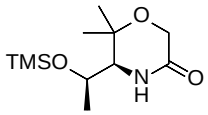
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 157.5, 136.8, 128.7, 128.2, 128.1, 73.3, 69.6, 67.0, 61.3, 27.7, 27.3, 21.2, 0.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3466 (m), 2965 (m), 2848 (w), 1716 (s), 1448 (s), 1472 (m), 1256 (m), 1225 (s), 1048 (s), 928 (s), 876 (m), 839 (s), 769 (s), 735 (m), 497 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{17}H_{29}NO_4Si^+$: 362.1764 $[M+Na]^+$; found: 362.1769.

$[\alpha]_D^{20}$ = −15.4 (*c* = 0.46, MeOH).

(*S*)-6,6-Dimethyl-5-((*R*)-1-((trimethylsilyl)oxy)ethyl)morpholin-3-one (127)



According to general procedure **GP9**, methyl *N*-((benzyloxy)carbonyl)-*O*-(trimethylsilyl)-L-threoninate (**126**) (1.48 g, 4.36 mmol) in EtOAc (14 mL) and Pd/C (340 mg) were stirred to give of the crude amine as a colorless oil (891 g, 4.34 mmol, 99%).

Then, the crude amine (880 mg, 4.28 mmol) in CH_2Cl_2 (21 mL), triethylamine (563 mg, 782 µL, 5.56 mmol) and chloroacetyl chloride (532 mg, 374 µL, 4.71 mmol) were stirred. In the next step the crude chloro acetamide was dissolved in THF (21 mL) and sodium hydride (60% in mineral oil, 257 mg, 6.42 mmol) was added and stirred. The crude mixture was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (2:1), d x h: 3.5 x 25 cm) to afford the product **127** (90 mg, 367 µmol, 9%) as a white solid.

$C_{11}H_{23}NO_3Si$ (245.39 g/mol):

MP: 96-97 °C.

TLC: R_f = 0.41 (SiO_2, CH_2Cl_2:ethyl acetate (1:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 6.26 (s, 1H, N*H*), 4.16 (d, $^2J_{HH}$ = 17.3 Hz, 1H, OCH_2), 4.10 (d, $^2J_{HH}$ = 17.4 Hz, 1H, OCH_2), 3.77 (p, $^3J_{HH}$ = 6.1 Hz, 1H, OC*H*), 3.16 (d, $^3J_{HH}$ = 5.7 Hz, 1H, NC*H*), 1.33 (s, 3H, C(CH_3)$_2$), 1.25 (d, $^3J_{HH}$ = 6.3 Hz, 3H, CHCH_3), 1.23 (s, 3H, C(CH_3)$_2$), 0.15 (s, 9H, Si(CH_3)$_3$).

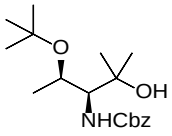
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 169.7, 73.2, 66.5, 63.2, 62.3, 24.8, 23.6, 20.2, 2.1.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3483 (m), 3212 (w), 2969 (w), 2922 (w), 1664 (s), 1458 (w), 1377 (w), 1338 (m), 1169 (m), 1117 (s), 1074 (m), 1021 (m), 871 (m), 808 (s), 719 (m), 650 (w), 525 (w), 420 (s).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{11}H_{23}NO_3Si^+$: 268.1345 $[M+Na]^+$; found: 268.1157.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −29.0 (c = 0.14, MeOH).

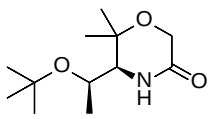
Benzyl ((3*S*,4*R*)-4-(*tert*-butoxy)-2-hydroxy-2-methylpentan-3-yl)carbamate (131)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with methylmagnesium bromide solution (3M in ether, 14.9 g, 14.4 mL, 43.2 mmol) and was cooled in an ice-bath. At 0 °C, a solution of methyl *N*-((benzyloxy)carbonyl)-*O*-(*tert*-butyl)-L-threoninate (**130**) (3.49 g, 10.8 mmol) in ether (28 mL) was added dropwise over 10 minutes to the Grignard solution. After addition the reaction was stirred for one hour at 0 °C and further 16 hours at room temperature. Afterwards the reaction mixture was quenched by slowly addition of aqueous saturated NH_4Cl solution (20 mL) at 0 °C. Then, the biphasic mixture was extracted with ether (3 x 50 mL), the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by column chromatography (SiO_2, ethyl acetate:cyclohexane (1:3), d x h: 3.5 x 17 cm) to afford the product **131** (2.68 g, 8.28 mmol, 77%) as a colorless oil.

$C_{18}H_{29}NO_4$ (323.43 g/mol):
TLC: R_f = 0.33 (SiO_2, ethyl acetate:cyclohexane (1:3)).
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.40-7.29 (m, 5H, ar-*H*), 5.49 (d, $^3J_{HH}$ = 10.2 Hz, 1H, N*H*), 5.16 (d, $^2J_{HH}$ = 12.3 Hz, 1H, Ph-CH_2), 5.11 (d, $^2J_{HH}$ = 12.3 Hz, 1H, Ph-CH_2), 4.35 (qd, $^3J_{HH}$ = 6.1 Hz, $^3J_{HH}$ = 2.1 Hz, 1H, OC*H*), 3.40 (dd, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 2.1 Hz, 1H, NC*H*), 1.33 (s, 3H, C(CH_3)$_2$), 1.26 (s, 9H, OC(CH_3)$_3$), 1.21 (d, $^3J_{HH}$ = 6.1 Hz, 3H, CHCH_3), 1.15 (s, 3H, C(CH_3)$_2$).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 157.4, 136.8, 128.6, 128.2, 128.1, 74.9, 73.2, 69.5, 66.9, 62.1, 29.6, 27.8, 27.4, 20.7.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3450 (w), 2974 (m), 2937 (w), 1718 (s), 1499 (s), 1371 (m), 1309 (w), 1291 (w), 1215 (s), 1060 (s), 937 (s), 735 (s), 695 (s), 502 (m).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{18}H_{29}NO_4^+$: 346.1989 [M+Na]$^+$; found: 346.1990.
$[\alpha]_D^{20}$ = +3.8 (*c* = 1.59, MeOH).

(*S*)-5-((*R*)-1-(*tert*-Butoxy)ethyl)-6,6-dimethylmorpholin-3-one (132)

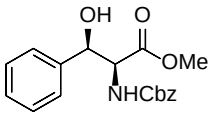


According to general procedure **GP9**, benzyl ((3*S*,4*R*)-4-(*tert*-butoxy)-2-hydroxy-2-methylpentan-3-yl)carbamate (**131**) (2.60 g, 8.04 mmol) in MeOH (26 mL) and Pd/C (600 mg) were stirred to give of the crude amine as a pale yellow oil (1.50 g, 7.93 mmol, 99%).

Then, the crude amine (1.40 g, 7.40 mmol) in CH_2Cl_2 (28 mL), triethylamine (973 mg, 1.35 mL, 9.62 mmol) and chloroacetyl chloride (919 mg, 647 µL, 8.14 mmol) were stirred. In the next step the crude chloro acetamide was dissolved in THF (28 mL) and sodium hydride (60% in mineral oil, 444 mg, 11.1 mmol) was added and stirred. The crude mixture was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (1:1), d x h: 3.5 x 20 cm) to afford the product **132** (895 mg, 3.11 mmol, 73%) as a white solid.

$C_{12}H_{23}NO_3$ (229.32 g/mol):
MP: 46-47 °C.
TLC: R_f = 0.31 (SiO_2, CH_2Cl_2:ethyl acetate (1:1)).
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = δ 6.47 (s, 1H, N*H*), 4.13 (d, $^2J_{HH}$ = 17.3 Hz, 1H, OCH_2), 4.07 (d, $^2J_{HH}$ = 17.3 Hz, 1H, OCH_2), 3.49 (dq, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, OC*H*), 3.13 (dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 1.3 Hz, 1H, NC*H*), 1.33 (s, 3H, C(CH_3)$_2$), 1.25 (s, 3H, C(CH_3)$_2$), 1.23 (d, $^3J_{HH}$ = 6.0 Hz, 3H, CHCH_3), 1.21 (s, 9H, OC(CH_3)$_3$).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 168.6, 75.2, 72.3, 66.8, 64.2, 62.9, 28.8, 27.5, 22.7, 19.8.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3239 (w), 2973 (m), 2936 (w), 1671 (s), 1485 (w), 1363 (m), 1287 (m), 1194 (s), 1169 (s), 1080 (s), 989 (w), 919 (w), 851 (m), 806 (m), 488 (w), 461 (w), 422 (m).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{12}H_{23}NO_3^+$: 252.1570 [M+Na]$^+$; found: 252.1567.
$[\alpha]_D^{20}$ = −15.5 (*c* = 1.47, MeOH).

Methyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)amino)-3-hydroxy-3-phenylpropanoate (135)

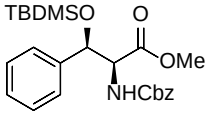


Under argon atmosphere, a heat-gun dried two-necked flask was charged with L-threo-phenylserine (**134**) (950 mg, 5.24 mmol) and MeOH (9.5 mL). The reaction mixture was cooled in an ice-bath and at 0 °C thionyl chloride (686 mg, 418 µL, 5.76 mmol) was added dropwise to the mixture and after addition the reaction mixture was refluxed for 16 hours. Afterwards the crude was concentrated under vacuum and directly used for the next step without further purification steps.
The crude hydrochloride salt was dissolved in THF (20 mL) and then DIPEA (1.36 g, 1.73 mL, 10.5 mmol) was added to the mixture. At 0 °C, benzyl chloroformate (983 mg, 874 µL, 5.76 mmol)

was added dropwise to the reaction solution over 10 minutes. Afterwards the mixture was stirred for 16 hours at room temperature and then aqueous HCl solution (1M, 30 mL) was added. The biphasic mixture was extracted with EtOAc (3 x 30 mL), the combined organic layers were washed with water (30 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (1:1), d x h: 3.5 x 21 cm) to afford the product **135** (1.63 g, 4.96 mmol, 95%) as a white solid.

$C_{18}H_{19}NO_5$ (329.35 g/mol):
MP: 102-103 °C.
TLC: R_f = 0.52 (SiO_2, cyclohexane:ethyl acetate (1:1)).
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.40-7.22 (m, 10H, ar-*H*), 5.66 (s, 1H, N*H*), 5.27 (s, 1H, OfC*H*), 4.99 (s, 2H, Ph-CH_2), 4.61 (d, $^3J_{HH}$ = 9.3 Hz, 1H, NC*H*), 3.75 (s, 3H, OCH_3), 2.97 (s, 1H, O*H*).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 171.3, 156.4, 139.7, 136.3, 128.6, 128.3, 128.2, 128.0, 126.0, 73.7, 67.1, 60.0, 52.8.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3398 (m), 1752 (s), 1697 (s), 1510 (s), 1450 (m), 1326 (m), 1254 (m), 1205 (s), 1095 (w), 1053 (s), 981 (w), 933 (w), 798 (w), 773 (w), 740 (m), 700 (s), 569 (m), 468 (m).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{18}H_{19}NO_5^+$: 352.1155 $[M+Na]^+$; found: 352.1156.
$[\boldsymbol{\alpha}]_D^{20}$ = −29.1 (*c* = 0.80, MeOH).

Methyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-3-phenyl-propanoate (136)

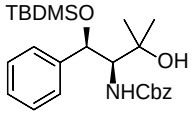


Under argon atmosphere, a heat-gun dried round-bottomed flask was charged with methyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)amino)-3-hydroxy-3-phenylpropanoate (**135**) (1.60 g, 4.86 mmol) and DMF (5 mL). Then, imidazole (662 mg, 9.72 mmol), DMAP (404 mg, 3.30 mmol), TBDMS chloride (1.03 g, 6.8 mmol) and afterwards the reaction mixture was stirred for 48 hours at room temperature. After stirring for 48 hours aqueous HCl solution (1M, 30 mL) was added to the reaction solution and the corresponding aqueous mixture was extracted with ether (3 x 30 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered, concentrated under vacuum and the crude mixture was purified by column chromatography (SiO_2,

cyclohexane:ethyl acetate (4:1), d x h: 3.5 x 20 cm) to afford the product **136** (1.07 g, 2.41 mmol, 50%) as a colorless oil.

$C_{24}H_{33}NO_5Si$ (443.62 g/mol):
TLC: R_f = 0.44 (SiO_2, cyclohexane:ethyl acetate (4:1)).
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.50-7.40 (m, 10H, ar-*H*), 5.67 (d, $^3J_{HH}$ = 9.8 Hz, 1H, OC*H*), 5.47 (d, $^3J_{HH}$ = 2.1 Hz, 1H, N*H*), 5.13 (s, 2H, Ph-CH_2), 4.64 (dd, $^3J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 2.2 Hz, 1H, NC*H*), 3.93 (s, 3H, OCH_3), 1.02 (s, 9H, SiC(CH_3)$_3$), 0.13 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 170.9, 156.2, 140.5, 136.5, 128.6, 128.3, 128.2, 128.2, 128.0, 126.3, 74.8, 67.0, 61.3, 52.6, 25.8, 18.2, −4.5, −5.4.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3251 (w), 2952 (w), 2929 (w), 2856 (w), 1727 (s), 1498 (s), 1253 (s), 1201 (s), 1094 (m), 1060 (s), 1027 (m), 1005 (m), 833 (s), 776 (s), 696 (s), 557 (w), 485 (w).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{24}H_{33}NO_5Si^+$: 466.2020 [M+Na]$^+$; found: 466.2026.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −36.2 (*c* = 0.52, MeOH).

Benzyl ((1*R*,2*S*)-1-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-3-methyl-1-phenylbutan-2-yl)-carbamate (137)



Under argon atmosphere a heat-gun dried two-neck flask was charged with methylmagnesium bromide solution (3M in ether, 3.12 g, 3.00 mL, 9.00 mmol) and was cooled in an ice-bath. Then, at 0 °C a solution of methyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)amino)-3-((*tert*-butyldimethyl-silyl)-oxy)-3-phenyl-propanoate (**136**) (998 mg, 2.25 mmol) in ether (7 mL) was added dropwise over 10 minutes to the Grignard solution. After addition, the reaction was stirred for one hour at 0 °C and further 16 hours at room temperature. Afterwards the reaction mixture was quenched by slowly addition of aqueous saturated NH_4Cl solution (10 mL) at 0 °C. Then the biphasic mixture was extracted with ether (3 x 20 mL), the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, ethyl acetate:cyclohexane (1:4), d x h: 3.5 x 17 cm) to afford the product **137** (909 mg, 2.05 mmol, 91%) as a colorless oil.

$C_{25}H_{37}NO_2Si$ (443.66 g/mol):

TLC: R_f = 0.31 (SiO_2, cyclohexane:ethyl acetate (3:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.29-7.10 (m, 10H, ar-*H*), 5.46 (d, $^3J_{HH}$ = 10.1 Hz, 1H, OC*H*), 5.16 (d, $^3J_{HH}$ = 1.8 Hz, 1H, N*H*), 4.86 (d, $^2J_{HH}$ = 12.4 Hz, 1H, Ph-CH_2), 4.80 (d, $^2J_{HH}$ = 12.4 Hz, 1H, Ph-CH_2), 3.46 (dd, $^3J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 1.7 Hz, 1H, NC*H*), 3.14 (s, 1H, O*H*), 1.36 (s, 3H, C(CH_3)$_2$), 1.14 (s, 3H, C(CH_3)$_2$), 0.82 (s, 9H, SiC(CH_3)$_3$), 0.00 (s, 3H, SiCH_3), −0.42 (s, 3H, SiCH_3).

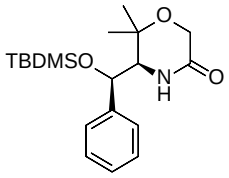
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 156.6, 141.5, 136.9, 128.6, 128.1, 127.9, 127.6, 127.0, 126.8, 75.1, 73.6, 66.7, 62.9, 27.9, 27.3, 26.1, 18.1, −3.6, −4.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3438 (w), 2953 (m), 2929 (m), 2889 (w), 2857 (w), 1710 (s), 1497 (s), 1454 (m), 1298 (m), 1255 (s), 1213 (s), 1048 (s), 1001 (m), 833 (s), 775 (s), 747 (m), 697 (s), 576 (m), 540 (m), 483 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{25}H_{37}NO_2Si^+$: 466.2384 [M+Na]$^+$; found: 466.2388.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −47.1 (*c* = 1.01, MeOH).

(*S*)-5-((*R*)-((*tert*-Butyldimethylsilyl)oxy)(phenyl)methyl)-6,6-dimethylmorpholin-3-one (138)



According to general procedure **GP9**, benzyl ((1*R*,2*S*)-1-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-3-methyl-1-phenylbutan-2-yl)-carbamate (**137**) (745 mg, 1.68 mmol) in MeOH (7 mL) and Pd/C (144 mg) were stirred to give of the crude amine as a colorless oil (520 mg, 1.68 mmol, 100%). Then, the crude amine (520 mg, 1.68 mmol) in CH_2Cl_2 (9 mL), triethylamine (221 mg, 307 µL, 2.18 mmol) and chloroacetyl chloride (209 mg, 147 µL, 1.85 mmol) were stirred. In the next step the crude chloro acetamide was dissolved in THF (9 mL) and sodium hydride (60% in mineral oil, 101 mg, 2.52 mmol) was added and stirred. The crude mixture was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (2:1), d x h: 3.5 x 18 cm) to afford the product **138** (414 mg, 1.18 mmol, 71%) as a beige solid.

$C_{19}H_{31}NO_3Si$ (349.55 g/mol):

MP: 84-85 °C.

TLC: R_f = 0.50 (SiO_2, CH_2Cl_2:ethyl acetate (2:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.38-7.27 (m, 5H, ar-*H*), 6.43 (s, 1H, N*H*), 4.43 (d, $^3J_{HH}$ = 7.8 Hz, 1H, OC*H*), 4.16 (d, $^2J_{HH}$ = 17.4 Hz, 1H, OCH_2), 4.14 (d, $^2J_{HH}$ = 17.4 Hz, 1H, OCH_2), 3.58 (dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 1.1 Hz, 1H), 1.29 (s, 3H, C(CH_3)$_2$), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.68 (s, 3H, C(CH_3)$_2$), 0.05 (s, 3H, SiCH_3), −0.36 (s, 3H, SiCH_3).

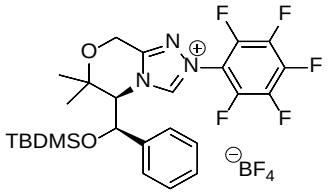
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 169.2, 141.0, 129.0, 128.9, 127.7, 75.2, 71.9, 65.1, 62.9, 26.9, 25.9, 19.6, 18.2, −4.2, −4.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3400 (w), 2929 (w), 2887 (w), 2956 (w), 1674 (s), 1428 (w), 1364 (w), 1320 (w), 1255 (m), 1100 (m), 1066 (m), 1003 (w), 833 (s), 775 (s), 700 (s), 571 (w), 509 (w), 422 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{19}H_{31}NO_3Si^+$: 372.1965 [M+Na]$^+$; found: 372.1965.

$[\alpha]_D^{20}$ = −10.3 (*c* = 0.41, MeOH).

(*S*)-5-((*R*)-((*tert*-Butyldimethylsilyl)oxy)(phenyl)methyl)-6,6-dimethyl-2-(perfluorophenyl)-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (139)



According to general procedure **GP8**, (*S*)-5-((*R*)-((*tert*-butyldimethylsilyl)oxy)(phenyl)methyl)-6,6-dimethylmorpholin-3-one (**138**) (270 mg, 772 µmol) in CH_2Cl_2 (4 mL) and trimethyloxonium tetrafluoroborate (126 mg, 849 µmol) were stirred to give of the crude imidate. Then, pentafluorophenylhydrazine (168 mg, 849 µmol) was added and stirred for six hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (655 mg, 676 µL6.18 mmol) and refluxed for 48 hours at 80 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH (1:60), d x h: 3.5 x 15 cm) to afford the product **139** (89 mg, 142 µmol, 18%) as a beige solid.

$C_{26}H_{31}F_5N_3O_2Si \cdot BF_4$ (627.43 g/mol):

MP: 70-71 °C.

TLC: R_f = 0.48 (SiO_2, CH_2Cl_2:MeOH (20:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.91 (s, carbene-C*H*), 7.49-7.32 (m, 3H, ar-*H*), 7.25-7.22 (m, 2H, ar-*H*), 5.39 (d, $^3J_{HH}$ = 2.8 Hz, 1H, TDMSOC*H*), 5.17 (d, $^2J_{HH}$ = 17.5 Hz, 1H, OCH_2), 5.04 (d,

$^{2}J_{HH}$ = 17.4 Hz, 1H, OCH_2), 4.77 (d, $^{3}J_{HH}$ = 2.8 Hz, 1H, NC*H*), 1.59 (s, 3H, C(CH_3)$_2$), 1.41 (s, 3H, C(CH_3)$_2$), 0.81 (s, 9H, SiC(CH_3)$_3$), 0.04 (s, 3H, SiCH_3), −0.22 (s, 3H, SiCH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 150.8, 146.4, 144.3-144.2 (m), 141.7-141.6 (m), 139.3, 137.1-136.7 (m), 129.5, 126.6, 111.0-110.6 (m), 73.8, 71.9, 68.4, 56.7, 25.9, 25.8, 25.7, 23.6, 18.1, −4.0, −4.4.

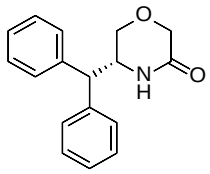
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ/ppm = −144.0-−144.1 (m), −145.5-−145.6 (m), −151.9, −157.7-−157.9 (m).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2930 (w), 2858 (w), 1588 (w), 1514 (m), 1473 (w), 1258 (m), 1071 (s), 1003 (s), 886 (m), 837 (s), 778 (m), 756 (m), 703 (m), 540 (w), 520 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{26}H_{31}F_5N_3O_2Si^+$: 540.2100 [M]$^+$; found: 540.2105.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −30.5 (*c* = 0.40, MeOH).

(*R*)-5-Benzhydrylmorpholin-3-one (144)



According to general procedure **GP9**, (*R*)-2-amino-3,3-diphenylpropan-1-ol (**143**) (1.32 g, 5.79 mmol) in CH_2Cl_2 (29 mL), triethylamine (762 mg, 1.06 mL, 7.53 mmol) and chloroacetyl chloride (719 mg, 507 µL, 6.37 mmol) were stirred. In the next step the crude chloro acetamide was dissolved in THF (29 mL) and sodium hydride (60% in mineral oil, 347 mg, 8.69 mmol) was added and stirred. The crude mixture was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (2:1), d x h: 3.5 x 23 cm) to afford the product **144** (1.09 g, 4.08 mmol, 70%) as a white solid

$C_{17}H_{17}NO_2$ (267.33 g/mol):

MP: 122-123 °C.

TLC: R_f = 0.38 (SiO_2, CH_2Cl_2:ethyl acetate (2:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.41-7.22 (m, 10H, ar-*H*), 5.93 (s, 1H, N*H*), 4.39-4.32 (m, 1H, C*H*Ph$_2$), 4.22 (d, $^{2}J_{HH}$ = 16.7 Hz, 1H, OCH_2), 4.15 (d, $^{2}J_{HH}$ = 16.7 Hz, 1H, OCH_2), 3.96 (d, $^{3}J_{HH}$ = 11.1 Hz, 1H, NC*H*), 3.79 (dd, $^{3}J_{HH}$ = 12.0 Hz, $^{3}J_{HH}$ = 3.7 Hz, 1H, NCH_2), 3.53 (dd, $^{3}J_{HH}$ = 12.0 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, NCH_2).

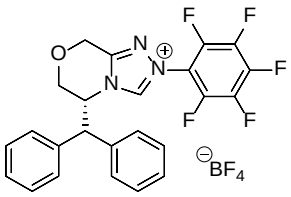
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ/ppm = 168.7, 140.2, 139.5, 129.6, 129.2, 128.2, 127.8, 127.7, 127.5, 68.1, 67.3, 55.2, 54.4.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3188 (w), 3109 (w), 2998 (w), 2870 (w), 1676 (s), 1544 (m), 1494 (m), 1317 (w), 1119 (s), 964 (m), 895 (m), 782 (m), 702 (m), 634 (m), 536 (s), 428 (s).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{17}H_{17}NO_2^+$: 290.1151 $[M+Na]^+$; found: 290.1150.

$[\alpha]_D^{20}$ = −24.5 (*c* = 0.62, MeOH).

(*S*)-5-Benzhydryl-2-(perfluorophenyl)-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (145)



According to general procedure **GP8**, (*S*)-3-benzhydrylmorpholine (**144**) (580 mg, 2.17 mmol) in CH_2Cl_2 (11 mL) and trimethyloxonium tetrafluoroborate (385 mg, 2.60 mmol) were stirred to give of the crude imidate. Then, pentafluorophenylhydrazine (473 mg, 2.39 mmol) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (1.84 g, 1.90 mL, 17.4 mmol) and MeCN (11 mL) and refluxed for 18 hours at 80 °C. The crude product was purified by column chromatography (SiO_2, pentane:ether (1:1), d x h: 2.5 x 12 cm)) followed by recrystallization from ether to afford the product **145** (160 mg, 293 µmol, 14%) as a white solid.

$C_{24}H_{17}F_5N_3O \cdot BF_4$ (458.41 g/mol):

TLC: R_f = 0.52 (SiO_2, pentane:ether (1:1)).

MP: 224-225 °C.

^1H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.66 (s, 1H, carbene-C*H*), 7.49-7.45 (m, 2H, ar-*H*), 7.43-7.30 (m, 8H, ar-*H*), 5.66 (dd, $^3J_{HH}$ = 11.8 Hz, $^4J_{HH}$ = 2.6 Hz, 1H, Ph-C*H*), 5.29 (d, $^3J_{HH}$ = 16.7 Hz, 1H, OCH_2), 5.07 (d, $^3J_{HH}$ = 16.7 Hz, 1H, OCH_2), 4.46 (d, $^3J_{HH}$ = 11.8 Hz, 1H, NC*H*), 4.25 (dd, $^3J_{HH}$ = 12.9 Hz, $^4J_{HH}$ = 2.8 Hz, 1H, CHCH_2), 4.17 (d, $^3J_{HH}$ = 12.8 Hz, 1H, CHCH_2).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ/ppm = 150.4, 145.5, 138.3, 137.9, 130.3, 129.8, 129.3, 129.1, 128.5, 128.4, 128.2, 128.2, 127.8, 65.0, 62.2, 60.4, 54.3.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ/ppm = −143.9-−144.2 (m), −145.2-−145.5 (m), −152.2, −157.8-−158.1 (m).

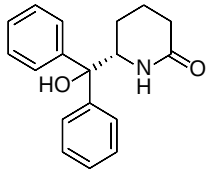
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3132 (w), 1591 (m), 1527 (s), 1445 (w), 1113 (m), 1030 (s), 996 (s), 850 (m), 751 (w), 701 (s), 631 (m), 519 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{24}H_{17}F_5N_3O^+$: 458.1286 $[M]^+$; found: 458.1290.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +28.0 (*c* = 0.29, MeOH).

5.3.2 Synthesis of Piperidine-Based Triazolium Salts

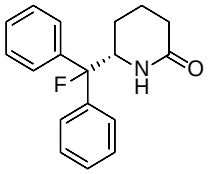
(*S*)-6-(Hydroxydiphenylmethyl)piperidin-2-one (150)



Under argon atmosphere, a two-necked flask was charged with methyl (*R*)-6-oxopiperidine-2-carboxylate (**149**) (1000 mg, 6.36 mmol) and THF (6 mL). Then, the corresponding solution was cooled in an ice-bath and at 0 °C phenylmagnesium bromide solution (3M in ether, 8.48 g, 8.48 mL, 25.4 mmol) was added dropwise over 15 minutes to the reaction mixture. After complete addition the mixture was stirred for 16 hours at room temperature. Then, the reaction solution was quenched by slowly addition of saturated aqueous NH_4Cl solution (20 mL). The biphasic mixture was extracted with EtOAc (3 x 50 mL) and then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by recrystallization in EtOH to yield the product **149** (923 mg, 3.28 mmol, 52%) was as a white solid.

$C_{18}H_{19}NO_2$ (281.35 g/mol):
MP: 139-140 °C.
TLC: R_f = 0.19 (SiO_2, cyclohexane:ethyl acetate (1:2)).
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.52-7.47 (m, 2H, ar-*H*), 7.40-7.35 (m, 2H, ar-*H*), 7.32-7.26 (m, 2H, ar-*H*), 7.24-7.17 (m, 3H, ar-*H*), 7.16-7.10 (m, 1H, ar-*H*), 5.65 (s, 1H, N*H*), 4.39 (dd, $^3J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 4.9 Hz, 1H, NC*H*), 2.58 (s, 1H, O*H*), 2.39-2.30 (m, 1H, CH_2), 2.23-2.12 (m, 1H, CH_2), 1.85-1.76 (m, 1H, CH_2), 1.64-1.52 (m, 2H, CH_2), 1.48-1.42 (m, 1H, CH_2).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 174.0, 143.9, 142.9, 129.3, 128.4, 128.0, 127.2, 126.0, 125.5, 78.7, 59.4, 31.7, 22.7, 20.0.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3394 (w), 3339 (w), 3059 (w), 2944 (w), 2869 (w), 1666 (s), 1493 (w), 1473 (w), 1448 (w), 1394 (w), 1361 (w), 1329 (w), 1308 (w), 1181 (w), 1126 (w), 1065 (w), 996 (w), 964 (w), 748 (m), 698 (m), 663 (w), 634 (w), 546 (w).
EA ($C_{18}H_{19}NO_2$) calc.: C 76.84, H 6.81, N 4.98; found: C 76.78, H 6.86, N 5.24.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −188.6 (*c* = 0.54, $CHCl_3$).

(*S*)-6-(Fluorodiphenylmethyl)piperidin-2-one (153)



Under argon atmosphere, a two-necked flask was charged with (*S*)-6-(hydroxydiphenyl-methyl)-piperidin-2-one (**150**) (574 mg, 2.04 mmol) and CH_2Cl_2 (19 mL). Then, the corresponding solution was cooled in an ice-bath and at 0 °C DAST (658 mg, 539 µL, 4.08 mmol) was added dropwise over 15 minutes to the reaction mixture. After complete addition the mixture was stirred for 16 hours at room temperature. Then, the reaction solution was quenched by slowly addition of saturated aqueous $NaHCO_3$ solution (20 mL) at 0°C. The biphasic mixture was extracted with CH_2Cl_2 (3 x 50 mL) and then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate (1:1) to CH_2Cl_2/MeOH (10:1), d x h: 3.5 x 10 cm) to afford the product **153** (544 mg, 1.92 mmol, 94%) as an orange oil.

$C_{18}H_{18}FNO$ (283.35 g/mol):

TLC: R_f = 0.44 (SiO_2, CH_2Cl_2:ethyl acetate (10:4)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.52-7.47 (m, 2H, ar-*H*), 7.43-7.26 (m, 8H, ar-*H*), 5.63 (s, 1H, N*H*), 4.46-4.32 (m, 1H, NC*H*), 2.45-2.36 (m, 1H, CH_2), 2.35-2.24 (m, 1H, CH_2), 1.96-1.87 (m, 1H, CH_2), 1.73-1.62 (m, 3H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 172.8, 140.4 (d, J_{CF} = 23.3 Hz), 139.7 (d, J_{CF} = 23.9 Hz), 129.3 (d, J_{CF} = 1.7 Hz), 128.8 (d, J_{CF} = 1.5 Hz), 128.6, 128.2, 125.2 (d, J_{CF} = 9.9 Hz), 124.8 (d, J_{CF} = 9.8 Hz), 98.5 (d, J_{CF} = 187.5 Hz), 58.7 (d, J_{CF} = 22.6 Hz), 31.5, 22.9 (d, J_{CF} = 3.6 Hz), 19.9.

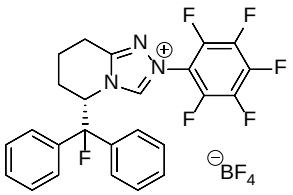
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ/ppm = −170.0.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3390 (w), 3059 (w), 3029 (w), 2944 (w), 2876 (w), 1655 (s), 1449 (m), 1299 (m), 1160 (w), 1078 (w), 962 (w), 740 (s), 694 (s), 500 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{18}H_{18}FNO^+$: 306.1265 [M+Na]$^+$; found: 306.1266.

$[\alpha]_D^{20}$ = −63.2 (*c* = 0.30, MeOH).

(*S*)-5-(Fluorodiphenylmethyl)-2-(perfluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-2-ium tetrafluoroborate (154)



According to general procedure **GP8**, (*S*)-6-(fluorodiphenylmethyl)piperidin-2-one (**153**) (530 mg, 1.87 mmol) in CH_2Cl_2 (10 mL) and trimethyloxonium tetrafluoroborate (304 mg, 2.06 mmol) were stirred to give of the crude imidate. Then, pentafluorophenylhydrazine (407 mg, 2.06 mmol) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (1.59 g, 1.64 mL, 15.0 mmol) and MeCN (10 mL) and refluxed for 18 hours at 80 °C. The crude product was purified by two column chromatography (SiO_2, CH_2Cl_2:MeOH (100:1), d x h: 3.5 x 21 cm followed by SiO_2, cyclohexane:ethyl acetate (1:1), d x h: 3.5 x 23 cm)) to afford the product **154** (139 mg, 286 µmol, 10%) as a yellow solid.

$C_{25}H_{18}F_6N_3 \cdot BF_4$ (474.43 g/mol):

TLC: R_f = 0.40 (SiO_2, CH_2Cl_2:MeOH (20:1)).

MP: 80-81 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = δ 8.31 (s, 1H, carbene-C*H*), 7.55-7.48 (m, 2H, ar-*H*), 7.48-7.44 (m, 2H, ar-*H*), 7.39 (t, $^3J_{HH}$ = 7.6 Hz, 4H, ar-*H*), 7.36-7.27 (m, 2H, ar-*H*), 6.12 (ddd, $^3J_{HF}$ = 29.3 Hz, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 3.7 Hz, 1H, NC*H*), 3.17-3.00 (m, 2H, CH_2), 2.37-2.18 (m, 3H, CH_2), 1.98-1.83 (m, 1H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 155.7, 144.9, 138.5 (d, J_{CF} = 20.7 Hz), 138.2 (d, J_{CF} = 17.6 Hz), 129.9 (d, J_{CF} = 2.2 Hz), 129.7, 129.3 (d, J_{CF} = 1.7 Hz), 129.0, 128.7, 124.7 (d, J_{CF} = 11.0 Hz), 124.5 (d, J_{CF} = 10.0 Hz), 100.9 (d, J_{CF} = 188.0 Hz), 62.1 (d, J_{CF} = 19.1 Hz), 22.7, 20.8, 16.3 (d, J_{CF} = 5.5 Hz).

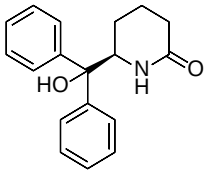
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ/ppm = −144.0-−144.3 (m), −145.6 (t, J_{FF} = 21.7 Hz), −152.5, −157.7-−158.0 (m), −167.1.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2976 (w), 1586 (m), 1515 (s), 1476 (w), 1450 (w), 1235 (w), 1072 (s), 1052 (s), 1032 (s), 992 (s), 843 (m), 748 (m), 697 (s), 646 (m), 635 (m), 520 (m), 466 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{25}H_{18}F_6N_3^+$: 474.1399 [M]$^+$; found: 474.1404.

$[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = −1.0 (*c* = 0.29, MeOH).

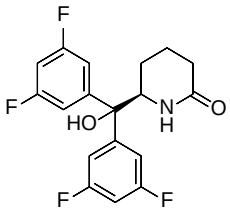
(*R*)-6-(Hydroxydiphenylmethyl)piperidin-2-one (164a)



Under argon atmosphere, a two-necked flask was charged with methyl (*S*)-6-oxopiperidine-2-carboxylate (**163**) (1.59 g, 10.1 mmol) and THF (6 mL). Then, the corresponding solution was cooled in an ice-bath and at 0 °C phenylmagnesium bromide solution (3M in ether, 7.36 g, 13.5 mL, 40.57 mmol) was added dropwise over 15 minutes to the reaction mixture. After complete addition the mixture was stirred for 16 hours at room temperature. Then the reaction solution was quenched by slowly addition of saturated aqueous NH_4Cl solution (20 mL). The biphasic mixture was extracted with EtOAc (3 x 50 mL) and then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by recrystallization in EtOH to yield the product **164a** (1.96 g, 6.97 mmol, 69%) was as a white solid.

$C_{18}H_{19}NO_2$ (281.35 g/mol):
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.59-7.55 (m, 2H, ar-*H*), 7.47-7.43 (m, 2H, ar-*H*), 7.37 (t, $^3J_{HH}$ = 7.7 Hz, 2H, ar-*H*), 7.32-7.24 (m, 3H, ar-*H*), 7.23-7.18 (m, 1H, ar-*H*), 5.80 (s, 1H, N*H*), 4.47 (dd, $^3J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 5.0 Hz, 1H, C*H*), 2.81 (br s, 1H, O*H*), 2.45-2.38 (m, 1H, CH_2), 2.31-2.19 (m, 1H, CH_2), 1.93-1.84 (m, 1H, CH_2), 1.72-1.49 (m, 3H, CH_2).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 174.3, 143.8, 142.7, 129.3, 128.5, 128.1, 127.2, 126.0, 125.5, 78.7, 59.5, 31.6, 22.7, 20.0.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +185.3 (*c* = 0.51, $CHCl_3$).

(*R*)-6-(bis(3,5-Difluorophenyl)(hydroxy)methyl)piperidin-2-one (164b)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with magnesium (450 mg, 18.6 mmol) and THF (20 mL). Afterwards 1-bromo-3,5-difluorobenzene (2.39 g, 1.42 mL,

12.4 mmol) was added dropwise to the magnesium and then the Grignard formation was started by heating with the heat gun. After the start the reaction mixture was stirred for four hours at 50 °C. Under argon atmosphere, a second two-necked flask was charged with methyl (*R*)-6-oxopiperidine-2-carboxylate (**163**) (485 mg, 3.09 mmol) and THF (1 mL). Then, the corresponding solution was cooled in an ice-bath and at 0 °C the freshly prepared Grignard reagent was added dropwise over 15 minutes to the reaction mixture. After complete addition the mixture was stirred for 16 hours at room temperature. Then the reaction solution was quenched by slowly addition of saturated aqueous NH_4Cl solution (20 mL). The biphasic mixture was extracted with EtOAc (3 x 50 mL) and then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by recrystallization in EtOH to yield the product **164b** (844 mg, 2.39 mmol, 77%) was a white solid.

$C_{18}H_{15}F_4NO_2$ (353.32 g/mol):

MP: >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm = 7.40-7.33 (m, 2H, ar-*H*), 7.30-7.23 (m, 2H, ar-*H*), 7.16-7.04 (m, 2H, ar-*H*), 6.32 (s, 1H, ar-*H*), 5.94 (s, 1H, ar-*H*), 4.68 (dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 5.4 Hz, 1H, NC*H*), 2.22-2.00 (m, 2H, CH_2), 1.83-1.73 (m, 1H, CH_2), 1.63-1.35 (m, 3H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*6) δ/ppm = 171.6, 163.8 (d, J_{CF} = 13.4 Hz), 163.5 (d, J_{CF} = 13.3 Hz), 161.3 (d, J_{CF} = 13.0 Hz), 161.1 (d, J_{CF} = 13.4 Hz), 148.9, 148.8, 148.7, 148.6, 109.6 (d, J_{CF} = 26.4 Hz), 108.8 (d, J_{CF} = 26.5 Hz), 103.2, 102.9, 102.7, 102.4, 102.2, 78.0, 57.3, 31.3, 22.4, 19.3.

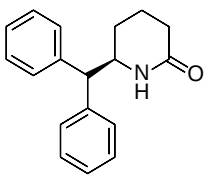
^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ/ppm = −108.9, −109.2.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3369 (w), 2950 (w), 1664 (m), 1620 (m), 1593 (s), 1439 (s), 1301 (m), 1116 (s), 981 (s), 855 (s), 786 (w), 145 (s), 604 (w), 510 (m), 458 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{18}H_{15}F_4NO_2^+$: 376.0931 [M+Na]$^+$; found: 376.0934.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +86.5 (*c* = 0.58, MeOH).

(*R*)-6-Benzhydrylpiperidin-2-one (165a)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with (*R*)-6-(hydroxydiphenylmethyl)piperidin-2-one (**164a**) (1.08 g, 3.85 mmol) and CH_2Cl_2 (44 mL). Then, at −20 °C, triethylsilane (2.24 g, 3.20 mL, 19.3 mmol) was added followed by dropwise addition of boron trifluoride diethyl etherate (ca. 48% BF_3, 3.42 g, 3.11 mL, 11.56 mmol) over 15 minutes to the reaction mixture. After complete addition the reaction mixture was stirred for three hours at room temperature followed by a second addition of triethylsilane (3.58 g, 5.12 mL, 30.82 mmol) and boron trifluoride diethyl etherate (ca. 48% BF_3, 9.11 g, 8.29 mL, 30.82 mmol) at −20 °C. Afterwards, the reaction mixture stirred for 36 hours at room temperature and then it was quenched by slowly addition of saturated aqueous $NaHCO_3$ (50 mL) at 0 °C. The corresponding biphasic mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl acetate (7:3), d x h: 3.5 x 25 cm) to afford the product **165a** (807 mg, 3.04 mmol, 79%) as a white solid.

$C_{18}H_{19}NO$ (265.36 g/mol):

MP: 239-240 °C.

TLC: R_f = 0.25 (SiO_2, CH_2Cl_2:ethyl acetate (7:3)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.31-7.08 (m, 10H, ar-*H*), 5.63 (s, 1H, N*H*), 4.08 (td, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 4.1 Hz, 1H, NC*H*), 3.68 (d, $^3J_{HH}$ = 10.6 Hz, 1H, C*H*Ph$_2$), 2.39-2.29 (m, 1H, CH_2), 2.27-2.16 (m, 1H, CH_2), 1.88-1.77 (m, 1H, CH_2), 1.75-1.67 (m, 1H, CH_2), 1.66-1.54 (m, 1H, CH_2), 1.34-1.21 (m, 1H, CH_2).

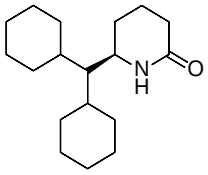
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 172.3, 141.1, 140.2, 129.5, 129.0, 128.3, 127.9, 127.7, 127.2, 59.1, 56.1, 31.5, 27.9, 20.0.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3397 (M9, 3335 (m), 2955 (w), 2932 (w), 1662 (s), 1448 (m), 1396 (m), 1305 (w), 1189 (m), 1066 (w), 996 (w), 964 (m), 779 (w), 750 (s), 695 (s), 661 (m), 633 (s), 605 (m), 543 (s), 465 (w), 429 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{18}H_{19}NO^+$: 266.1383 $[M+H]^+$; found: 266.1382.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +90.0 (*c* = 0.51, MeOH).

(*R*)-6-(Dicyclohexylmethyl)piperidin-2-one (166)



An autoclave inlet was charged with (*R*)-6-benzhydrylpiperidin-2-one (**165a**) (401 mg, 1.51 mmol) and MeOH (9 mL). To the corresponding mixture rhodium on alox (5 wt.%, 200 mg) was added and this mixture was put in an autoclave. After purging three times with hydrogen the reaction mixture was stirred for 16 hours at 10 bar hydrogen pressure. Then the mixture was filtered through Celite and the Celite cake was washed with EtOAc (3 x 10 mL). The crude mixture was concentrated under vacuum to yield the product **166** (415 mg, 1.50 mmol, 99%) as a beige solid.

$C_{18}H_{31}NO$ (277.45 g/mol):

MP: 118-119 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 5.55 (s, 1H, N*H*), 3.60 (dd, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 3.7 Hz, 1H, NC*H*), 2.44-2.34 (m, 1H, CH_2), 2.33-2.21 (m, 1H, CH_2), 1.94-1.84 (m, 1H, CH_2), 1.79-1.48 (m, 15H, CH_2, cy-CH_2, cy-CH, C*H*Cy$_2$), 1.29-1.01 (m, 10H, CH_2, cy-CH_2, cy-CH, C*H*Cy$_2$), 1.00-0.95 (m, 1H, CH_2, cy-CH_2, cy-CH, C*H*Cy$_2$).

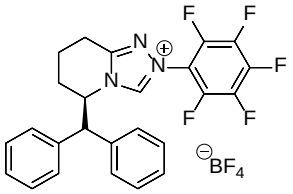
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 172.6, 53.9, 53.7, 37.4, 37.0, 32.9, 32.3, 32.0, 31.9, 31.4, 27.7, 27.1, 27.1, 27.0, 27.0, 26.6, 26.5, 20.7.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3199 (w), 3050 (w), 2918 (m), 2846 (w), 1594 (w), 1521 (s), 1495 (s), 1432 (w), 1309 (m), 1241 (m), 1179 (m), 1092 (w), 1050 (w), 738 (s), 692 (s), 494 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{18}H_{31}NO^+$: 300.2298 $[M+Na]^+$; found: 300.2297.

$[\boldsymbol{\alpha}]_D^{20}$ = +6.9 (*c* = 0.31, MeOH).

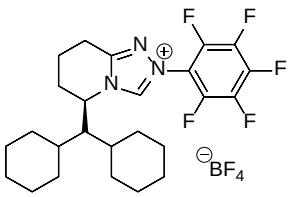
(*R*)-5-Benzhydryl-2-(perfluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-2-ium tetrafluoroborate (167)



According to general procedure **GP8**, (*R*)-6-benzhydrylpiperidin-2-one (**165a**) (400 mg, 1.51 mmol) in CH_2Cl_2 (8 mL) and trimethyloxonium tetrafluoroborate (289 mg, 1.96 mmol) were stirred to give of the crude imidate. Then, pentafluorophenylhydrazine (328 mg, 1.66 mmol) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (1.84 g, 1.90 mL, 17.4 mmol) and MeCN (7 mL) and refluxed for 18 hours at 80 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH (30:1), d x h: 2.5 x 12 cm)) followed by recrystallization from ether/CH_2Cl_2 to afford the product **167** (246 mg, 453 µmol, 30%) as a white solid.

$C_{25}H_{19}F_5N_3 \cdot BF_4$ (543.24 g/mol):
MP: 97-98 °C.
TLC: R_f = 0.32 (SiO_2, CH_2Cl_2:MeOH (20:1)).
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.46 (s, 1H, carbene-C*H*), 7.51-7.44 (m, 2H, ar-*H*), 7.44-7.36 (m, 6H, ar-*H*), 7.35-7.29 (m, 2H, ar-*H*), 5.78 (dt, $^3J_{HH}$ = 11.8 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, Ph-C*H*), 4.31 (d, $^3J_{HH}$ = 11.4 Hz, 1H, NC*H*), 3.40-3.26 (m, 1H, CH_2), 3.20-3.06 (m, 1H, CH_2), 2.29-2.02 (m, 4H, CH_2).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 154.2, 144.6, 144.2-143.35 (m), 141.9-141.2 (m), 139.7-139.1 (m), 139.0, 138.7, 137.3-136.2 (m), 130.1, 129.6, 128.8, 128.6, 128.1, 128.0, 60.9, 55.7, 24.2, 21.1, 14.7.
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ/ppm = −144.1-−144.3 (m), −146.1-−146.3 (m), −152.4, −158.0-−158.6 (m).
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3123 (w), 1584 (m), 1514 (s), 1452 (w), 1299 (w), 1237 (w), 1048 (s), 913 (w), 842 (m), 705 (s), 630 (w), 519 (m).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{25}H_{19}F_5N_3^+$: 456.1494 $[M]^+$; found: 456.1496.
$[\alpha]_D^{20}$ = −67.4 (c = 0.58, MeOH).

(*R*)-5-(Dicyclohexylmethyl)-2-(perfluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]-pyridin-2-ium tetrafluoroborate (168)



According to general procedure **GP8**, (*R*)-6-(dicyclohexylmethyl)piperidin-2-one (**166**) (400 mg, 1.44 mmol) in CH_2Cl_2 (8 mL) and trimethyloxonium tetrafluoroborate (277 mg, 1.87 mmol) were stirred to give of the crude imidate. Then, pentafluorophenylhydrazine (314 mg, 1.58 mmol) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (1.07 g, 1.11 mL, 10.1 mmol) and MeCN (8 mL) and refluxed for 16 hours at 80 °C. The crude product was purified by two column chromatography (SiO_2, CH_2Cl_2:MeOH (30:1), d x h: 3.5 x 24 cm followed by SiO_2, cyclohexane:ethyl acetate (1:1), d x h: 2.5 x 16 cm)) to afford the product **168** (155 mg, 279 µmol, 19%) as a white solid.

$C_{25}H_{31}F_5N_3 \cdot BF_4$ (468.54 g/mol):

TLC: R_f = 0.43 (SiO_2, CH_2Cl_2:MeOH (20:1)).

MP: 92-93 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 10.07 (s, 1H, carbene-C*H*), 4.93-4.82 (m, 1H, NC*H*), 3.36-3.24 (m, 1H, CH_2), 2.93 (dd, $^3J_{HH}$ = 17.7 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, CH_2), 2.31-2.17 (m, 2H, CH_2), 2.11-1.98 (m, 1H, CH_2), 1.97-1.83 (m, 5H, CH_2, cy-CH_2), 1.81-1.60 (m, 9H, cy-C*H*, cy-CH_2), 1.32-1.03 (m, 12H, cy-CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 155.3, 144.9, 144.8-144.24 (m), 142.4-141.6 (m), 139.6-139.1 (m), 137.3-136.5 (m), 61.7, 51.5, 37.2, 37.1, 34.2, 32.8, 30.6, 30.3, 27.1, 27.0, 26.8, 26.7, 26.3, 26.1, 23.9, 21.8, 17.9.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ/ppm = −145.4-−145.6 (m), −146.4-−146.7 (m), −152.5 (s), −158.89 (t, $^3J_{FF}$ = 22.3 Hz).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2925 (m), 2853 (w), 1589 (m), 1528 (m), 1515 (w), 1446 (w), 1396 (w), 1351 (m), 1075 (s), 1055 (s), 1033 (s), 1004 (s), 909 (w), 793 (w), 521 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{25}H_{31}F_5N_3^+$: 468.2433 $[M]^+$; found: 468.2433.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +53.7 (*c* = 0.55, MeOH).

5.3.3 Preparative Cross-Benzoin Reaction

General Procedure for the Asymmetric Cross-Benzoin Reaction

Under argon atmosphere, a heat-gun dried GC-vial was charged with benzaldehyde (0.10 mmol), hydrocinnamaldehyde (0.15 mmol), triazolium salt (0.02 mmol) and CH_2Cl_2 (0.1 mL). Then, the reaction mixture was treated with DIPEA (0.1 mmol) and stirred for 16 hours at room temperature. Afterwards the crude mixture was concentrated under vacuum and purified by preparative TLC.

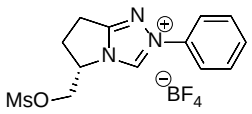
Determination of the chemoselectivity:
The chemoselectivity of the cross-benzoin reaction was determined by ^{1}H-NMR analysis of the crude mixture based on the signals of the benzylic proton of benzoin (5.95 ppm) and benzylic proton of the cross-benzoin product (5.05 ppm).

Determination of the enantiomeric excess:
HPLC (Daicel Chiracel IC, heptane/*i*-PrOH = 95:5, 0.5 mL/min, 40 °C): t_R (major) = 18.5 min, t_R (minor) = 34.4 min.

5.4 Synthesis of Iridium Complexes derived from chiral bidentate NHC-Phosphine Ligands

5.4.1 Synthesis of Chiral Bidentate NHC-Phosphine Ligands

(*S*)-5-(((Methylsulfonyl)oxy)methyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (174)



According to general procedure **GP8**, (*S*)-(5-oxopyrrolidin-2-yl)methyl methanesulfonate (**173**) (504 mg, 2.61 mmol) in CH_2Cl_2 (17 mL) and trimethyloxonium tetrafluoroborate (425 mg, 2.87 mmol) were stirred to give of the crude imidate. Then, phenylhydrazine (310 mg, 285 µL, 2.87 mmol) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (4.04 g, 4.17 mL, 38.1 mmol) and MeCN (8 mL) and refluxed for 16 hours at 80 °C. The crude product was purified by two column chromatography (SiO_2, CH_2Cl_2:MeOH (20:1), d x h: 5 x 13 cm) to afford the product **174** (806 mg, 2.11 mmol, 81%) as a yellow gum.

$C_{13}H_{16}N_3O_3S\ BF_4$ (381.16 g/mol):

TLC: R_f = 0.48 (SiO_2, CH_2Cl_2:MeOH (10:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 10.06 (s, 1H, carbene-C*H*), 7.85-7.77 (m, 2H, ar-*H*), 7.66-7.56 (m, 3H, ar-*H*), 5.01-4.94 (m, 1H, CH_2OMs), 4.55 (dd, $^3J_{HH}$ = 12.2 Hz, $^4J_{HH}$ = 4.1 Hz, 1H, CH_2OMs), 3.41-3.20 (m, 2H, CH_2), 3.16-3.10 (m, 2H, CH_2), 3.09 (s, 3H, SO_2CH_3), 2.88-2.75 (m, 1H, C*H*).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 163.3, 137.8, 136.1, 131.7, 130.8, 121.7, 69.5, 60.3, 38.0, 30.0, 22.4.

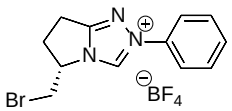
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ/ppm = −150.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3133 (w), 3033 (w), 2942 (w), 1690 (w), 1591 (m), 1352 (s), 1173 (s), 1033 (s), 970 (s), 811 (m), 761 (m), 687 (m), 522 (s).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{13}H_{16}N_3O_3S^+$: 294.0907 $[M]^+$; found: 294.0911.

$[\alpha]_D^{20}$ = −31.4 (*c* = 0.98, MeOH).

(*S*)-5-(Bromomethyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (176)



According to general procedure **GP8**, (*S*)-5-(bromomethyl)pyrrolidin-2-one (**175**) (178 mg, 1.00 mmol) in CH_2Cl_2 (7 mL) and trimethyloxonium tetrafluoroborate (163 mg, 1.10 mmol) were stirred to give of the crude imidate. Then, phenylhydrazine (114 mg, 104 µL, 1.05 mmol) was added and stirred for four hours. After concentration of the reaction mixture the crude solid was dissolved in trimethyl orthoformate (5.21 g, 5.37 mL, 49.1 mmol) and refluxed for 16 hours at 80 °C. The crude product was purified by two column chromatography (SiO_2, CH_2Cl_2:MeOH (30:1), d x h: 3.5 x 16 cm) to afford the product **176** (321 mg, 877 µmol, 88%) as a beige solid.

$C_{12}H_{13}N_3Br\ BF_4$ (365.96 g/mol):

MP: 112-113 °C.

TLC: R_f = 0.49 (SiO_2, CH_2Cl_2:MeOH (10:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 10.11 (s, 1H, carbene-C*H*), 7.87-7.81 (m, 2H, ar-*H*), 7.67-7.56 (m, 3H, ar-*H*), 5.39 (dq, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, NC*H*), 4.22 (dd, $^3J_{HH}$ = 12.0 Hz, $^4J_{HH}$ = 3.8 Hz, 1H, CH_2Br), 3.85 (dd, $^3J_{HH}$ = 12.0 Hz, $^4J_{HH}$ = 3.5 Hz, 1H, CH_2Br), 3.49-3.33 (m, 1H, CH_2), 3.31-3.21 (m, 1H, CH_2), 3.19-3.07 (m, 1H, CH_2), 2.82-2.70 (m, 1H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 163.4, 137.2, 136.1, 131.6, 130.8, 121.4, 61.1, 34.8, 32.6, 22.5.

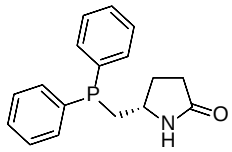
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ/ppm = −151.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3137 (w), 3109 (w), 1685 (w), 1592 (m), 1520 (m), 1385 (w), 1221 (m), 1019 (s), 761 (s), 684 (s), 651 (m), 519 (m), 487 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{12}H_{13}N_3Br^+$: 278.0287 $[M]^+$; found: 278.0291.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −29.2 (*c* = 0.98, MeOH).

(*S*)-5-((Diphenylphosphanyl)methyl)pyrrolidin-2-one (178)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with (*S*)-(5-oxopyrrolidin-2-yl)methyl methanesulfonate (**173**) (334 mg, 1.73 mmol) and THF (3 mL). Then, the reaction mixture was degassed by three freeze-pump-thaw cycles. At 0 °C, potassium diphenylphosphide solution (0.5M, 5.19 mL, 4.82 g, 2.60 mmol) was added dropwise over five minutes and afterwards the mixture was stirred overnight at room temperature. At ambient temperature water (10 mL) was added and then the resulting biphasic mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, MeOH:ethyl acetate (1:50), d x h: 3.5 x 13 cm) to afford the product **178** (286 mg, 1.01 mmol, 58%) as a white solid.

$C_{17}H_{18}NOP$ (283.31 g/mol):

MP: 98-99 °C.

TLC: R_f = 0.45 (SiO_2, EtOAc:MeOH (50:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.49-7.40 (m, 4H, ar-*H*), 7.40-7.29 (m, 6H, ar-*H*), 5.89 (s, 1H, N*H*), 3.65 (p, $^3J_{HH}$ = 6.7 Hz, 1H, NC*H*), 2.37-2.18 (m, 5H, PCH_2, CH_2), 1.91-1.79 (m, 1H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 177.7, 138.4 (d, J_{CP} = 12.1 Hz), 133.5, 133.2 (d, J_{CP} = 19.4 Hz), 131.1 (d, J_{CP} = 11.4 Hz), 129.5 (d, J_{CP} = 6.6 Hz), 129.2 (d, J_{CP} = 5.6 Hz), 52.6 (d, J_{CP} = 17.5 Hz), 36.9 (d, J_{CP} = 14.3 Hz), 30.6, 29.5 (d, J_{CP} = 8.8 Hz).

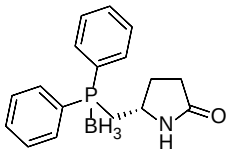
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −23.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3226 (br m), 3069 (w), 3048 (w), 2955 (w), 1681 (s), 1432 (m), 1343 (w), 1277 (m), 1253 (m), 1184 (m), 1065 (m), 963 (w), 890 (w), 742 (s), 682 (s), 515 (m), 492 (m), 465 (s), 421 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{17}H_{18}NOP^+$: 306.1018 $[M+Na]^+$; found: 306.1020.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −3.6 (*c* = 0.97, MeOH).

(*S*)-5-((Diphenylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (174)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with borane diphenylphosphine complex (**173**) (540 mg, 2.70 mmol) and THF (4 mL). At 0 °C, sodium hydride (95%, 68.2 mg, 2.70 mmol) was added to the reaction solution and the resulting reaction mixture was stirred for 45 minutes at 0 °C. Afterwards (*S*)-(5-oxopyrrolidin-2-yl)methyl methanesulfonate (386 mg, 2.00 mmol) was added to the red reaction solution and then stirred for 30 minutes at 0 °C and further two hours at room temperature. After full conversion (TLC test) the reaction mixture was quenched with water (10 mL) and then the resulting biphasic mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, MeOH:ethyl acetate (1:40), d x h: 3.5 x 14 cm) to afford the product **174** (582 mg, 1.96 mmol, 98%) as a white gum.

$C_{17}H_{18}NOP \cdot BH_3$ (297.14 g/mol):

TLC: R_f = 0.51 (SiO_2, EtOAc:MeOH (25:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.75-7.62 (m, 4H, ar-*H*), 7.58-7.43 (m, 6H, ar-*H*), 5.99 (br s, 1H, N*H*), 3.95-3.85 (m, 1H, NC*H*), 2.55 (td, $^3J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, PCH_2), 2.48-2.37 (m, 1H, CH_2), 2.37-2.19 (m, 3H, PCH_2, CH_2), 1.86-1.68 (m, 1H, CH_2), 1.45-0.58 (br m, 3H, BH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 177.1, 132.4 (d, J_{CP} = 9.4 Hz), 132.0, 131.9, 131.8 (d, J_{CP} = 3.0 Hz), 129.3 (d, J_{CP} = 2.1 Hz), 129.2 (d, J_{CP} = 2.0 Hz), 50.1 (d, J_{CP} = 1.6 Hz), 34.1 (d, J_{CP} = 35.2 Hz), 29.9, 29.8 (d, J = 10.4 Hz).

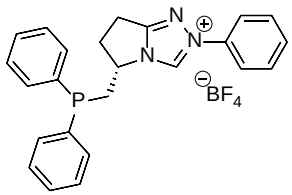
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −11.8 (br s).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3222 (w), 3055 (w), 2377 (m), 1688 (s), 1435 (m), 1414 (w), 1281 (w), 1261 (w), 1106 (m), 1058 (m), 887 (w), 735 (s), 690 (s), 592 (s), 472 (s).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{17}H_{18}NOP \cdot BH_3^+$: 320.1349 $[M+Na]^+$; found: 320.1352.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +13.0 (*c* = 1.00, MeOH).

(*S*)-5-((Diphenylphosphanyl)methyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (177)



In the glovebox a heat-gun dried round-bottom flask was charged with (*S*)-5-((diphenylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (**180**) (200 mg, 673 µmol) and CH_2Cl_2 (4.7 mL). Then, trimethyloxonium tetrafluoroborate (109 mg, 740 µmol) was added in one portion to the reaction mixture. The resulting solution was stirred for 16 hours at room temperature. Then, the hydrazine (80.0 mg, 73.4 µL, 740 µmol) was added in one portion and after stirring for four hours at room temperature the reaction flask was taken out of the glovebox and the crude mixture was concentrated under vacuum. The resulting solid was dissolved in triethyll orthoformate (1.78 g, 2.00 mL, 12.0 mmol) and refluxed at 115 °C for six to 90 minutes. Afterwards, the crude product was purified by two column chromatography (SiO_2, CH_2Cl_2:MeOH (50:1), d x h: 2.5 x 15 cm) to afford the product **177** (248 mg, 526 µmol, 78%) as a pale yellow gum.

$C_{24}H_{23}N_3P\ BF_4$ (471.25 g/mol):

MP: 71-72 °C.

TLC: R_f = 0.28 (SiO_2, CH_2Cl_2:MeOH (20:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 9.72 (s, 1H, carbene-C*H*), 7.70-7.64 (m, 2H, ar-*H*), 7.60-7.53 (m, 3H, ar-*H*), 7.52-7.45 (m, 4H, ar-*H*), 7.41-7.32 (m, 3H, ar-*H*), 7.28-7.21 (m, 2H, ar-*H*), 7.18-7.10 (m, 1H, ar-*H*), 5.26-5.12 (m, 1H, NC*H*), 3.41 (ddd, $^2J_{HP}$ = 17.4 Hz, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, PCH_2), 3.28-3.15 (m, 1H, PCH_2), 3.13-3.02 (m, 2H, CH_2), 2.95-2.82 (m, 2H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 162.4, 137.3, 136.7 (d, J_{CP} = 11.4 Hz), 136.5 (d, J_{CP} = 9.3 Hz), 135.8, 134.0 (d, J_{CP} = 21.4 Hz), 132.8 (d, J_{CP} = 19.1 Hz), 131.4, 130.7, 130.4, 129.8, 129.5, 129.5, 129.4, 121.1, 60.5 (d, J_{CP} = 17.2 Hz), 34.2 (d, J_{CP} = 2.6 Hz), 34.0 (d, J_{CP} = 3.6 Hz), 22.7 (d, J_{CP} = 4.7 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −28.0.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ/ppm = −151.0.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2923 (w), 2854 (w), 1662 (w), 1589 (w), 118 (w), 1050 (s), 976 (m), 875 (w), 741 (s), 694 (s), 505 (m).

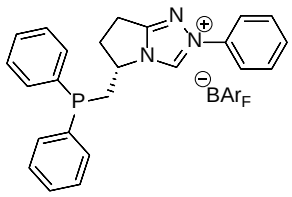
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{24}H_{23}N_3P^+$: 384.1624 $[M]^+$; found: 384.1627.

$[\alpha]_D^{20}$ = −6.8 (*c* = 0.58, MeOH).

General Procedure (GP10): Synthesis of phosphine-NHC triazolium BAr_F salts

In the glovebox, a heat-gun dried round-bottomed flask was charged with the phosphine lactam (1.0 eq.) and CH_2Cl_2 (7 ml per mmol lactam). Then, trimethyloxonium tetrafluoroborate (1.1 eq.) was added in one portion and the resulting solution was stirred for 16 hours at room temperature. Then, the hydrazine (1.1 eq.) was added in one portion and after stirring for four hours at room temperature the reaction flask was taken out of the glovebox and the crude mixture was treated with sodium BAr_F (1.5 eq.). After stirring for 16 hours, the reaction mixture was fitered over a pad of silica gel and the pad was washed with CH_2Cl_2/MeOH (20:1) solution. The crude solution was concentrated under vacuum and then the resulting gum was dissolved in triethyl orthoformate (17.8 eq.) and refluxed at 115 °C for 90 minutes. Afterwards, the crude product was concentrated under vacuum and purified by column chromatography.

(*S*)-5-((Diphenylphosphanyl)methyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (181a)



According to general procedure **GP10**, (*S*)-5-((diphenylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (**180**) (100 mg, 337 µmol) in CH_2Cl_2 (2.4 mL) and trimethyloxonium tetrafluoroborate (57.7 mg, 371 µmol) were stirred to give of the crude imidate. Then, phenylhydrazine (40.1 mg, 36.8 µL, 371 µmol) was added and stirred for four hours. Afterwards, the reaction solution was treated with sodium BAr_F (448 mg, 506 µmol) and stirred for 16 hours at room temperature. After concentration of the reaction mixture and filtration over silica gel the crude gum was dissolved in triethyl orthoformate (889 mg, 988 µL, 6.00 mmol) and refluxed for 90 minutes at 115 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH (100:1), d x h: 2.5 x 18 cm) to afford the product **181a** (316 mg, 253 µmol, 75%) as a pale yellow solid.

$C_{24}H_{23}N_3P$ BAr_F (1247.66 g/mol):

MP: 52-53 °C.

TLC: R_f = 0.40 (SiO_2, CH_2Cl_2:MeOH (50:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 9.30 (s, 1H, carbene-C*H*), 7.73 (s, 8H, ar-*H*), 7.67-7.59 (m, 5H, ar-*H*), 7.56 (s, 4H, ar-*H*), 7.58-7.47 (m, 3H, ar-*H*), 7.48-7.36 (m, 7H, ar-*H*), 4.90-4.78 (m, 1H, NC*H*), 3.42 (ddd, $^2J_{HP}$ = 17.8 Hz, $^2J_{HH}$ = 9.4 Hz, $^3J_{HH}$ = 5.1 Hz, 1H, PCH_2), 3.34-3.20 (m, 1H, CH_2), 3.20-3.06 (m, 1H, CH_2), 2.92 (dd, $^3J_{HP}$ = 14.5 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), CH_2, 2.88-2.74 (m, 1H, CH_2), 2.63 (ddd, $^2J_{HP}$ = 14.3 Hz, $^2J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 3.4 Hz, 1H, PCH_2).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 163.3, 162.8 (q, J_{CF} = 49.8 Hz), 161.8 (q, J_{CF} = 49.7 Hz), 135.4, 135.1 (d, J_{CP} = 15.0 Hz), 134.9 (d, J_{CP} = 9.7 Hz), 133.7 (d, J_{CP} = 20.4 Hz), 132.8, 132.7, 132.6, 131.3, 130.9 (d, J_{CF} = 69.2 Hz), 129.7-129.5 (m), 129.4-129.1 (m), 125.2 (q, J_{CF} = 272.5 Hz), 121.4, 118.3-117.8 (m), 61.3 (d, J_{CP} = 16.8 Hz), 35.8 (d, J_{CP} = 8.6 Hz), 34.7 (d, J_{CP} = 17.1 Hz), 22.6.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −26.4.

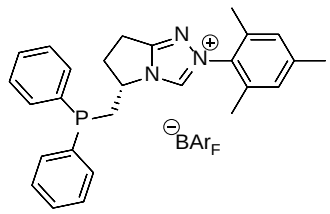
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ/ppm = −62.3.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 1352 (m), 1271 (s), 1111 (s), 885 (m), 837 (m), 743 (w), 711 (w), 680 (m), 668 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{24}H_{23}N_3P^+$: 384.1624 $[M]^+$; found: 384.1631.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −6.6 (*c* = 0.62, MeOH).

(*S*)-5-((Diphenylphosphanyl)methyl)-2-mesityl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (181b)

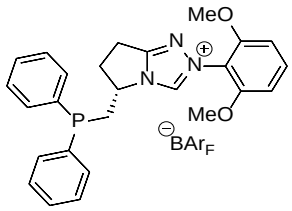


According to general procedure **GP10**, (*S*)-5-((diphenylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (**180**) (100 mg, 337 µmol) in CH_2Cl_2 (2.4 mL) and trimethyloxonium tetrafluoroborate (57.7 mg, 371 µmol) were stirred to give of the crude imidate. Then, mesitylhydrazine (freshly prepared from 1-mesitylhydrazine hydrochloride [69.2 mg, 371 µmol] in ether [5 mL] after extraction with saturated aqueous Na_2CO_3 solution [5 mL]) was added and stirred for four hours.

Afterwards, the reaction solution was treated with sodium BAr_F (448 mg, 506 µmol) and stirred for 16 hours at room temperature. After concentration of the reaction mixture and filtration over silica gel the crude gum was dissolved in triethyl orthoformate (889 mg, 988 µL, 6.00 mmol) and refluxed for 90 minutes at 115 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH (100:1), d x h: 2.5 x 20 cm) to afford the product **181b** (371 mg, 288 µmol, 85%) as a pale yellow gum.

$C_{27}H_{29}N_3P$ BAr_F (1289.74 g/mol):
TLC: R_f = 0.45 (SiO_2, CH_2Cl_2:MeOH (50:1)).

(*S*)-2-(2,6-Dimethoxyphenyl)-5-((diphenylphosphanyl)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (181c)



According to general procedure **GP10**, (*S*)-5-((diphenylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (**180**) (290 mg, 976 µmol) in CH_2Cl_2 (7 mL) and trimethyloxonium tetrafluoroborate (159 mg, 1.07 mmol) were stirred to give of the crude imidate. Then, 1-(2,6-dimethoxyphenyl)hydrazine (freshly prepared from di-*tert*-butyl 1-(2,6-dimethoxyphenyl)-hydrazine-1,2-dicarboxylate [432 mg, 1.17 mmol] and HCl in dioxane [4M, 2.90 g, 2.44 mL, 9.76 mmol] in ether [5 mL] after extraction with saturated aqueous Na_2CO_3 solution [10 mL]) was added and stirred for four hours. Afterwards, the reaction solution was treated with sodium BAr_F (1.30 g, 1.46 mol) and stirred for 16 hours at room temperature. After concentration of the reaction mixture and filtration over silica gel the crude gum was dissolved in triethyl orthoformate (2.82 g, 3.18 mL, 17.4 mmol) and refluxed for 90 minutes at 115 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH (100:1), d x h: 3.5 x 10 cm) to afford the product **181c** (240 mg, 183 µmol, 19%) as a yellow solid.

$C_{26}H_{27}N_3O_2P$ BAr_F (1307.71 g/mol):
MP: 61-62 °C.
TLC: R_f = 0.57 (SiO_2, CH_2Cl_2:MeOH (50:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 9.26 (s, 1H, carbene-C*H*), 7.73 (s, 9H, ar-*H*), 7.59-7.51 (m, 7H, ar-*H*), 7.47-7.38 (m, 7H, ar-*H*), 6.75 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H, ar-*H*), 4.78-4.67 (m, 1H, NC*H*), 3.81 (s, 6H, ar-OCH_3), 3.36 (ddd, $^{2}J_{HP}$ = 17.6, $^{3}J_{HH}$ = 9.3 Hz, $^{4}J_{HH}$ = 4.8 Hz, 1H, PCH_2), 3.29-3.19 (m, 1H, CH_2), 3.14-3.00 (m, 1H, CH_2), 2.87 (ddd, $^{2}J_{HP}$ = 14.2 Hz, $^{3}J_{HH}$ = 4.9 Hz, $^{4}J_{HH}$ = 1.0 Hz, 1H, PCH_2), 2.77-2.56 (m, 2H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2) δ/ppm = 162.3 (q, J_{CF} = 50.0 Hz), 162.2, 155.8, 140.9, 135.4, 134.8, 133.7 (d, J_{CP} = 20.3 Hz), 132.8 (d, J_{CP} = 19.2 Hz), 131.0, 130.4, 129.9 (d, J_{CP} = 7.7 Hz), 129.7 (d, J_{CP} = 7.4 Hz), 129.7-129.5 (m), 129.4-129.1 (m), 125.2 (q, J_{CF} = 272.5 Hz), 121.1, 118.2-117.9 (m), 113.1, 105.1, 60.9 (d, J_{CP} = 18.1 Hz), 57.0, 36.0 (d, J_{CP} = 8.4 Hz), 34.8 (d, J_{CP} = 17.3 Hz), 22.6.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −25.7.

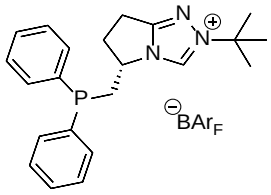
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2) δ/ppm = −62.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2169 (w), 2140 (w), 1586 (w), 1351 (m), 1275 (m), 1166 (m), 1047 (s), 873 (m), 667 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{26}H_{27}N_3O_2P^+$: 444.1835 $[M]^+$; found: 444.1843.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −2.5 (*c* = 0.72, MeOH).

(*S*)-2-(*tert*-Butyl)-5-((diphenylphosphanyl)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]-triazol-2-ium BAr$_F$ (181d)



According to general procedure **GP10**, (*S*)-5-((diphenylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (**180**) (100 mg, 337 µmol) in CH_2Cl_2 (2.5 mL) and trimethyloxonium tetrafluoroborate (57.7 mg, 371 µmol) were stirred to give of the crude imidate. Then, *tert*-butylhydrazine (freshly prepared from *tert*-butylhydrazine hydrochloride [54.6 mg, 438 µmol] in ether [2 mL] after extraction with saturated aqueous Na_2CO_3 solution [3 mL]) was added and stirred for four hours. Afterwards, the reaction solution was treated with sodium BAr$_F$ (448 mg, 506 µmol) and stirred for 16 hours at room temperature. After concentration of the reaction mixture and filtration over silica gel the crude gum was dissolved in triethyl orthoformate (889 mg, 1.00 mL, 6.00 mmol) and refluxed for 90 minutes at 115 °C. The crude product was purified by column chromatography

(SiO_2, CH_2Cl_2:MeOH (100:1), d x h: 2.5 x 20 cm) to afford the product **181d** (278 mg, 226 µmol, 67%) as a yellow gum.

$C_{22}H_{27}N_3P$ BAr_F (1227.67 g/mol):

TLC: R_f = 0.35 (SiO_2, CH_2Cl_2:MeOH (50:1)).

^{1}H NMR (400 MHz, CD_2Cl_2) δ/ppm = 8.75 (s, 1H, carbene-C*H*), 7.64 (s, 8H, ar-*H*), 7.47 (s, 4H, ar-*H*), 7.44-7.30 (m, 10H, ar-*H*), 4.68-4.54 (m, 1H, NC*H*), 3.24-3.15 (m, 1H, CH_2), 3.10-3.02 (m, 1H, CH_2), 3.01-2.91 (m, 1H, CH_2), 2.71 (dd, $^2J_{HP}$ = 14.4 Hz, $^3J_{HH}$ = 4.7 Hz, 1H, PCH_2), 2.67-2.57 (m, 1H, CH_2), 2.52 (ddd, $^2J_{HP}$ = 14.4 Hz, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, PCH_2), 1.52 (s, 9H, C(CH_3)$_3$).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2) δ/ppm = 162.8 (q, J_{CF} = 49.6 Hz), 162.8, 161.8 (d, J_{CP} = 49.7 Hz), 135.6 (d, J_{CP} = 8.4 Hz), 135.4, 134.5 (d, J_{CP} = 13.7 Hz), 133.5 (d, J_{CP} = 20.3 Hz), 132.8 (d, J_{CP} = 19.2 Hz), 130.8 (d, J_{CF} = 45.4 Hz), 129.9 (d, J_{CP} = 7.8 Hz), 129.8 (d, J_{CP} = 7.3 Hz), 129.7-129.4 (m), 129.3-129.1 (m), 125.2 (q, J_{CF} = 272.4 Hz), 121.1, 118.2-117.9 (m), 66.0, 60.7 (d, J_{CP} = 18.1 Hz), 36.0 (d, J_{CP} = 8.9 Hz), 34.4 (d, J_{CP} = 17.0 Hz), 29.0, 22.4.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −26.0.

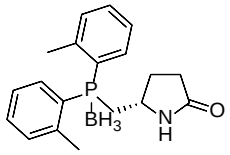
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2) δ/ppm = −62.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 1352 (s), 1272 (s), 1113 (s), 930 (m), 885 (w), 743 (w), 711 (m), 667 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{22}H_{27}N_3P^+$: 364.1937 $[M]^+$; found: 364.1942.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −2.6 (*c* = 0.44, MeOH).

(*S*)-5-((di-*o*-Tolylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (182a)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with borane di(*o*-tolyl)phosphine complex (371 mg, 1.63 mmol) and THF (2 mL). At 0 °C, sodium hydride (95%, 41.1 mg, 1.63 mmol) was added to the reaction solution and the resulting reaction mixture was stirred for 45 minutes at 0 °C. Afterwards (*S*)-(5-oxopyrrolidin-2-yl)methyl methanesulfonate (**173**) (242 mg, 1.25 mmol) was added to the red reaction solution and then stirred for 30 minutes at 0 °C and further two hours at room temperature. After full conversion (TLC test) the reaction mixture was quenched with water (10 mL) and then the resulting biphasic mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (20 mL), dried over

Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, MeOH:ethyl acetate (1:30), d x h: 3.5 x 20 cm) to afford the product **182a** (342 mg, 1.05 mmol, 84%) as a white solid.

$C_{19}H_{22}NOP \cdot BH_3$ (325.20 g/mol):

MP: 100-101 °C.

TLC: R_f = 0.44 (SiO_2, EtOAc:MeOH (30:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.85-7.71 (m, 2H, ar-*H*), 7.49-7.38 (m, 2H, ar-*H*), 7.40-7.31 (m, 2H, ar-*H*), 7.23-7.14 (m, 2H, ar-*H*), 5.57 (s, 1H, N*H*), 4.02-3.88 (m, 1H, NC*H*), 2.70-2.52 (m, 2H, PCH_2, CH_2), 2.35-2.17 (m, 3H, PCH_2, CH_2), 2.05 (s, 5H, ar-CH_3), 1.86-1.75 (m, 1H, CH_2), 1.42-0.76 (br m, 3H, BH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 177.6, 142.7, 142.5, 142.2 (d, J_{CP} = 8.3 Hz), 142.0 (d, J_{CP} = 6.0 Hz), 132.9 (d, J_{CP} = 9.5 Hz), 132.7 (d, J_{CP} = 9.7 Hz), 131.9 (d, J_{CP} = 2.5 Hz), 130.4 (d, J_{CP} = 5.0 Hz), 129.0 (d, J_{CP} = 3.2 Hz), 127.0 (d, J_{CP} = 11.0 Hz), 126.8 (d, J_{CP} = 11.0 Hz), 126.4, 50.0, 35.5 (d, J_{CP} = 14.6 Hz), 29.9, 29.4 (d, J_{CP} = 8.6 Hz), 21.5, 21.2.

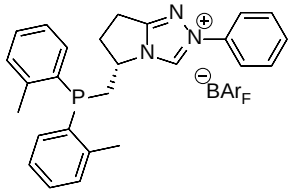
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −12.4 (br s).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2381 (w), 1687 (s), 1450 (m), 1279 (m), 1199 (w), 1131 (w), 1062 (m), 743 (s), 593 (w), 491 (m), 456 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{19}H_{22}NOP^+$: 334.1331 [M+Na]$^+$; found: 334.1333.

$[\alpha]_D^{20}$ = −11.2 (*c* = 0.91, MeOH).

(*S*)-5-((di-*o*-Tolylphosphanyl)methyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (183a)



According to general procedure **GP10**, (*S*)-5-((di-*o*-tolylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (**182a**) (100 mg, 308 µmol) in CH_2Cl_2 (2.2 mL) and trimethyloxonium tetrafluoroborate (52.7 mg, 339 µmol) were stirred to give of the crude imidate. Then, phenylhydrazine (36.6 mg, 33.6 µL, 339 µmol) was added and stirred for four hours. Afterwards, the reaction solution was treated with sodium BAr_F (409 mg, 462 µmol) and stirred for 16 hours at room temperature. After

concentration of the reaction mixture and filtration over silica gel the crude gum was dissolved in triethyl orthoformate (812 mg, 903 µL, 5.48 mmol) and refluxed for 90 minutes at 115 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH (100:1), d x h: 2.5 x 24 cm) to afford the product **183a** (330 mg, 259 µmol, 84%) as a yellow gum.

$C_{26}H_{27}N_3P$ BAr_F (1275.71 g/mol):

TLC: R_f = 0.43 (SiO_2, CH_2Cl_2:MeOH (60:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 9.18 (s, 1H, carbene-C*H*), 7.73 (s, 8H, ar-*H*), 7.68-7.57 (m, 5H, ar-*H*), 7.56 (s, 4H, ar-*H*), 7.34-7.16 (m, 8H, ar-*H*), 4.94-4.83 (m, 1H, NC*H*), 3.42 (ddd, $^2J_{HP}$ = 17.7 Hz, $^2J_{HH}$ = 9.3 Hz, $^3J_{HH}$ = 4.7 Hz, 1H, PCH_2), 3.33-3.23 (m, 1H, CH_2), 3.20-3.10 (m, 1H, CH_2), 2.90-2.80 (m, 2H, CH_2), 2.62 (ddd, $^2J_{HP}$ = 14.5 Hz, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 3.7 Hz, 1H, PCH_2), 2.46 (s, 3H, ar-CH_3), 2.40 (s, 3H, ar-CH_3).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 163.3, 162.3 (q, J_{CF} = 50.0 Hz), 143.4 (d, J_{CP} = 27.4 Hz), 142.8 (d, J_{CP} = 26.7 Hz), 135.4, 135.2 (d, J_{CP} = 11.6 Hz), 133.8 (d, J_{CP} = 7.8 Hz), 133.4 (d, J_{CP} = 9.4 Hz), 132.7, 131.9, 131.5 (d, J_{CP} = 5.5 Hz), 131.3, 131.1, 130.7, 130.5, 129.7-129.2 (m), 125.2 (q, J_{CF} = 272.5 Hz), 121.4, 118.2-117.9 (m), 61.4 (d, J_{CP} = 18.3 Hz), 35.9 (d, J_{CP} = 9.3 Hz), 33.4 (d, J_{CP} = 17.1 Hz), 22.6, 21.7 (d, J_{CP} = 12.9 Hz), 21.5 (d, J_{CP} = 12.4 Hz).

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −48.0.

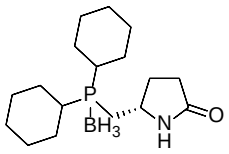
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ/ppm = −62.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 1609 (w), 1588 (w), 1352 (s), 1271 (s), 1113 (s), 885 (m), 838 (m), 745 (m), 711 (m), 681 (m), 668 (m), 449 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{26}H_{27}N_3P^+$: 412.1937 $[M]^+$; found: 412.1941.

$[\alpha]_D^{20}$ = −16.6 (*c* = 0.87, MeOH).

(*S*)-5-((Dicyclohexylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (182b)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with borane dicyclohexylphosphine complex (714 mg, 3.37 mmol) and THF (6 mL). At 0 °C, sodium hydride (95%, 85.1 mg, 3.37 mmol) was added to the reaction solution and the resulting reaction mixture was stirred for 45 minutes at 0 °C. Afterwards (*S*)-(5-oxopyrrolidin-2-yl)methyl methanesulfonate

(**173**) (500 mg, 2.59 mmol) was added to the red reaction solution and then stirred for 30 minutes at 0 °C and further two hours at room temperature. After full conversion (TLC test) the reaction mixture was quenched with water (10 mL) and then the resulting biphasic mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, MeOH:ethyl acetate (1:30), d x h: 3.5 x 12 cm) to afford the product **182b** (147 mg, 477 µmol, 18%) as a white gum.

$C_{17}H_{30}NOP{\cdot}BH_3$ (309.24 g/mol):

TLC: R_f = 0.43 (SiO_2, EtOAc:MeOH (20:1)).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 6.31 (br s, 1H, N*H*), 3.95-3.85 (m, 1H, NC*H*), 2.45-2.23 (m, 3H, PCH_2, CH_2), 1.93-1.59 (m, 15H, CH_2, cy-CH_2), 1.42-1.17 (m, 10H, CH_2, cy-CH_2), 0.80-−0.08 (m, 3H, BH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = 177.1, 51.3, 32.7 (d, J_{CP} = 32.6 Hz), 31.9 (d, J_{CP} = 33.5 Hz), 30.1, 30.0, 27.4, 27.1, 26.9, 26.9, 26.8, 26.8 (d, J_{CP} = 5.2 Hz), 26.6, 26.5 (d, J_{CP} = 2.7 Hz), 26.4 (d, J_{CP} = 2.8 Hz), 26.0.

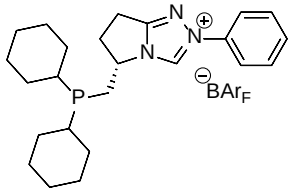
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = 21.8 (br s).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3251 (m), 2910 (s), 2844 (s), 1742 (s), 1709 (s), 1397 (m), 1243 (s), 1200 (w), 1126 (w), 1079 (w), 1057 (s), 999 (m), 962 (w), 927 (s), 681 (m), 527 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{17}H_{30}NOP{\cdot}BH_3^+$: 332.2291 $[M+Na]^+$; found: 332.2286.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +25.4 (*c* = 0.95, MeOH).

(*S*)-5-((di-Cyclohexyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (183b)

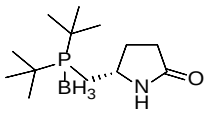


According to general procedure **GP10**, (*S*)-5-((dicyclohexylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (**182b**) (100 mg, 323 µmol) in CH_2Cl_2 (2.3 mL) and trimethyloxonium tetrafluoroborate (52.6 mg, 355 µmol) were stirred to give of the crude imidate. Then, phenylhydrazine (38.4 mg, 35.2 µL, 355 µmol) was added and stirred for four hours. Afterwards,

the reaction solution was treated with sodium BAr_F (429 mg, 85 µmol) and stirred for 16 hours at room temperature. After concentration of the reaction mixture and filtration over silica gel the crude gum was dissolved in triethyl orthoformate (957 mg, 1.06 mL, 6.46 mmol) and refluxed for 120 minutes at 115 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH (100:1), d x h: 2.5 x 20 cm) to afford the product **183b** (267 mg, 212 µmol, 66%) as a yellow solid.

$C_{24}H_{35}N_3P$ BAr_F (1259.76 g/mol):
MP: 59-60 °C.
TLC: R_f = 0.38 (SiO_2, CH_2Cl_2:MeOH (50:1)).
^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 10.25 (s, 1H, carbene-C*H*), 7.72 (s, 8H, ar-*H*), 7.69-7.64 (m, 5H, ar-*H*), 7.56 (s, 4H, ar-*H*), 5.07-4.94 (m, 1H, NC*H*), 3.45-3.06 (m, 3H, PCH_2, CH_2), 2.77-2.61 (m, 1H, CH_2), 2.44-2.29 (m, 1H, CH_2), 2.25-2.07 (m, 1H, CH_2), 1.98-1.56 (m, 11H, cy-CH_2, cy-CH_2), 1.46-1.14 (m, 11H, cy- CH_2, cy-C*H*).
^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 163.0, 161.8 (q, J_{CF} = 49.9 Hz), 137.1, 135.4, 131.3 (d, J_{CP} = 1.9 Hz), 129.7-129.4 (m), 129.4-129.1 (m), 125.2 (q, J_{CF} = 272.4 Hz), 121.5, 121.4, 121.1, 118.2-117.8 (m), 59.5, 37.5 (d, J_{CP} = 7.7 Hz), 33.4 (d, J_{CP} = 32.4 Hz), 32.0 (d, J_{CP} = 33.2 Hz), 27.6, 27.2, 27.0 (d, J_{CP} = 2.4 Hz), 26.9, 26.7 (d, J_{CP} = 6.4 Hz), 26.2, 22.4 (d, J_{CP} = 5.1 Hz).
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = −13.4.
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ/ppm = −62.9.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2934 (w), 2858 (w), 1352 (s), 1272 (s), 1112 (s), 885 (m), 837 (m), 758 (w), 711 (m), 681 (m), 668 (m).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{24}H_{35}N_3P^+$: 396.2563 $[M]^+$; found: 396.2569.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −5.6 (*c* = 0.42, MeOH).

(*S*)-5-((di-*tert*-Butylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (182c)

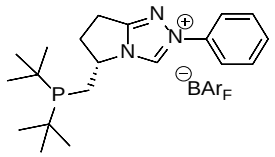


Under argon atmosphere, a heat-gun dried two-necked flask was charged with borane di(*tert*-butyl)phosphine complex (1.0 g, 6.25 mmol) and THF (10 mL). At 0 °C, sodium hydride (95%, 158 mg, 6.25 mmol) was added to the reaction solution and the resulting reaction mixture was

stirred for 45 minutes at 0 °C. Afterwards (*S*)-(5-oxopyrrolidin-2-yl)methyl methanesulfonate (**173**) (929 mg, 4.81 mmol) was added to the red reaction solution and then stirred for 30 minutes at 0 °C and further two hours at room temperature. After full conversion (TLC test) the reaction mixture was quenched with water (20 mL) and then the resulting biphasic mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, MeOH:ethyl acetate (1:50), d x h: 3.5 x 22 cm) to afford the product **182c** (734 mg, 2.85 mmol, 59%) as a white solid.

$C_{13}H_{26}NOP{\cdot}BH_3$ (257.16 g/mol):
MP: 197-198 °C.
TLC: R_f = 0.25 (SiO_2, EtOAc:MeOH (40:1)).
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 6.49 (s, 1H), 4.02-3.90 (m, 1H, NC*H*), 2.47-2.22 (m, 3H, PCH_2, CH_2), 2.00-1.93 (m, 1H, CH_2), 1.83-1.63 (m, 2H, CH_2), 1.29-1.21 (m, 18H, PC(CH_3)$_3$), 0.86-0.07 (br m, 3H, BH_3).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ/ppm = δ 177.1, 51.9, 32.8 (d, J_{CP} = 26.8 Hz), 32.0 (d, J_{CP} = 27.5 Hz), 30.1, 30.1 (d, J_{CP} = 10.2 Hz), 27.9, 27.8, 26.3 (d, J_{CP} = 26.0 Hz).
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = 39.8 (br s).
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3198 (w), 2969 (w), 2902 (w), 2385 (m), 2351 (m), 1706 (s), 1649 (m), 1467 (m), 1369 (m), 1282 (m), 1076 (s), 1021 (m), 741 (m), 629 (s), 547 (w), 493 (s), 461 (m), 416 (m).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{12}H_{13}N_3Br^+$: 280.1974 [M+Na]$^+$; found: 280.1976.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +22.6 (*c* = 0.95, MeOH).

(*S*)-5-((di-*tert*-Butyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (183c)



According to general procedure **GP10**, (*S*)-5-((di-*tert*-butylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (**182c**) (301 mg, 1.17 mmol) in CH_2Cl_2 (9 mL) and trimethyloxonium tetrafluoroborate (190 mg, 1.29 mmol) were stirred to give of the crude imidate. Then, phenylhydrazine (139 mg, 128 µL, 1.29 mmol) was added and stirred for four hours Afterwards, the reaction solution was treated with sodium BAr_F (429 mg, 85 µmol) and stirred for 16 hours at room temperature. After

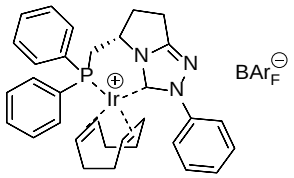
concentration of the reaction mixture and filtration over silica gel the crude gum was dissolved in triethyl orthoformate (3.47 g, 3.85 mL, 23.4 mmol) and refluxed for 120 minutes at 115 °C. The crude product was purified by two column chromatography (SiO_2, CH_2Cl_2:MeOH (100:1), d x h: 2.5 x 17 cm) to afford the product **183c** (380 mg, 315 µmol, 27%) as a pale yellow gum.

$C_{20}H_{31}N_3P$ BAr_F (1207.68 g/mol):
TLC: R_f = 0.60 (SiO_2, CH_2Cl_2:MeOH (50:1)).
^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 9.97 (s, 1H, carbene-C*H*), 7.64 (s, 8H, ar-*H*), 7.63-7.51 (m, 5H, ar-*H*), 7.47 (s, 4H, ar-*H*), 4.77-4.67 (m, 1H, NC*H*), 3.35-3.04 (m, 4H, PCH_2, CH_2), 2.67-2.53 (m, 1H, CH_2), 2.14 (dd, $^2J_{HP}$ = 15.4 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, PCH_2), 1.74-1.63 (m, 1H, CH_2), 1.14 (d, $^2J_{HP}$ = 12.0 Hz, 9H, PC(CH_3)$_3$), 0.98 (d, $^2J_{HP}$ = 12.2 Hz, 9H, PC(CH_3)$_3$).
^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 163.1, 162.3 (q, J_{CF} = 49.8 Hz), 135.4 (d, J_{CP} = 5.0 Hz), 132.6, 131.3, 129.6 (q, J_{CF} = 5.8 Hz), 129.3 (q, J_{CF} = 5.8 Hz), 125.2 (q, J_{CF} = 272.4 Hz), 121.5, 118.3-117.8 (m), 64.1 (d, J_{CP} = 20.6 Hz), 36.3 (d, J_{CP} = 7.9 Hz), 32.8 (d, J_{CP} = 17.3 Hz), 32.1 (d, J_{CP} = 15.5 Hz), 29.6 (d, J_{CP} = 12.4 Hz), 29.4 (d, J_{CP} = 12.7 Hz), 28.1 (d, J_{CP} = 9.0 Hz), 22.2.
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = 16.3.
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ/ppm = −62.8.
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2958 (w), 1469 (w), 1352 (s), 1271 (s), 1112 (s), 885 (m), 838 (m), 757 (w), 712 (m), 681 (m), 668 (m), 448 (w).
HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{20}H_{31}N_3P^+$: 344.2250 $[M]^+$; found: 344.2248.
$[\alpha]_D^{20}$ = −10.1 (*c* = 0.66, MeOH).

General Procedure (GP11): Synthesis of iridium-complexes

In the glovebox, a heat-gun dried round-bottomed flask was charged with the triazolium salt (1.0 eq), chloro(1,5-cyclooctadiene)iridium(I) dimer (0.5 eq.) and THF (30 ml per mmol lactam). Then, potassium *tert*-butoxide (1.2 eq.) was added in one portion and the reaction mixture was stirred for 16 hours at room temperature. After concentration under reduced pressure, the crude product was purified by column chromatography.

Iridium complex 184



According to general procedure **GP11**, (*S*)-5-((diphenylphosphanyl)methyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (**181a**) (34.9 mg, 28.0 µmol), chloro(1,5-cyclooctadiene)iridium(I) dimer (9.4 mg, 14.0 µmol) in THF (0.9 mL) and potassium *tert*-butoxide (3.77 mg, 33.6 µmol) were stirred for 16 hours at room temperature. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:pentane (4:1), d x h: 2.5 x 13 cm) to afford the product **184** (14.3 mg, 9.00 µmol, 33%) as a red solid.

$C_{32}H_{34}IrN_3P$ BAr_F (1610.19 g/mol):

MP: 101-102 °C.

TLC: R_f = 0.48 (SiO_2, CH_2Cl_2:pentane (4:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.80-7.54 (m, 22H, ar-*H*), 7.50-7.45 (m, 3H, ar-*H*), 7.31-7.24 (m, 2H, ar-*H*), 4.98-4.82 (m, 2H, olefinic-C*H*), 4.64 (t, $^3J_{HH}$ = 7.2 Hz, 1H, olefinic-C*H*), 3.69 (p, $^3J_{HH}$ = 7.1 Hz, 1H, olefinic-C*H*), 3.31-3.13 (m, 3H, PCH_2, CH_2), 3.06 (ddd, $^2J_{HP}$ = 14.8 Hz, $^3J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, PCH_2), 2.70-2.60 (m, 1H, CH_2), 2.61-2.41 (m, 2H, CH_2), 2.21-2.00 (m, 3H, CH_2, C*H*), 1.77-1.47 (m, 4H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 168.8 (d, J_{CP} = 11.0 Hz), 162.3 (q, J_{CF} = 49.8 Hz), 160.0, 139.6, 135.6 (d, J_{CP} = 13.2 Hz), 135.4, 134.0, 133.4, 133.1, 131.9 (d, J_{CP} = 2.6 Hz), 131.5 (d, J_{CP} = 9.8 Hz), 130.8, 130.2 (d, J_{CP} = 10.9 Hz), 130.0, 129.7 (d, J_{CP} = 10.4 Hz), 129.4-129.1 (m), 125.6, 125.2 (q, J_{CF} = 272.4 Hz), 121.1, 118.3-117.7 (m), 91.4 (d, J = 8.8 Hz), 87.2 (d, J_{CP} = 13.6 Hz), 85.4, 82.1, 57.7 (d, J_{CP} = 2.2 Hz), 35.7 (d, J_{CP} = 4.2 Hz), 35.0, 34.9, 33.9, 33.6, 27.8 (d, J_{CP} = 7.4 Hz), 21.3.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = 16.6.

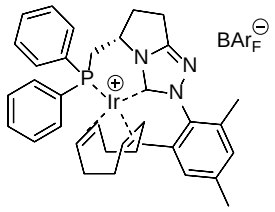
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ/ppm = −62.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2945 (w), 1352 (s), 1273 (s), 1114 (s), 885 (w), 838 (w), 744 (m), 711 (m), 681 (m), 518 (w), 448 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{32}H_{34}IrN_3P^+$: 684.2114 $[M]^+$; found: 684.2085.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +17.0 (*c* = 0.11, CH_2Cl_2).

Iridicum complex 185a



According to general procedure **GP11**, (*S*)-5-((diphenylphosphanyl)methyl)-2-mesityl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (**181b**) (40.0 mg, 31.0 µmol), chloro(1,5-cyclooctadiene)iridium(I) dimer (10.4 mg, 15.5 µmol) in THF (1 mL) and potassium *tert*-butoxide (4.17 mg, 37.2 µmol) were stirred for 16 hours at room temperature. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:pentane (3:1), d x h: 2.5 x 13 cm) to afford the product **185a** (22.0 mg, 14.0 µmol mmol, 46%) as a red solid.

$C_{39}H_{55}IrN_3P$ BAr_F (1721.84 g/mol):

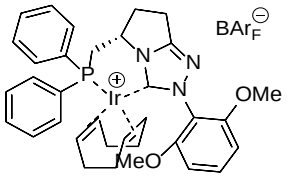
TLC: R_f = 0.58 (SiO_2, CH_2Cl_2:pentane (4:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.76-7.68 (m, 7H, ar-*H*), 7.68-7.62 (m, 2H, ar-*H*), 7.61-7.35 (m, 11H, ar-*H*), 7.03 (s, 2H, ar-*H*), 5.12-5.02 (m, 1H, olefinic-C*H*), 4.86-4.74 (m, 1H, olefinic-C*H*), 4.18-4.08 (m, 1H, olefinic-C*H*), 3.80 (p, $^3J_{HH}$ = 7.1 Hz, 1H, olefinic-C*H*), 3.27-3.12 (m, 3H, PCH_2, CH_2), 2.95 (ddd, $^2J_{HP}$ = 14.9 Hz, $^3J_{HH}$ = 12.5, $^3J_{HH}$ = 2.9 Hz, 1H, PCH_2), 2.60-2.42 (m, 2H, CH_2), 2.36 (s, 3H, ar-CH_3), 2.31-2.17 (m, 2H, CH_2), 2.16 (s, 3H, ar-CH_3), 2.11-1.98 (m, 2H, CH_2), 1.93 (s, 3H, ar-CH_3), 1.81-1.68 (m, 1H, C*H*), 1.69-1.49 (m, 4H, CH_2).

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = 13.8.

^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ/ppm = −62.9.

Iridium complex 185b



According to general procedure **GP11**, (S)-2-(2,6-dimethoxyphenyl)-5-((diphenylphosphanyl)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (**181c**) (150 mg, 115 µmol), chloro(1,5-cyclooctadiene)iridium(I) dimer (38.6 mg, 57.5 µmol) in THF (2.5 mL) and potassium *tert*-butoxide (113 mg, 138 µmol) were stirred for 16 hours at room temperature. The

crude product was purified by column chromatography (SiO_2, CH_2Cl_2:pentane (4:1), d x h: 2.5 x 13 cm) to afford the product **185b** (85.0 mg, 53.0 µmol, 46%) as a red solid.

$C_{34}H_{38}IrN_3O_2P$ BAr_F (1607.11 g/mol):

MP: 103-104 °C.

TLC: R_f = 0.49 (SiO_2, CH_2Cl_2:pentane (4:1)).

^{1}H NMR (400 MHz, CD_2Cl_2) δ/ppm = 7.77-7.69 (m, 10H, ar-*H*), 7.60-7.43 (m, 11H, ar-*H*), 7.30-7.22 (m, 2H, ar-*H*), 6.72 (d, $^3J_{HH}$ = 2.9 Hz, 1H, ar-*H*), 6.70 (d, $^3J_{HH}$ = 3.2 Hz, 1H, ar-*H*), 5.23-5.13 (m, 1H, olefinic-C*H*), 4.95-4.84 (m, 1H, olefinic-C*H*), 4.10-4.00 (m, 2H, olefinic-C*H*), 3.83 (s, 3H, ar-OCH_3), 3.54 (s, 3H, ar-OCH_3), 3.29-3.19 (m, 1H, NC*H*), 3.19-3.10 (m, 2H, CH_2), 3.11-3.06 (m, 1H, PCH_2), 3.01 (ddd, $^2J_{HP}$ = 14.8 Hz, $^3J_{HH}$ = 11.9 Hz, $^4J_{HH}$ = 3.2 Hz, 1H, PCH_2), 2.59-2.48 (m, 2H, CH_2), 2.33-2.04 (m, 4H, CH_2), 1.74-1.60 (m, 3H, CH_2), 1.56-1.44 (m, 1H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = δ 170.2, 162.3 (q, J_{CF} = 49.8 Hz), 159.1, 157.5, 157.1, 135.9 (d, J_{CP} = 12.8 Hz), 135.4, 133.0, 132.7 (d, J_{CP} = 2.5 Hz), 131.8, 131.7, 131.6, 129.8 (d, J_{CP} = 11.0 Hz), 129.6 (q, J_{CF} = 5.8 Hz), 129.5 (d, J_{CP} = 10.1 Hz), 129.3 (q, J_{CF} = 5.8 Hz), 125.2 (q, J_{CF} = 272.5 Hz), 118.3-117.6 (m), 104.8 (d, J_{CP} = 4.5 Hz), 91.2 (d, J_{CP} = 12.3 Hz), 89.7 (d, J_{CP} = 9.8 Hz), 83.6, 77.2, 58.0, 56.7 (d, J_{CP} = 14.8 Hz), 34.9 (d, J_{CP} = 12.6 Hz), 34.6, 34.2, 33.8 (d, J_{CP} = 32.3 Hz), 29.2, 28.3, 21.1.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = 14.6.

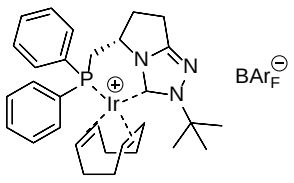
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2) δ/ppm = −62.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2950 (w), 1604 (w), 1484 (w), 1352 (m), 1273 (s), 1111 (s), 885 (m), 838 (m), 780 (w), 742 (w), 711 (m), 681 (m), 518 (w), 494 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{34}H_{38}IrN_3O_2P^+$: 744.2327 $[M]^+$; found: 744.2327.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −16.0 (*c* = 0.20, CH_2Cl_2).

Iridium complex 185c



According to general procedure **GP11**, (*S*)-2-(*tert*-butyl)-5-((diphenylphosphanyl)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (**181d**) (80.0 mg, 65.2 µmol), chloro(1,5-cyclo-

octadiene)-iridium(I) dimer (21.9 mg, 32.6 µmol) in THF (1.5 mL) and potassium *tert*-butoxide (8.78 mg, 78.2 µmol) were stirred for 16 hours at room temperature. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:pentane (2:1), d x h: 2.5 x 23 cm) to afford the product **185c** (74.0 mg, 48.0 µmol, 74%) as an orange solid.

$C_{30}H_{38}IrN_3P$ BAr_F (1659.97 g/mol):

MP: 129-130 °C.

TLC: R_f = 0.25 (SiO_2, CH_2Cl_2:pentane (2:1)).

^{1}H NMR (400 MHz, CD_2Cl_2): δ/ppm = 7.74 (s, 8H, ar-*H*), 7.57 (s, 4H, ar-*H*), 7.54-7.40 (m, 8H, ar-*H*), 7.21-7.13 (m, 2H, ar-*H*), 5.04 (t, $^3J_{HH}$ = 7.0 Hz, 1H, olefinic-C*H*), 4.97-4.82 (m, 2H, olefinic-C*H*), 4.34 (p, $^3J_{HH}$ = 7.3 Hz, 1H, olefinic-C*H*), 3.24-2.94 (m, 5H, PCH_2, CH_2), 2.76-2.50 (m, 3H, CH_2), 2.20-1.96 (m, 4H, CH_2), 1.88-1.76 (m, 1H, C*H*), 1.69 (s, 9H, C(CH_3)$_3$), 1.57-1.44 (m, 2H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ/ppm = 168.6 (d, J_{CP} = 12.2 Hz), 162.8 (q, J_{CP} = 49.5 Hz), 158.3, 135.57-135.18 (m), 134.2 (d, J_{CP} = 49.1 Hz), 133.0, 132.1, 131.7-131.5 (m), 131.2 (d, J_{CP} = 9.7 Hz), 130.0 (d, J_{CP} = 10.9 Hz), 129.8-129.5 (m), 129.4-129.2 (m), 129.0, 125.2 (q, J_{CF} = 272.4 Hz), 121.1, 118.4-117.8 (m), 88.2 (d, J_{CP} = 6.4 Hz), 84.2, 82.6, 79.8 (d, J_{CP} = 17.9 Hz), 62.7, 58.0 (d, J_{CP} = 2.9 Hz), 37.5, 33.8 (d, J_{CP} = 12.9 Hz), 33.5 (d, J_{CP} = 10.1 Hz), 31.9, 30.3, 26.9, 26.7, 21.1.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = 19.1.

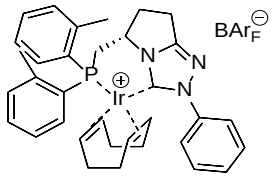
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2) δ/ppm = −62.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2952 (w), 2926 (w), 1352 (s), 1275 (s), 1157 (m), 1118 (s), 886 (w), 837 (w), 744 (m), 697 (m), 681 (m), 667 (m), 522 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{30}H_{38}IrN_3P^+$: 664.2428 $[M]^+$; found: 664.2416.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −12.5 (*c* = 0.53, CH_2Cl_2).

Iridium complex 185d



According to general procedure **GP11**, (*S*)-5-((di-*o*-tolylphosphanyl)methyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (**183a**) (40.1 mg, 31.4 µmol), chloro(1,5-cyclo-

octadiene)iridium(I) dimer (10.5 mg, 15.7 µmol) in THF (1 mL) and potassium *tert*-butoxide (5.16 mg, 37.7 µmol) were stirred for 16 hours at room temperature. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:pentane (5:2), d x h: 1.5 x 16 cm) to afford the product **185d** (15.7 mg, 10.0 µmol, 32%) as a red solid.

$C_{38}H_{53}IrN_3P$ BAr_F (1708.53 g/mol):

MP: 99-100 °C.

TLC: R_f = 0.78 (SiO_2, CH_2Cl_2:pentane (5:1)).

^{1}H NMR (400 MHz, CD_2Cl_2) δ/ppm = 8.45 (dd, $^3J_{HP}$ = 17.2 Hz, $^3J_{HH}$ = 7.5 Hz, 1H, ar-*H*), 7.76-7.68 (m, 10H, ar-*H*), 7.62-7.58 (m, 3H, ar-*H*), 7.58-7.50 (m, 5H, ar-*H*), 7.50-7.37 (m, 4H, ar-*H*), 7.16 (t, $^3J_{HH}$ = 7.6 Hz, 1H, ar-*H*), 6.80 (dd, $^4J_{HP}$ = 12.5, $^3J_{HH}$ = 7.8 Hz, 1H, ar-*H*), 4.97-4.85 (m, 2H, olefinic-C*H*), 4.54-4.45 (m, 1H, olefinic-C*H*), 3.53 (p, $^3J_{HH}$ = 7.1 Hz, 1H, olefinic-C*H*), 3.32-3.18 (m, 1H, PCH_2), 3.18-3.12 (m, 2H, PCH_2, CH_2), 3.01-2.91 (m, 1H, CH_2), 2.80 (s, 3H, ar-CH_3), 2.63-2.35 (m, 4H, CH_2), 2.22-2.14 (m, 1H, CH_2), 2.14 (s, 3H, ar-CH_3), 2.07-2.01 (m, 1H, CH_2), 1.80-1.70 (m, 1H, C*H*), 1.66-1.46 (m, 4H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 168.5, 162.3 (q, J_{CF} = 50.0 Hz), 159.7, 142.8, 142.2 (d, J_{CP} = 30.6 Hz), 139.8, 135.4, 133.9, 133.6, 132.7 (d, J_{CP} = 8.3 Hz), 132.3, 130.8, 129.9, 129.6, 129.3, 129.0, 126.8, 125.8, 125.2 (q, J_{CF} = 272.5 Hz), 121.1, 118.2-117.8 (m), 89.5 (d, J_{CP} = 8.3 Hz), 85.2, 84.8, 83.1, 56.8, 36.0, 35.8, 34.9 (d, J_{CP} = 12.2 Hz), 31.7, 27.3, 27.1, 23.3, 21.2.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = 20.0.

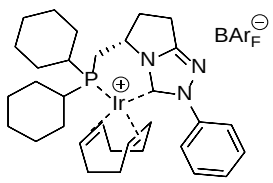
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2) δ/ppm = −62.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2931 (w), 1352 (m), 1273 (s), 1115 (s), 981 (w), 886 (w), 838 (w), 754 (w), 712 (m), 681 (m), 464 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{38}H_{38}IrN_3P^+$: 712.2429 $[M]^+$; found: 712.2437.

$[\alpha]_D^{20}$ = −140.0 (*c* = 0.40, CH_2Cl_2).

Iridium complex 185e



According to general procedure **GP11**, (*S*)-5-((*di*-cyclohexyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (**183b**) (80.0 mg, 63.5 µmol), chloro(1,5-cyclo-octadiene)iridium(I) dimer (21.3 mg, 31.8 µmol) in THF (1.4 mL) and potassium *tert*-butoxide (8.55 mg, 76.2 µmol) were stirred for 16 hours at room temperature. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:pentane (3:1), d x h: 1.5 x 13 cm) to afford the product **185e** (30.0 mg, 19.0 µmol, 30%) as a red solid.

$C_{32}H_{46}IrN_3P$ BAr_F (1559.15 g/mol):

TLC: R_f = 0.70 (SiO_2, CH_2Cl_2:pentane (4:1)).

^{1}H NMR (400 MHz, CD_2Cl_2) δ/ppm = 7.93-7.87 (m, 2H, ar-*H*), 7.73 (s, 8H, ar-*H*), 7.59-7.52 (m, 7H, ar-*H*), 5.49 (t, $^3J_{HH}$ = 7.2 Hz, 1H, olefinic-C*H*), 4.83-4.74 (m, 1H, olefinic-C*H*), 4.45-4.31 (m, 1H, olefinic-C*H*), 4.10-3.98 (m, 1H, olefinic-C*H*), 3.25-3.07 (m, 4H, NC*H*, PCH_2, CH_2), 2.79-2.71 (m, 1H, CH_2), 2.60-2.44 (m, 2H, PCH_2, CH_2), 2.35-2.23 (m, 2H, cy-CH_2), 2.19-1.91 (m, 7H, cy-CH_2, cy-C*H*), 1.90-1.78 (m, 4H, cy-CH_2), 1.75-1.63 (m, 3H, cy-CH_2, cy-C*H*), 1.61-1.50 (m, 2H, cy-CH_2), 1.44-1.14 (m, 10H, cy-CH_2), 1.13-0.99 (m, 1H, cy-CH_2), 0.98-0.89 (m, 1H, cy-CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 169.4 (d, J_{CP} = 10.6 Hz), 162.3 (q, J_{CF} = 49.8 Hz), 159.8, 139.5, 135.4, 130.2, 129.8, 129.7-129.4 (m), 129.4-129.1 (m), 125.2 (q, J_{CF} = 272.3 Hz), 124.3, 121.1, 118.2-117.90 (m), 87.6 (d, J_{CP} = 7.1 Hz), 86.6, 80.7, 80.5 (d, J_{CP} = 14.7 Hz), 57.4, 37.8, 37.7 (d, J_{CP} = 23.8 Hz), 36.0, 34.7 (d, J_{CP} = 10.2 Hz), 32.1 (d, J_{CP} = 27.6 Hz), 30.9, 30.1, 29.5, 27.5-26.9 (m), 26.7, 26.6, 26.5, 22.6 (d, J_{CP} = 28.2 Hz), 21.2.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = 23.6.

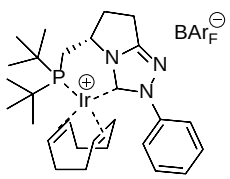
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2) δ/ppm = −62.9.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2960 (w), 1352 (m), 1272 (s), 1163 (m), 1121 (s), 885 (m), 837 (w), 713 (m), 681 (m), 667 (m), 580 (w), 445 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{32}H_{46}IrN_3P^+$: 696.3055 $[M]^+$; found: 696.3057.

$[\alpha]_D^{20}$ = −16.0 (*c* = 0.26, CH_2Cl_2).

Iridium complex 185f



According to general procedure **GP11**, (*S*)-5-((di-*tert*-butyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium BAr_F (**185f**) (200 mg, 166 µmol), chloro(1,5-cyclo-octadiene)iridium(I) dimer (55.8 mg, 83.0 µmol) in THF (3.7 mL) and potassium *tert*-butoxide (163 mg, 199 µmol) were stirred for 16 hours at room temperature. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:pentane (2:1), d x h: 1.5 x 16 cm) to afford the product **185f** (89.0 mg, 59.0 µmol, 36%) as a red solid.

$C_{28}H_{42}IrN_3P$ BAr_F (1507.07 g/mol):

MP: 160-161 °C.

TLC: R_f = 0.33 (SiO_2, CH_2Cl_2:pentane (3:1)).

^{1}H NMR (400 MHz, CD_2Cl_2) δ/ppm = 8.07-7.99 (m, 2H, ar-*H*), 7.73 (s, 8H, ar-*H*), 7.58-7.52 (m, 7H, ar-*H*), 5.90 (t, $^3J_{HH}$ = 7.3 Hz, 1H, olefinic-C*H*), 4.69 (q, $^3J_{HH}$ = 7.6 Hz, 1H, olefinic-C*H*), 4.51-4.36 (m, 2H, olefinic-C*H*), 3.26-3.09 (m, 4H, NC*H*, CH_2), 2.74 (dd, $^2J_{HP}$ = 15.8 Hz, $^3J_{HH}$ = 7.5 Hz, 1H, PCH_2), 2.68-2.48 (m, 2H, CH_2), 2.26 (ddd, $^2J_{HP}$ = 15.0 Hz, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 3.8 Hz, 1H, PCH_2), 2.09-1.88 (m, 3H, CH_2), 1.66-1.50 (m, 4H, CH_2), 1.46 (d, $^3J_{HP}$ = 13.5 Hz, 9H, PC(CH_3)$_3$), 1.40-1.26 (m, 4H, CH_2), 1.13 (d, $^3J_{HP}$ = 13.8 Hz, 9H, PC(CH_3)$_3$).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 169.1 (d, J_{CP} = 9.8 Hz), 162.3 (q, J_{CF} = 49.9 Hz), 159.5, 139.4, 135.4, 130.0, 129.7, 129.7-129.4 (m), 129.4-129.1 (m), 125.2 (q, J_{CF} = 272.4 Hz), 123.9, 121.1, 118.3-117.8 (m), 114.8, 88.0, 83.5 (d, J_{CP} = 6.6 Hz), 81.8, 75.7 (d, J_{CP} = 15.4 Hz), 57.5, 39.4 (d, J_{CP} = 16.6 Hz), 37.7 (d, J_{CP} = 4.1 Hz), 36.8 (d, J_{CP} = 18.7 Hz), 36.3, 34.6 (d, J_{CP} = 9.5 Hz), 30.9 (d, J_{CP} = 4.8 Hz), 30.3 (d, J_{CP} = 3.6 Hz), 27.1, 26.1 (d, J_{CP} = 2.7 Hz), 24.3 (d, J_{CP} = 22.6 Hz), 21.2.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = 47.7.

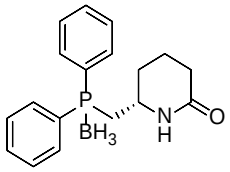
^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2) δ/ppm = −62.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2958 (w), 1352 (m), 1272 (s), 1164 (m), 1120 (s), 885 (w), 827 (m), 713 (m), 681 (m), 667 (m), 444 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{28}H_{42}IrN_3P^+$: 644.2741 $[M]^+$; found: 644.2752.

$[\alpha]_D^{20}$ = −13.0 (*c* = 0.06, CH_2Cl_2).

(*S*)-6-((Diphenylphosphanyl)methyl)piperidin-2-one BH_3 complex (186)



Under argon atmosphere, a heat-gun dried two-necked flask was charged with borane diphenylphosphine complex (377 mg, 1.89 mmol) and THF (3 mL). At 0 °C, sodium hydride (95%, 47.6 mg, 1.89 mmol) was added to the reaction solution and the resulting reaction mixture was stirred for 45 minutes at 0 °C. Afterwards (*S*)-(6-oxopiperidin-2-yl)methyl methanesulfonate (**156**) (301 mg, 1.45 mmol) was added to the red reaction solution and then stirred for 30 minutes at 0 °C and further two hours at room temperature. After full conversion (TLC test) the reaction mixture was quenched with water (10 mL) and then the resulting biphasic mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, MeOH:ethyl acetate (1:60), d x h: 3.5 x 15 cm) to afford the product **186** (389 mg, 1.25 mmol, 86%) as a white gum.

$C_{18}H_{20}NOP{\cdot}BH_3$ (311.17 g/mol):

TLC: R_f = 0.28 (SiO_2, EtOAc:MeOH (50:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.75-7.62 (m, 4H, ar-*H*), 7.57-7.42 (m, 6H, ar-*H*), 6.14 (br s, 1H, N*H*), 3.79-3.69 (m, 1H, NC*H*), 2.58-2.45 (m, 1H, PCH_2), 2.44-2.18 (m, 3H, PCH_2, CH_2), 1.98-1.76 (m, 2H, CH_2), 1.72-1.57 (m, 1H, CH_2), 1.52-1.41 (m, 1H, CH_2), 1.32-0.63 (br m, 3H, BH_3).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 171.5, 132.4 (d, J_{CP} = 9.4 Hz), 132.0 (d, J_{CP} = 9.3 Hz), 131.9, 131.9 (d, J_{CP} = 2.5 Hz), 129.4 (d, J_{CP} = 3.8 Hz), 129.3 (d, J_{CP} = 3.9 Hz), 128.8 (d, J_{CP} = 2.4 Hz), 128.2, 49.0 (d, J_{CP} = 2.4 Hz), 34.2 (d, J_{CP} = 34.8 Hz), 31.3, 30.9 (d, J_{CP} = 8.8 Hz), 19.5.

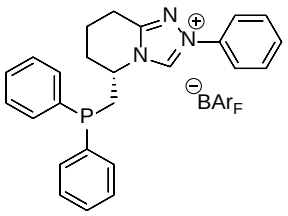
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ/ppm = −11.3 (br s).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3346 (w), 3055 (w), 2948 (w), 2872 (w), 2378 (m), 1655 (s), 1435 (s), 1335 (m), 1305 (m), 1106 (m), 1061 (s), 998 (w), 823 (w), 735 (s), 690 (s), 594 (m), 497 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{18}H_{20}NOP{\cdot}BH_3^+$: 334.1506 $[M+Na]^+$; found: 334.1512.

$[\alpha]_D^{20}$ = +5.8 (*c* = 1.00, MeOH).

(*S*)-5-((Diphenylphosphanyl)methyl)-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-2-ium BAr_F (187)



According to general procedure **GP10**, (*S*)-5-((dicyclohexylphosphanyl)methyl)pyrrolidin-2-one BH_3 complex (**186**) (100 mg, 321 µmol) in CH_2Cl_2 (2.3 mL) and trimethyloxonium tetrafluoroborate (55.0 mg, 353 µmol) were stirred to give of the crude imidate. Then, phenylhydrazine (38.2 mg, 35.0 µL, 353 µmol) was added and stirred for four hours. Afterwards, the reaction solution was treated with sodium BAr_F (427 mg, 482 µmol) and stirred for 16 hours at room temperature. After concentration of the reaction mixture and filtration over silica gel the crude gum was dissolved in triethyl orthoformate (957 mg, 1.06 mL, 6.46 mmol) and refluxed for 120 minutes at 115 °C. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH (50:1), d x h: 2.5 x 21 cm) to afford the product **187** (302 mg, 241 µmol, 75%) as a pale yellow gum.

$C_{25}H_{25}N_3P$ BAr_F (1251.69 g/mol):

TLC: R_f = 0.45 (SiO_2, CH_2Cl_2:MeOH (10:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 9.41 (s, 1H, carbene-C*H*), 7.69 (s, 8H, ar-*H*), 7.62-7.40 (m, 12H, ar-*H*), 7.39-7.29 (m, 7H, ar-*H*), 4.55-4.45 (m, 1H, NC*H*), 3.11-2.95 (m, 2H, CH_2), 2.77 (dd, $^2J_{HP}$ = 14.7 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, PCH_2), 2.62 (ddd, $^2J_{HP}$ = 14.8 Hz, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 2.5 Hz, 1H, PCH_2), 2.32-2.08 (m, 3H, CH_2), 1.97-1.82 (m, 1H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ/ppm = 161.7 (q, J_{CF} = 49.8 Hz), 154.3, 135.9 (d, J_{CP} = 17.0 Hz), 134.9, 134.5 (d, J_{CP} = 7.7 Hz), 134.2 (d, J_{CP} = 9.3 Hz), 133.9, 133.1 (d, J_{CP} = 20.3 Hz), 132.2 (d, J_{CP} = 18.7 Hz), 130.8, 130.3, 129.7 (d, J_{CP} = 7.8 Hz), 129.4 (d, J_{CP} = 7.4 Hz), 129.2 (q, J_{CF} = 5.8 Hz), 128.9 (q, J_{CF} = 5.8 Hz), 128.7, 128.6, 124.7 (q, J_{CF} = 272.6 Hz)., 120.4, 117.6 (d, J_{CP} = 5.1 Hz), 57.0 (d, J_{CP} = 16.7 Hz), 35.1 (d, J_{CP} = 18.2 Hz), 28.9 (d, J_{CP} = 8.7 Hz), 21.3, 16.8.

^{31}P{^{1}H} NMR ($CDCl_3$): δ/ppm = −25.4.

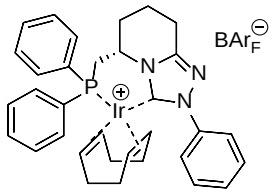
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ/ppm = −62.4.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2972 (w), 2951 (w), 1677 (w), 1352 (s), 1272 (s), 1117 (s), 1087 (s), 885 (m), 837 (m), 742 (m), 711 (m), 680 (s), 668 (s), 448 (w).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{25}H_{25}N_3P^+$: 398.1781 $[M]^+$; found: 398.1787.

$[\alpha]_D^{20}$ = −16.1 (*c* = 1.19, MeOH).

Iridium complex 188



According to general procedure **GP11**, (*S*)-5-((diphenylphosphanyl)methyl)-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-2-ium BAr_F (**187**) (120 mg, 95.1 µmol), chloro(1,5-cyclooctadiene)-iridium(I) dimer (31.9 mg, 47.6 µmol) in THF (2.1 mL) and potassium *tert*-butoxide (12.8 mg, 114 µmol) were stirred for 16 hours at room temperature. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:pentane (5:1), d x h: 2.5 x 13 cm) to afford the product **188** (87.0 mg, 56.0 µmol mmol, 59%) as an orange solid.

$C_{33}H_{36}IrN_3P$ BAr_F (1693.98 g/mol):

MP: 81-82 °C.

TLC: R_f = 0.56 (SiO_2, CH_2Cl_2:pentane (5:1)).

^{1}H NMR (400 MHz, CD_2Cl_2) δ/ppm = 7.83-7.65 (m, 12H, ar-*H*), 7.61-7.50 (m, 10H, ar-*H*), 7.51-7.41 (m, 3H, ar-*H*), 7.25-7.14 (m, 2H, ar-*H*), 5.18-5.05 (m, 1H, olefinic-C*H*), 4.99-4.88 (m, 2H, olefinic-C*H*), 3.49 (p, $^3J_{HH}$ = 7.1 Hz, 1H, olefinic-C*H*), 3.29-3.17 (m, 1H, CH_2), 3.03 (dt, $^2J_{HP}$ = 17.0 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, PCH_2), 2.96-2.80 (m, 2H, CH_2), 2.67 (dd, $^2J_{HP}$ = 15.5 Hz, $^3J_{HH}$ = 6.7 Hz, 1H, PCH_2), 2.61-2.46 (m, 2H, CH_2), 2.47-2.36 (m, 1H, CH_2), 2.26-2.04 (m, 4H, CH_2), 1.99-1.86 (m, 1H, C*H*), 1.78-1.50 (m, 4H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2) δ/ppm = 174.8 (d, J_{CP} = 12.2 Hz), 162.8 (q, J_{CF} = 49.8 Hz), 152.5, 139.1, 135.4, 135.2 (d, J_{CP} = 13.1 Hz), 133.6, 133.2-132.8 (m), 131.9, 131.7 (d, J_{CP} = 2.6 Hz), 131.4, 131.2 (d, J_{CP} = 9.7 Hz), 130.4, 130.2 (d, J_{CP} = 10.8 Hz), 130.1-129.8 (m), 129.8, 129.7, 129.8-129.5 (m), 129.4-129.2 (m), 129.1-128.9 (m), 125.2 (q, J_{CF} = 272.4 Hz), 124.6, 121.1, 118.6-117.3 (m), 91.5 (d, J_{CP} = 8.0 Hz), 86.5, 86.1 (d, J_{CP} = 14.2 Hz), 82.8, 57.0 (d, J_{CP} = 4.0 Hz), 36.4 (d, J_{CP} = 4.0 Hz), 35.7, 33.3 (d, J_{CP} = 37.1 Hz), 29.7 (d, J_{CP} = 12.5 Hz), 27.4, 22.5, 17.7.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ/ppm = 11.5.

^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2) δ/ppm = −62.8.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2923 (w), 1353 (s), 1274 (s), 1116 (s), 885 (w), 838 (w), 744 (m), 712 (m), 681 (m), 522 (m).

HRMS (ESI (+), 3600 V, 180 °C, MeOH): (*m/z*) calc. for $C_{33}H_{36}IrN_3P^+$: 698.2272 $[M]^+$; found: 698.2281.

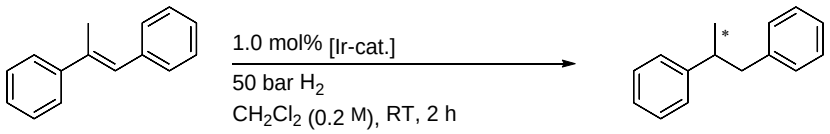
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −68.0 (*c* = 0.05, CH_2Cl_2).

5.4.2 Hydrogenation of Model Substrates

General Procedure: Hydrogenation at elevated pressure (50 bar)

A glas vial (13 x 40 mm) containing a magnetic stirring bar was charged with the model substrate (0.1 mmol) and CH_2Cl_2 (0.2 mL). Then, the iridium complex (1 mol%) was added to the reaction solution and after placing the vial in the autoclave it was purged and pressurized with hydrogen gas (50 bar). After stirring for four hours at room temperature the hydrogen atmosphere was released and the crude product was concentrated under vacuum. The crude mixture was dissolved with ether, filtered through a short plug of silica gel, eluting with pentane/ether (1:1) and concentrated under vacuum. The crude product was analyzed by GC and HPLC analysis.

(*E*)-1,2-Diphenyl-1-propene (189)



189 **190**

Conversion determination by GC:

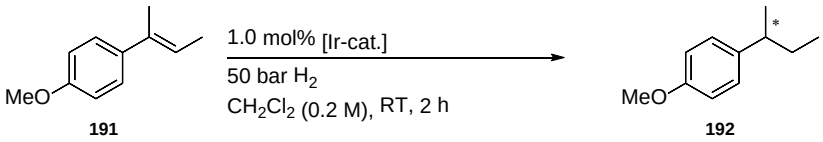
GC(Restek Rxt-1701, 0.25 mm x 0.25 µm x 30 m, 60 kPa He, 100 °C/2 min, 7 °C·min^{-1}, 250 °C/10 min): t_R = 18.3 min (**190**), t_R = 21.4 min (**189**).

Enantiomeric excess determination by HPLC:

HPLC (Daicel Chiracel OJ, heptane/*i*-PrOH = 99:1, 0.5 mL/min, 25 °C):

t_R ((***R***)-**190**) = 14.7 min, t_R ((***S***)-**190**) = 24.2 min.

(*E*)-2-(4-Methoxyphenyl)-2-butene (192)



191 **192**

Conversion determination by GC:

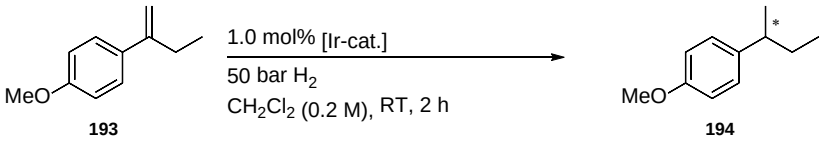
GC(Restek Rxt-1701, 0.25 mm x 0.25 µm x 30 m, 60 kPa He, 100 °C/2 min, 7 °C·min^{-1}, 250 °C/10 min): t_R = 12.1 min (**192**), t_R = 14.8 min (**191**).

Enantiomeric excess determination by HPLC:

HPLC (Daicel Chiracel OD-H, heptane, 0.5 mL/min, 25 °C):

t_R ((***S***)-**192**) = 14.0 min, t_R ((***R***)-**192**) = 15.8 min.

1-(But-1-en-2-yl)-4-methoxybenzene (194)



193 **194**

Conversion determination by GC:

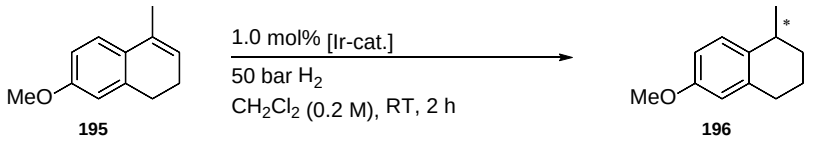
GC(Restek Rxt-1701, 0.25 mm x 0.25 µm x 30 m, 60 kPa He, 100 °C/2 min, 7 °C·min^{-1}, 250 °C/10 min): t_R = 12.1 min (**194**), t_R = 13.1 (**193**).

Enantiomeric excess determination by HPLC:

HPLC (Daicel Chiracel OD-H, heptane, 0.5 mL/min, 25 °C):

t_R ((***S***)-**194**) = 14.0 min, t_R ((***R***)-**194**) = 15.8 min.

6-Methoxy-1-methyl-3,4-dihydronaphthalene (196)



195 **196**

Conversion determination by GC:

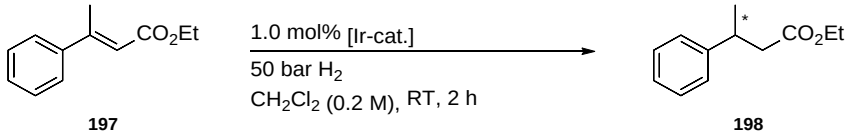
GC(Restek Rxt-1701, 0.25 mm x 0.25 µm x 30 m, 60 kPa He, 100 °C/2 min, 7 °C·min^{-1}, 250 °C/10 min): t_R = 17.1 min (**196**), t_R = 18.4 min (**195**).

Enantiomeric excess determination by HPLC:

HPLC (Daicel Chiracel OD-H, heptane, 0.5 mL/min, 25 °C):

t_R ((***R***)-**196**) = 25.7 min, t_R ((***S***)-**196**) = 33.6 min.

(*E*)-Ethyl 3-phenylbut-2-enoate (198)



197 **198**

Conversion determination by GC:

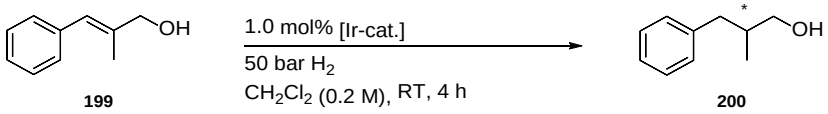
GC(Restek Rxt-1701, 0.25 mm x 0.25 µm x 30 m, 60 kPa He, 100 °C/2 min, 7 °C·min^{-1}, 250 °C/10 min): t_R = (**197**), t_R = (**198**).

Enantiomeric excess determination by HPLC:

HPLC (Daicel Chiracel OD-H, heptane/*i*-PrOH = 99:1, 0.5 mL/min, 25 °C):

t_R ((***R***)-**198**) = 11.1 min, t_R ((***S***)-**198**) = 21.1 min.

(*E*)-2-Methyl-3-phenylprop-2-en-1-ol (200)



199 **200**

Conversion determination by GC:

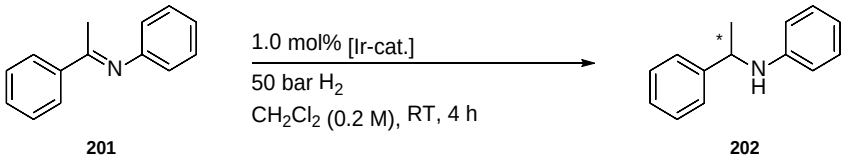
GC(Restek Rxt-1701, 0.25 mm x 0.25 µm x 30 m, 60 kPa He, 100 °C/2 min, 7 °C·min^{-1}, 250 °C/10 min): t_R = 14.3 min (**200**), t_R = 16.0 min (**199**).

Enantiomeric excess determination by HPLC:

HPLC (Daicel Chiracel OD-H, heptane/*i*-PrOH = 95:5, 0.5 mL/min, 40 °C):

t_R ((***R***)-**200**) = 15.3 min, t_R ((***S***)-**200**) = 17.6 min.

_N_-(1-Phenylethylidene)-aniline (202)



201 **202**

Conversion determination by GC:

GC(Macherey-Nagel Optima 5-Amin, 0.25 mm x 0.25 µm x 30 m, 60 kPa He, 100 °C/8 min, 5 °C·min^{-1}, 250 °C/10 min): t_R = 12.6 min (**202**), t_R = 13.1 min (**201**).

Enantiomeric excess determination by HPLC:

HPLC (Daicel Chiracel OD-H, heptane/*i*-PrOH = 99:1, 0.5 mL/min, 40 °C):

t_R ((***S***)-**202**) = 22.2 min, t_R ((***R***)-**202**) = 29.5 min.

6. Appendix

6.1 List of Abbreviations

Ac	acetyl
ACDC	asymmetric counteranion directed catalysis
AcOH	acetic acid
aq.	aqueous
Ar	aryl
BAr_F	tertrakis[3,5-bis(trifluoro-methyl)phenyl]borate
BH	Baylis-Hillman
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
Bn	benzyl
BOC	*tert*-butoxylcarbonyl
br	broad
Bu	butyl
°C	Grad Celsius
c	concentration
CAC	chloroacetyl chloride
calc.	calculated
cat.	Catalyst
Cbz	carboxybenzyl
CH_2Cl_2	dichloromethane
COD	cycloocta-1,5-diene
conv.	Conversion
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	day(s) or doublet (NMR)
DAST	(dimethylamino)sulfur trifluoride
DABCO	1,4-diazabicyclo[2.2.2]octan
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DIAD	diisopropyl azodicarboxylate

DIPEA	*N*,*N*-diisopropylethylamine
DMAP	*N*,*N*-4-(dimethylamino)pyridine
DMF	dimethylformamide
DMP	2,2-dimethoxypropane
DMSO	dimethyl sulfoxide
E	opposite
EA	elemental analysis
ee	enantiomeric excess
eq.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOH	ethanol
GC	gas chromatography
h	hour(s)
HFIP	hexafluoro-2-propanol
HPLC	high performance liquid chromatography
Hz	Hertz
i-Pr	2-propyl
J	coupling constant
K	Kelvin (NMR)
KIE	kinetic isotope effect
M	molar [mol/L] or metal
m	multiplet (NMR) or medium (IR)
MBH	Morita-Baylis-Hillman
MP	melting point
m/z	mass-to-charge ratio
Me	methyl
MeOH	methanol
Mes	mesitylene
min	minute(s)
mL	milliliter
MS	mass spectrometry or molecular sieves
NADH	nicotinamide adenine dinucleotide
n.d.	not determined
NHC	*N*-heterocyclic carbene

NMR	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
o	ortho
o-Tol	*ortho*-tolyl
p	para
p-TsOH	*para*-toluenesulfonic acid
PC	propylene carbonate
Ph	phenyl
PHOX	phosphino-oxazoline
PhNCS	phenyl isothiocyanate
ppm	parts per million
q (NMR)	quartet
quint (NMR)	quintet
rac.	Racemic
RDS	rate-determining step
R_f	retention factor
RT	room temperature
s	singlet (NMR) or strong (IR)
sat.	saturated
sec.	second(s)
T	time
t (NMR)	triplet
t or *tert*	tertiary
TRIP	(*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenph osphate
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TDS	dimethylthexylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl

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8. Summary

The general aim of this doctoral thesis was the development and synthesis of different chiral bifunctional phosphines as catalysts for the asymmetric Morita-Baylis-Hillman reaction. Moreover, the mechanism of the reaction was investigated using the back reaction screening technology.
In chapter two, the synthesis of four different catalyst generations starting from commercially available amino acids was described (Figure 20). The effect of the chiral backbone, the H-bond donor moiety and the phosphine residue on the enantioselectivity of the MBH reaction was investigated by evaluating these catalysts.

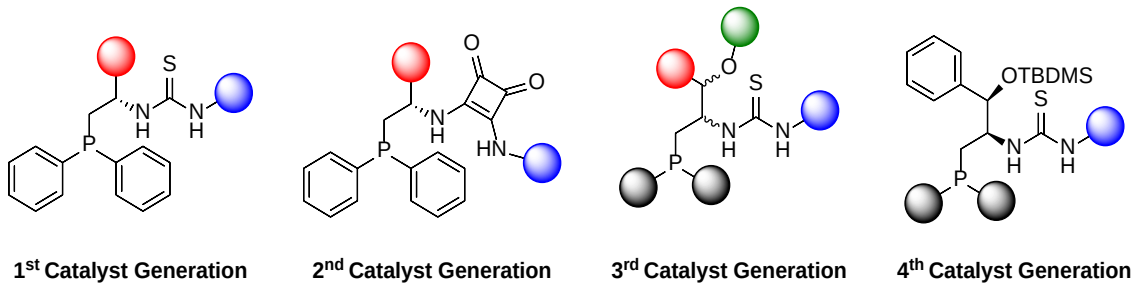

Figure 50: Overview about synthesized catalyst generations.

Moreover, the potential of mass spectrometric back reaction screening for the evaluation of catalysts for asymmetric MBH reactions was demonstrated. Screening of 62 bifunctional phosphines has led to an efficient catalyst for the reaction of methyl acrylate with aldehydes, showing improved enantioselectivity and scope compared to previously reported catalysts (Figure 21). Finally, the back reaction screening protocol was successfully extended to multi-catalyst screening of crude catalyst mixtures containing up to six bifunctional phosphines.

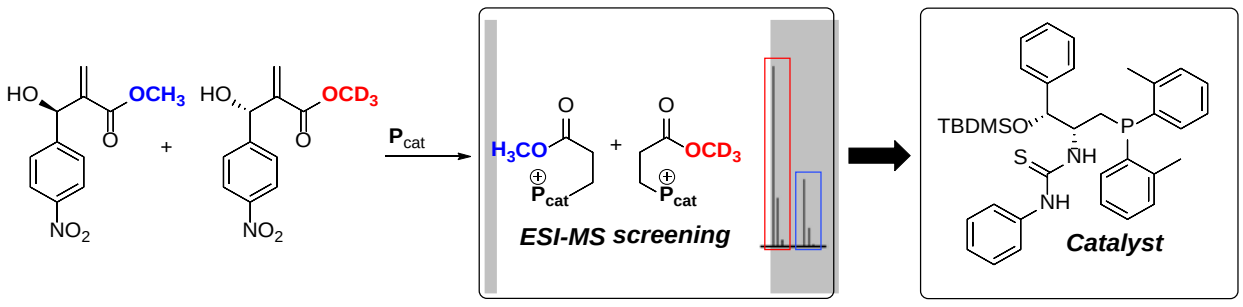

Figure 51: Evaluation of chiral bifunctional phosphines by back reaction screening.

In addition, the results from back reaction screening and additional kinetic studies have provided evidence that the enantioselectivity is determined in the C–C bond-forming step which is turnover-limiting.

In chapter three, the synthesis of two different catalyst classes is described in chapter three (Figure 31). For morpholine-based precatalysts, the effects of the chiral backbone, the *N*-residue on the triazolium ring and the substituents next to the stereogenic center on the chemo- and enantioselectivity of the cross-benzoin reaction were investigated. Moreover, for piperidine-based triazolium salts the effect of the chiral backbone and the impact of an additional hydrogen-bonding subunit on the outcome of the cross-coupling of aldehydes was studied.

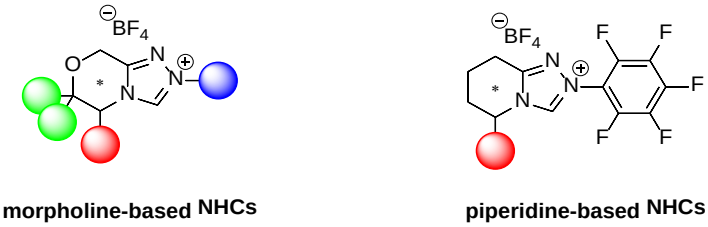

Figure 52: Catalyst classes for the asymmetric cross-benzoin reaction.

Only threonine-derived morpholine-based precatalysts gave good results in terms of chemo- and enantioselectivity. For NHC-catalyst **122a** (R = Me) and **122c** (R = Et) good chemo selectivities and reactivities were obtained, indicating the importance of the *N*-pentafluoro phenyl residue on the triazolium unit. Moreover, for catalyst **122c** higher enantioselectivity was achieved by installing a *N*-mesyl group such as in catalyst **123b** (Figure 53).

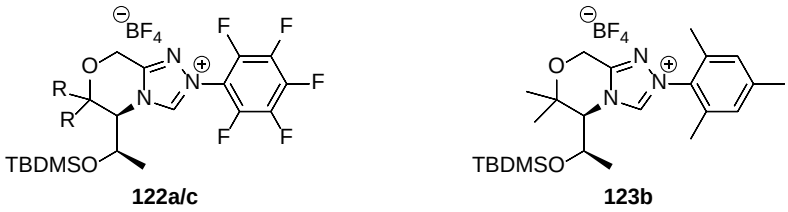

Figure 53: New possible NHC-precatalyst for the asymmetric cross-benzoin reaction.

In chapter four, the synthesis of eight new chiral bidentate NHC-phosphine ligands and the formation of the corresponding iridium complexes is described in chapter four (Figure 45). The influence of each structural unit (*N*-residue on the triazolium ring, *P*-residues, size of fused-ring system) on the asymmetric hydrogenation of model substrates was investigated. Unfortunately, with unfunctionalized olefins only low conversions and low enantioselectivities were achieved for

most ligands. Only catalyst **185c**, with an *N*-alkyl group at the triazolium unit showed high reactivity towards unfunctionalized alkenes. On the other hand, alkenes with functional groups such as a hydroxy or ester group and an imine were suitable substrates for the hydrogenation reaction but only low to moderate enantioselectivities were observed. The best rests were obtained with catalyst **185e**, which gave high conversion and moderate enantioselectivities in the reduction of allylic alcohol **199** (>99% conversion, 50% *ee*) and of imine **201** (>99% conversion, 64% *ee*).

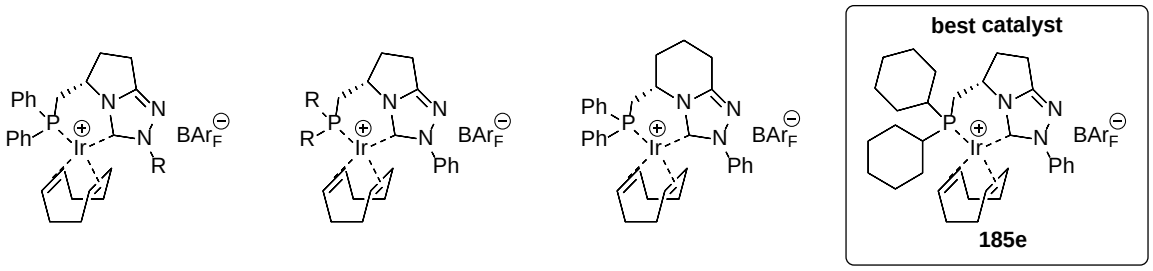

Figure 54: Iridium complexes derived from chiral bidentate NHC-phosphine ligands.

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Place of Birth: Basel, Switzerland
Nationality: Swiss

Education

11.2012-11-2016	PhD studies under the supervision of Prof. Dr. Andreas Pfaltz University of Basel, Switzerland *"Asymmetric Morita-Baylis-Hillman Reaction: Catalyst Development and Mechanistic Insights Based on Mass Spectrometric Back Reaction Screening"*
10.2012	M. Sc. in Chemistry, University of Basel, Switzerland
05.2012-10.2012	Master thesis under the supervision of Prof. Dr. Andreas Pfaltz University of Basel, Switzerland *"Screening of Chiral Organocatalysts for the Morita-Baylis-Hillman Reaction by Mass Spectrometric Monitoring of the Back Reaction"*
09.2011	B. Sc. in Chemistry, University of Basel, Switzerland

Awards

4. Award for the best group contribution to all sessions of the Syngenta workshop for talented young chemists, 2016

3. 2016 SCNAT/SCS Chemistry Travel Award

2. SCS-DSM prize for the best poster in the Organic Chemistry section (Runner's up), Fall Meeting of the Swiss Chemical Society, EPFL (CH), September 2015

1. SCS-DSM prize for the best poster in the Organic Chemistry section (Winner), Fall Meeting of the Swiss Chemical Society, EPFL (CH), September 2013

Presentations and Workshops:

10. Poster presentation*: "Asymmetric Morita-Baylis-Hillman Reaction: Catalyst Development and Mechanistic Insights"*, Swiss Industrial Chemistry Symposium, University of Basel (CH), October 2016.

9. Poster presentation*: "Asymmetric Morita-Baylis-Hillman Reaction: Catalyst Development and Mechanistic Insights"*, University of Zurich (CH), September 2016.

8. Workshop and Poster Presentation: *"Asymmetric Morita-Baylis-Hillman Reaction: Catalyst Development and Mechanistic Insights"* Syngenta Workshop 2016 for Talented PhD Chemistry Students, Stein (CH), September 2016.

7. Poster presentation*: "Asymmetric Morita-Baylis-Hillman Reaction: Catalyst Development and Mechanistic Insights"*, Gordon Research Conference in Stereochemistry, Salve Regina University (RI, USA), July 2016.

6. Poster presentation*: "Multi-Catalyst Screening for the Asymmetric Morita-Baylis-Hillman Reaction by Mass Spectrometric Monitoring of the Back Reaction"*, Fall Meeting of the Swiss Chemical Society, EPFL (CH), September 2015.

5. Poster presentation*: "Multi-Catalyst Screening for the Asymmetric Morita-Baylis-Hillman Reaction by Mass Spectrometric Monitoring of the Back Reaction"* 44th National Organic Symposium, University of Maryland (MD, USA), July 2015.

4. Poster presentation*:* "*Screening of Chiral Organocatalysts for the Morita-Baylis-Hillman Reaction by Mass Spectrometric Monitoring of the Back Reaction*", ACS GCI Pharmaceutical Roundtables: Green Chemistry makes a difference, Roche Basel (CH), April 2015.

3. Poster presentation*:* "*Screening of Chiral Organocatalysts for the Morita-Baylis-Hillman Reaction by Mass Spectrometric Monitoring of the Back Reaction*", Gordon Research Conference in Stereochemistry, Salve Regina University (RI, USA), August 2014.

2. Poster presentation: "*Screening of Chiral Organocatalysts for the Morita-Baylis-Hillman Reaction by Mass Spectrometric Monitoring of the Back Reaction*", 33rd Regio Symposium of the Cross-Border Universities, Study on Organic and Bioorganic Chemistry, Mittelwihr (Fr), September 2013.

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Teaching Experiences and Other Professional Activities

11.2012-11.2016	Tutorial supervision for chemistry lectures given by Prof. Dr. Andreas Pfaltz
11.2012-11.2016	Direct supervision of undergraduate students in chemistry, during three and eight weeks laboratory practical courses in the research group of Prof. Dr. Andreas Pfaltz
01.2013-12.2015	Laboratory teaching assistant of bachelor students in biology, pharmacy and chemistry in basic and advanced organic chemistry
04.2012-09.2012	Direct supervision of advanced student Mirjam Schreier, during her master thesis in chemistry in the research group of Prof. Dr. Andreas Pfaltz
07.2011-07.2012	Division of Radiopharmaceutical Chemistry, University Hospital of Basel (CH) Synthesis of ^{90}Y-DOTATOC radiopharmaceuticals for therapy of neuroendocrine tumors (student job, part time)
01.2010-10.2012	Bachem AG, Bubendorf (CH) Teaching commercial apprentice in chemistry for the final apprenticeship examination

During my education at the University of Basel I attended lectures given by:

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