Development and Evaluation of Chiral Catalysts for Asymmetric C-C and C-H Bond Forming Reactions

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Christian Ebner

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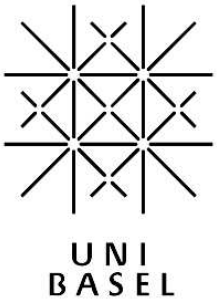

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Prof. Dr. Andreas Pfaltz
Prof. Dr. Helma Wennemers

Basel, den 21.02.2012

Prof. Dr. Martin Spiess
Dekan

Nonnenstieg 8, 37075 Göttingen
Telefon: 0551-54724-0
Telefax: 0551-54724-21
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"Chiral dihydrobenzo[1,4]oxazines as catalysts for the asymmetric transfer-hydrogenation of α,β-unsaturated aldehydes"

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Chapter 1

ESI-MS Screening of Racemic Catalyst Mixtures

1.1 Introduction

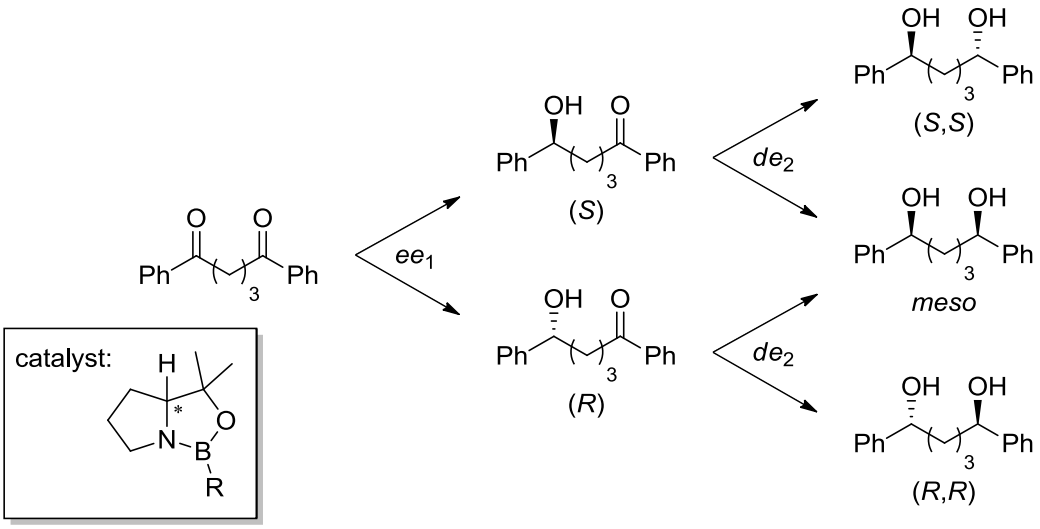
The field of asymmetric catalysis is one of the most important areas in modern organic synthesis and its relevance has been illustrated when the Nobel Prize in 2001 was given to KNOWLES, NOYORI and SHARPLESS for their work in this field.[1] Although many chiral catalysts have been already designed, there is still a great range of reactions where the development of novel highly selective catalysts is required. However, selectivity is not a predictable property of a catalyst for asymmetric transformations. Thus, catalyst screening is essential when working in the field of asymmetric catalysis. For this reason high-throughput screening became a more and more important field of research, allowing the fast measurement of enantiomeric excesses.[2] Consequently the screening of a catalyst library, even if it contains a large number of compounds, is no longer the bottleneck in the development of an enantioselective catalytic process. In fact the synthesis of such a library is very labor-intensive as chiral catalysts have to be obtained in high optical purity. Especially for structurally novel catalysts this might require the development of new methodologies for the preparation of these compounds prior to evaluation of their properties. As this is a very time-consuming approach and success cannot be guaranteed, this effort is often not taken and many potential catalysts remain unexplored.

Screening methods that allow the determination of a catalyst by testing its racemic form would strongly enhance the range of possible structures that can be explored. Moreover, structural optimization of a catalyst could be accelerated considerably in cases where the preparation of enantiomerically pure derivatives is difficult.

1.1.1 Previously Reported Approaches Towards Selectivity Determination by Testing Racemates

Only few methods that allow the potential of chiral catalysts to be estimated by testing the racemic form have been reported previously.

KAGAN and co-workers showed that it is possible to evaluate the enantiodiscrimination potential of a racemic catalyst in the sequence of two consecutive reactions at two prochiral units of a substrate.[3] As model reaction they describe the enantioselective borane reduction of ketones catalyzed by chiral oxazaborolidines (scheme 1).

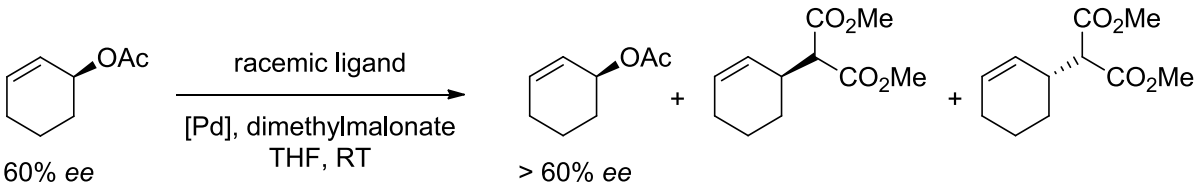


Scheme 1. *Testing racemic chiral catalysts in the enantioselective borane reduction of ketones according to KAGAN and co-workers.*[3]

However this methodology relies on certain requirements that have to be fulfilled. First, the presence of a stereogenic center after the first reduction step should not influence the selectivity of the catalyst for the second step. Therefore they used a diketone with three methylene-units between the two functional groups as a model substrate. If those reactive centers are now sufficiently separated, the reduction of the second ketone-function should proceed with the same selectivity as the reduction of the first ($ee_1 = de_2$). Furthermore they assumed that the same catalyst enantiomer is performing both the first and the second reduction. Therefore a reaction had to be chosen in which the second step is relatively fast compared to the catalyst release after the first step. If these assumptions are true, the first reduction step will proceed with the selectivity induced by the catalyst (ee_1) forming either the (*R*) or the (*S*) product, depending on which catalyst enantiomer was involved and on its selectivity. As the same catalyst enantiomer is now involved in the second reduction as in the first step, the second stereogenic center is supposed to be formed preferentially with the same configuration as the first stereogenic center. Only the minor enantiomer will end up being the *meso*-substrate. This means, the higher the selectivity of the catalyst is, the higher the *de* of the (*R*,*R*)- respectively the (*S*,*S*)-diol will be. From this *de* value and with the assumptions made above the *ee* induced by the catalyst for each stereogenic center can be calculated ($ee_{diol} = ee_1 \times de_2 = ee_1^2$ since $ee_1 = de_2$). For the example shown above comparable results from this screening method and the preparative reaction using enantiopure catalysts have been obtained. However, KAGAN and co-workers reported as well that they investigated two additional catalytic reactions based on this methodology, rhodium-catalyzed hydrosilylation and

ruthenium-catalyzed transfer hydrogenation. For those cases they were not able to observe any diastereoselectivity and therefore the determination of the catalyst´s selectivity was not possible. The reason for this was found in the fact that the binding interactions between the catalyst and the reactant were not sufficient and therefore the catalyst dissociated from the substrate between the two consecutive reaction steps. These findings show, that conditions needed for this screening approach are only met in very special cases.

In 2001 LLOYD-JONES and co-workers published a very intriguing concept to estimate the selectivity of a chiral catalyst by testing its racemic form.[4] The concept relies on the use of scalemic substrate mixtures (enantioenriched substrate with defined enantiomeric excess). By reacting with a racemic catalyst under pseudo-zeroth-order conditions (saturation conditions under which the reaction rate does not display a direct relationship with the substrate concentration) the enantiomeric excess of such a substrate changes upon proceeding conversion. As pseudo-zeroth-order conditions are rather common in kinetic resolutions,[5] the method seems to be fairly generally applicable. The model reaction on which this method was validated was the kinetic resolution of allylic acetates by palladium-catalyzed allylic substitution (scheme 2).



Scheme 2. *Estimation of the selectivity by reacting a racemic Pd-catalyst with a scalemic substrate mixture according to LLOYD-JONES and co-workers.[4]*

For a catalyst with perfect enantioselectivity (selectivity factor $s = k_{fast}/k_{slow} = \infty$) each of the catalyst enantiomers do only react with one of the substrate enantiomers. As both catalyst enantiomers do react at the same rate (pseudo-zeroth-order conditions) the two substrate enantiomers are consumed in equal amounts until all of the minor enantiomer has been converted to product and the substrate *ee* increases with conversion. On the other hand, for an unselective catalyst ($s = 1$) the two catalyst enantiomers do react with both of the substrate enantiomers in a statistic fashion and the substrate *ee* remains constant throughout the reaction. If the evolution of the substrate *ee* is now followed over proceeding conversion different graphs depending on the catalyst selectivity have been calculated (figure 1, left). As shown, catalyst with a higher selectivity will give a graph with a higher slope. When then two

racemic Trost-ligands have been tested, two different graphs were obtained (figure 1, right). The one obtained from the ligand bearing a five-membered ring back-bone showed the higher slope suggesting a higher selectivity of the corresponding catalyst compared to the one bearing a six-membered ring back-bone. Indeed when the enantiopure catalysts were tested in the preparative kinetic resolution reaction, the same selectivity trend was observed.

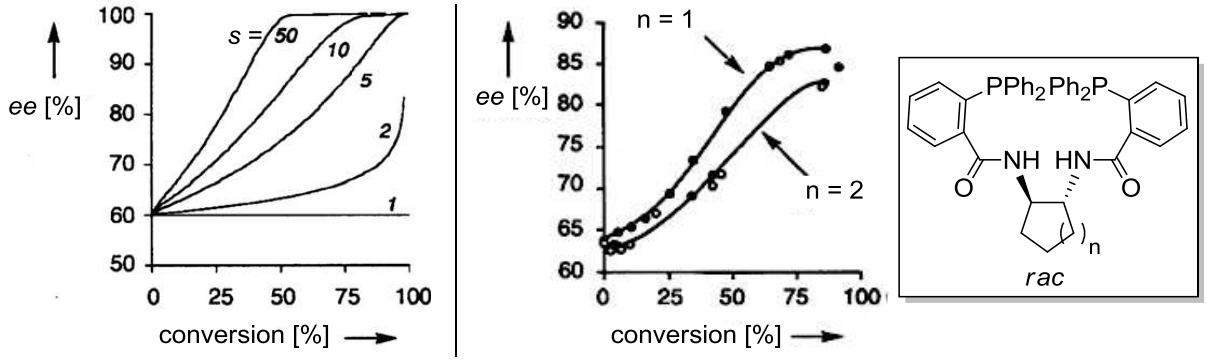
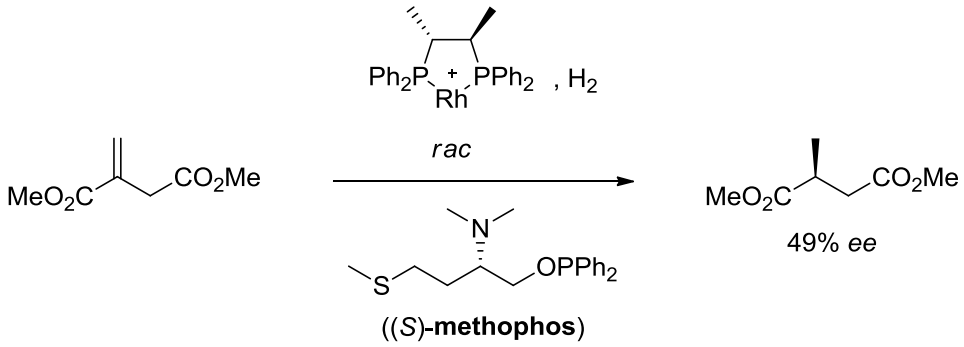


Figure 1. *Evolution of the substrate ee upon proceeding conversion. Left: calculated graphs for different catalyst selectivities; right: experimental data from testing racemic* TROST*-ligands.*[4]

However there are as well certain drawbacks connected with this methodology. As several data points have to be collected in order to create a graph as shown in figure 1, the screening itself is very laborious. Furthermore it cannot be applied to enantioselective reactions of prochiral substrates but only to kinetic resolutions. And finally it allows only an approximate estimation and not the exact determination of the enantioselectivity of different catalysts.

A different approach in this context, is the so-called chiral poisoning.[6] In this case not a racemic catalyst mixture is used but a chiral additive which deactivates one of the catalyst enantiomers prior to the transformation to be evaluated, It was demonstrated by FALLER and PARR that in the rhodium-catalyzed hydrogenation of dimethyl itaconate with a racemic mixture of chiraphos as ligand a certain extent of enantiomeric excess can be obtained upon addition of (*S*)-methophos as chiral poison (scheme 3).



Scheme 3. *Chiral poisoning of a racemic catalyst mixture in the rhodium catalyzed hydrogenation.*[6]

However it has to be mentioned that using enantiopure (*R*,*R*)-chiraphos without additional methophos the hydrogenation proceeds in considerable higher selectivity yielding >98% *ee*. This shows that either the poisoning was not sufficient or the additive has a deleterious effect on the selectivity of the catalyst. Furthermore suitable chiral poisons might not always be available for various catalysts.

Those above mentioned approaches to enable selectivity determination by testing racemic catalyst mixtures are still suffering from certain restrictions and limitations. PFALTZ and co-workers previously reported a screening method based on the detection of reaction intermediates by electrospray ionization mass spectrometry (ESI-MS),[7] which could have the potential to be modified towards testing racemates for selectivity determination.[8]

1.1.2 ESI-MS Screening of Enantiopure Catalysts

1.1.2.1 ESI-MS as a Tool for Detection of Organo-Metal Compounds in Solution

Besides MALDI (matrix assisted laser desorption ionization), electrospray ionization (ESI) is one of the mildest ionization techniques, allowing the transfer of intact molecular ions into the gas phase without defragmentation.[9] The charged compounds being analyzed can either be transient species, or protonated/deprotonated forms or ion adducts of neutral species. As only charged species can be visualized, ESI-MS enables the detection of charged reaction intermediates in the presence of a great excess of uncharged molecules.

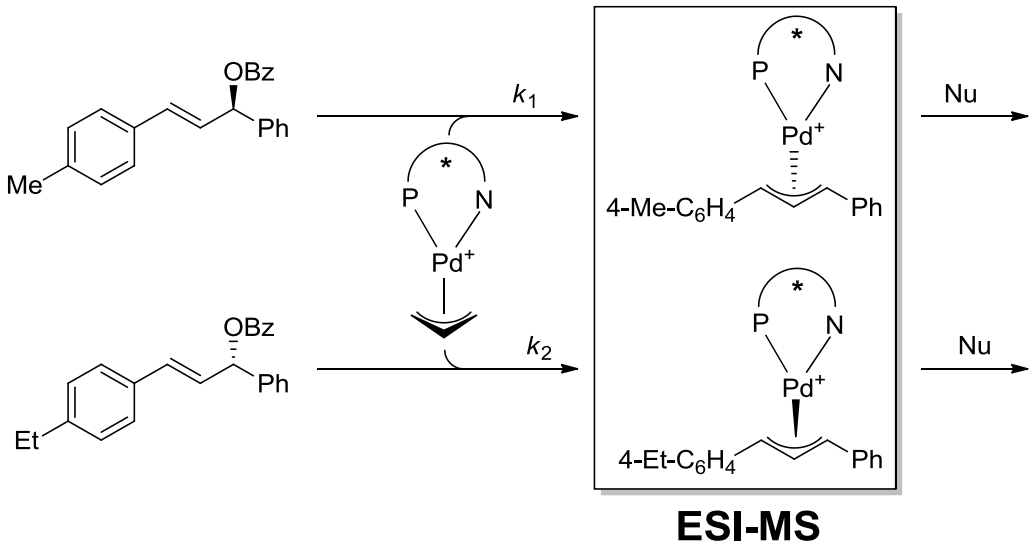
In 1968 DOLE and co-workers reported the possibility of generating gas-phase ions by electrospraying of a polymer solution into an evaporation chamber.[10] The method was then significantly improved by YAMASHITA and FENN which were able to combine electrospray

ionization with mass spectrometry.[11] Together with the MALDI technique and NMR spectroscopy these findings had a significant impact in the field of analyzing biological macromolecules and its importance has been illustrated by awarding FENN (ESI-MS)[12] along with TANAKA (MALDI-MS)[13] and WÜTHRICH (NMR)[14] with the Nobel Prize in 2002.

The first characterization of an ionic transition metal complex by ESI-MS was reported in 1990 by CHAIT and co-workers who detected bipyridil and 1,10-phenantroline ruthenium complexes.[15] In 1999 HINDERLING and CHEN applied for the first time ESI-MS for a reactivity screening of olefin polymerization catalyst libraries.[16] Upon mixture of eight complexes in comparable concentration with ethylene and ESI-MS analysis of the resulting charged species with a mass of $m/z > 2000$ they could show that the most abundant signal obtained after MS/MS analysis corresponded to the most active catalyst as such high mass was only reached upon very successful polymerization. Later ADLHART and CHEN described a similar approach for ruthenium catalyzed ring-opening metathesis polymerization (ROMP).[17] As reaction intermediates in this example are uncharged they were trapping those with a monomer-unit containing a side chain bearing a cationized functional group. Thus, the formed species became charged and detectable by ESI-MS, allowing for the reactivity determination of neutral complexes in solution.[18]

1.1.2.2 ESI-MS Screening in the Palladium Catalyzed Kinetic Resolution of Allylic Esters

In their first example for the evaluation of a chiral catalyst by ESI-MS screening, MARKERT and PFALTZ described an easy and fast screening method to determine the intrinsic selectivity of palladium catalysts in the kinetic resolution of allylic esters.[19] The selectivity in this reaction equals the relative ratios of the two rate-constants k_1 over k_2 and thereby the ratio of the two Pd-allyl species formed as reaction intermediates (scheme 4). As common kinetic resolutions start from enantiomeric substrates and therefore the intermediates formed would have the same mass, here mass labels had to be introduced on the substrates. Substitution in the *para*-position of the benzyl ring has shown to be suitable as this position is sufficiently far away from the reaction center and has no influence on the outcome of the reaction. Starting from these two so-called quasi-enantiomeric mass labeled substrates the intermediates formed become now distinguishable by a mass-spectrometric method. Determining the ratio of the two corresponding MS signals gives therefore direct access to the ratio of k_1/k_2 and by this two the selectivity of the catalyst used.



Scheme 4. *Selectivity determination in the palladium catalyzed kinetic resolution of allylic esters by ESI-MS upon use of mass-labeled pseudo-enantiomeric substrates.*[19]

When for example an achiral catalyst was tested, the intermediate ratio was determined to be at 50:50 (s = 1) as expected (figure 2, left). On the other hand, with a chiral and enantioselective catalyst an intermediate ratio of 9:91 (s = 10) was observed (figure 2, right).

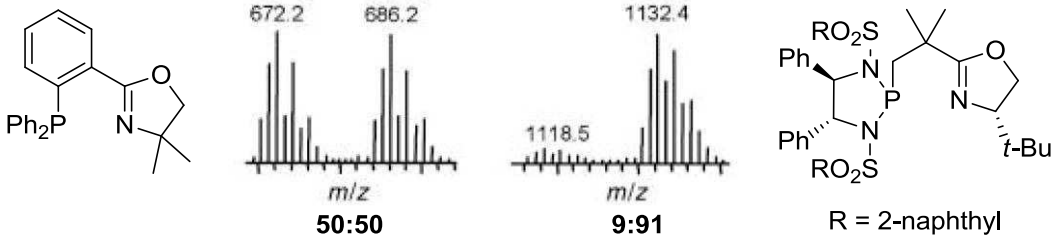
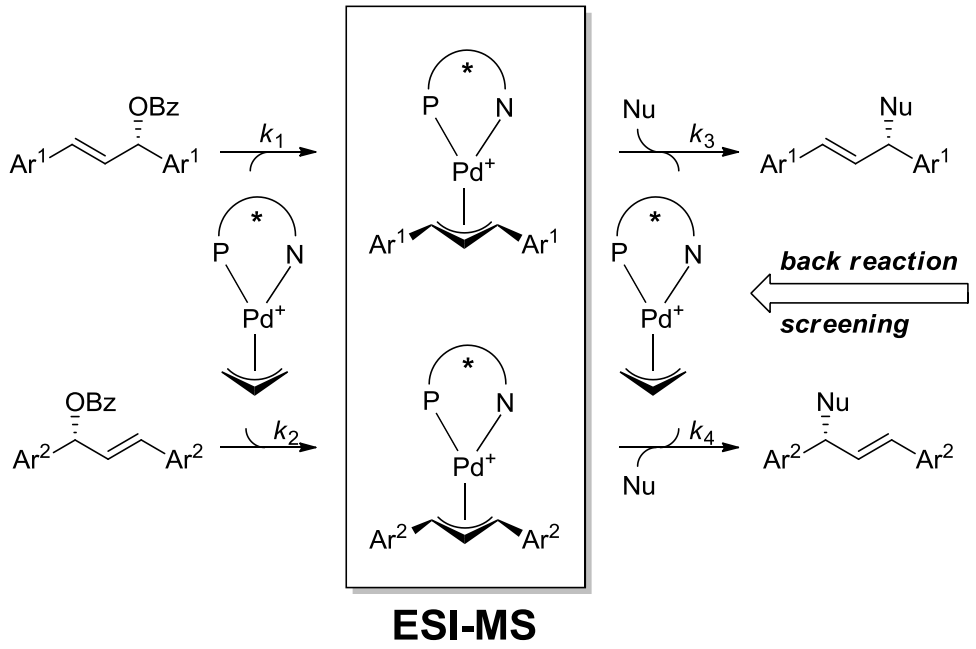


Figure 2. *Selectivity determination by ESI-MS screening of different catalyst. Left: an achiral ligand leads to an unselective catalyst (intermediates formed in a 50:50 ratio, s = 1); right: a chiral ligand leads to a selective catalyst (intermediates formed in a 9:91 ratio, s = 10).*[19]

A great advantage of this method, besides the time saving, is the determination of the intrinsic selectivity of the catalyst. Selectivity determination by performing the preparative catalytic reaction can lead to falsified results as catalytically active impurities or unselective background reactions have an influence on the enantiomeric excess of the isolated reaction product. However, this method could at that time only be applied to kinetic resolutions and not to enantioselective reactions of prochiral substrates as different mass-labels have two be installed on the two different enantiomers of the substrate. If the stereogenic center is formed during the reaction instead of being present in the starting material this of course is no more possible.

1.1.2.3 ESI-MS Screening in the Palladium Catalyzed Allylic Alkylation

In 2008 MÜLLER and PFALTZ reported an extension of the ESI-MS screening method to overcome this problem.[20] Rather than using the prochiral starting material in the screening they performed a back reaction screening starting from the catalysis products bearing the chiral information. They validated this approach by applying it in the palladium-catalyzed allylic substitution reaction (scheme 5). Here the selectivity determining step is the nucleophilic addition onto the palladium-allyl intermediate.



Scheme 5. *Back reaction screening approach to enable selectivity determination in the palladium-catalyzed allylic substitution.*[20]

This variation was possible due to the principle of microscopic reversibility,[21] which says that the ratio of the rate constants k_3/k_4 (which equals the selectivity in the allylic substitution) equals the ratio of the rate constants of the corresponding back reaction (k_{-3}/k_{-4}). The concept of ESI-MS screening of a back reaction has further been successfully applied to Diels-Alder reactions, both organo- and copper-catalyzed, by TEICHERT and PFALTZ[22] and organo-catalyzed conjugate additions by FLEISCHER and PFALTZ.[23]

1.1.2.4 Simultaneous Screening of Catalyst Libraries by ESI-MS

All the above mentioned ESI-MS screening methods rely on the detection of mass-spectrometrically distinguishable reaction intermediates. This opens the possibility of a simultaneous parallel screening of catalyst libraries as long as the individual catalysts are different in mass (figure 3). This was first shown by PFALTZ and co-workers in the kinetic resolution of allylic acetates using differently substituted P,P-ligands.[24] Such a parallel approach has as well been applied for all other reactions for which an ESI-MS screening has been established.[20,22-23]

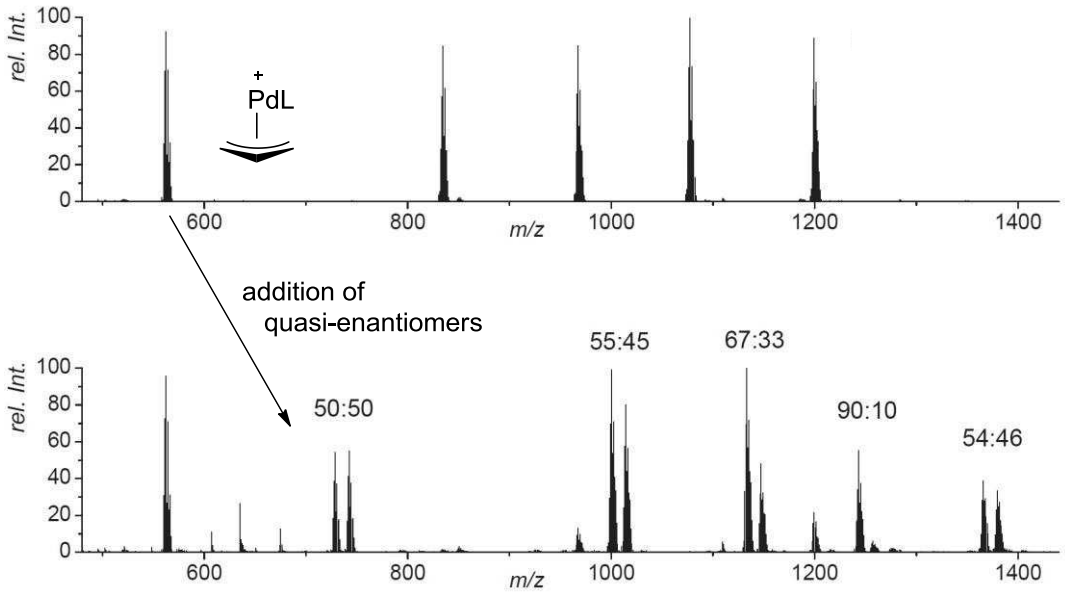


Figure 3. *Simultaneous ESI-MS screening of catalyst of different mass (top: set of 5 different precatalysts; bottom: formation of 5 different intermediate pairs after quasi-enantiomer addition).*[8]

As the described ESI-MS screening protocols avoid selectivity determination by conducting the preparative reaction, including work-up and product analysis, they provide a rapid access to the selectivity of different catalyst, especially when simultaneous screenings are performed. However, the very time-consuming synthesis of a library of different optically pure chiral catalyst is still required for all of the above mentioned ESI-MS methods and thus they just move the bottleneck from the screening part to the synthesis part for the development of novel catalysts.

1.1.3 Objectives of This Work

The aim of this project was the development of an ESI-MS screening method, based on the approach of PFALTZ and co-workers[7] and the concept of LLOYD-JONES,[4] which allows for the rapid and facile selectivity determination of different racemic catalysts in the allylic substitution reaction.

This reaction was chosen as it is a very well-studied reaction where detailed knowledge about the mechanism was gained. Furthermore MÜLLER and PFALTZ have previously demonstrated that this reaction can be screened in the reverse direction.[20] Moreover this reaction has been proven to be an important and very powerful method for the asymmetric formation of C-C and C-heteroatom bonds.[25]

For this purpose a set of different chiral ligands had to be synthesized in racemic form. The structure of those ligands was based on phosphino-oxazoline (PHOX) ligands (figure 4). It has been previously shown that PHOX ligands form very active and selective palladium-catalysts for the allylic substitution reaction.[26] However, the only aryl-PHOX ligand that was studies has been Ph-PHOX as the asymmetric synthesis of other aryl-derivatives is very challenging. Therefore this kind of ligands seems to be well suited to be tested in their racemic form.

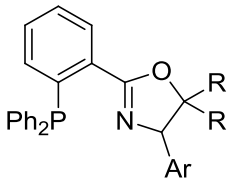
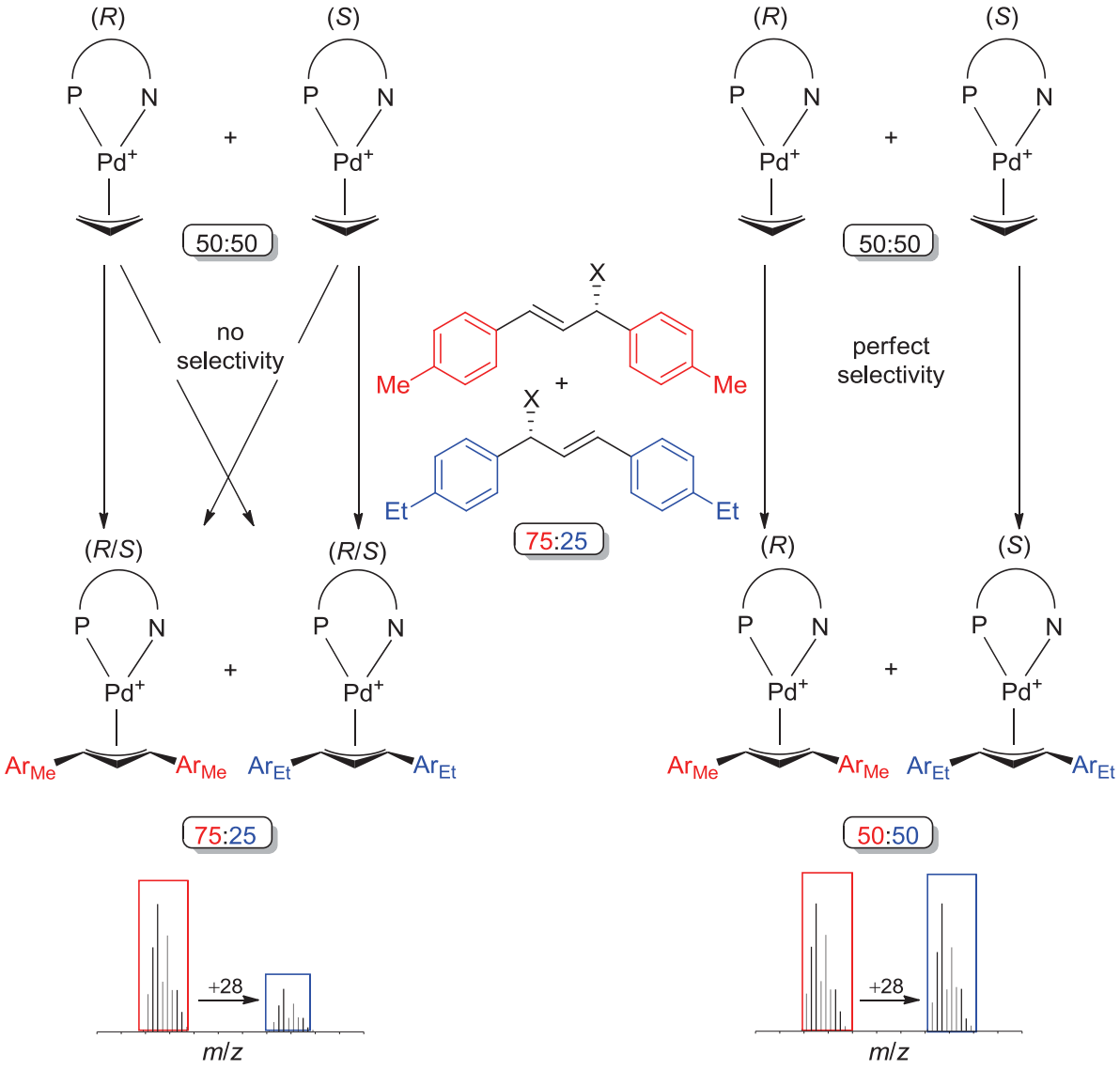


Figure 4. *Aryl-PHOX ligands to be synthesized and evaluated in the allylic substitution reaction in their racemic forms.*

1.2 The Concept of Testing Racemic Catalyst Mixtures by ESI-MS Screening

1.2.1 Relation Between Catalyst Selectivity and Detected Intermediate Ratio

Combining the concept of selectivity determination by testing racemic catalysts as described by LLOYD-JONES[4] and the concept of ESI-MS back reaction screening in the allylic substitution reaction as described by MÜLLER and PFALTZ[20] should allow to develop a protocol for selectivity determination which is very time-saving in both the synthesis of a catalyst library and the screening of those catalysts.



Scheme 6. *Concept of selectivity determination by ESI-MS screening of racemic catalyst mixtures (Ar_{Me} = 4-Me-C_6H_4, Ar_{Et} = 4-Et-C_6H_4). (Left: result obtained upon testing an unselective catalyst; right: result obtained upon testing catalyst with perfect selectivity; bottom: simulated mass-spectra).*

Starting from a scalemic mixture of mass-labeled pseudo-enantiomeric substrates, upon reaction with a racemic catalyst mixture the mass-spectrometric detectable reaction intermediates would form in different ratios depending on the selectivity of the catalyst. In theory two extreme cases are possible (scheme 6). If the catalyst shows no selectivity (s = 1), each of the catalyst enantiomers reacts with each of the two substrates without any differentiation and therefore in a statistical fashion (scheme 6, left). Thus, the substrate ratio defines the ratio in which the detectable catalysis intermediates are formed. If the substrates have been applied in the 75:25 ratio, the detected intermediate ration will end up to be 75:25 as well. On the other hand, for a catalyst with perfect selectivity ($s = \infty$), each of the catalyst enantiomers does only react with its matching substrate counterpart (scheme 6, right). For example the (*R*)-catalyst with the (*S*)-substrate (labeled with two methyl-groups, red) and the (*S*)-catalyst with the (*R*)-substrate (labeled with two ethyl-groups, blue). In this ideal case a 50:50 ratio of the catalysis intermediates would be observed by ESI-MS. In reality different catalysts of course will show selectivities in between those two extreme cases. The higher selective they are, the lower the detected intermediate ratios will be and vice versa. The exact relation between a catalyst´s selectivity factor *s* and the intermediate ratio can be calculated from the following equation (equation 1) assuming pseud-zeroth-order conditions, where *R* is the detected intermediate ratio and *Q* the ratio in which the two mass-labeled quasi-enantiomeric substrates have been applied (for derivation of this equation see chapter 8).

$$s = \frac{Q^2 - R + \sqrt{(R - Q^2)^2 - (R \cdot Q - Q)^2}}{R \cdot Q - Q} \qquad (\textbf{\textit{equation 1}})$$

1.2.2 Sensitivity of the Method and Choice of Substrate Ratio

The enantiomeric excess of a catalyst can easily be calculated from equation 1 after performing the racemate screening. Figure 5 shows the relation of the enantiomeric excess calculated from the screening and the detected intermediate ratio for different substrate ratios used. The lower the slope of such a curve is, the more sensitive the screening method is, as then little changes in the detected intermediate ratio do not have a big influence on the *ee* which is calculated. Or with other words, a catalyst providing a slightly different *ee* compared to another catalyst would lead to a significant different intermediate ratio detected by ESI-MS. Comparing the graphs for the different substrate ratios used as shown in figure 5 it can be seen that the higher the substrate ratio is, the higher the sensitivity of the method becomes. This is not very surprising as the intermediate ratio can only end up being between 1:1 and the

substrate ratio. This means that a higher substrate ratio leads to a higher range in which the data points can be found. Just looking at this finding, a very high substrate ratio seems to be desirable to use. But the other side of the coin is the detection limit. If the substrate ratio applied becomes too high, the minor signal might vanish in the noise signal. Furthermore a few turnovers of the catalyst do have a lower influence on the substrate ratio if it is closely to 1:1. Taking this into account a substrate ratio of 3:1 seems to be the best compromise between above mentioned points.

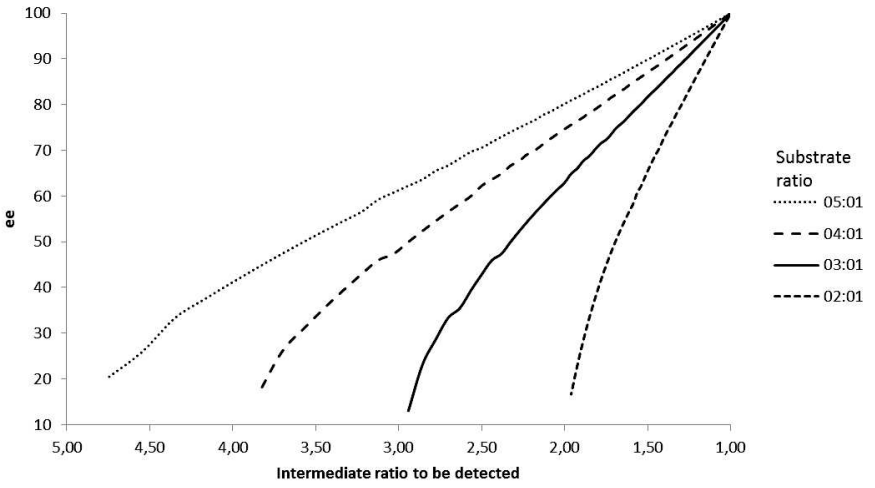


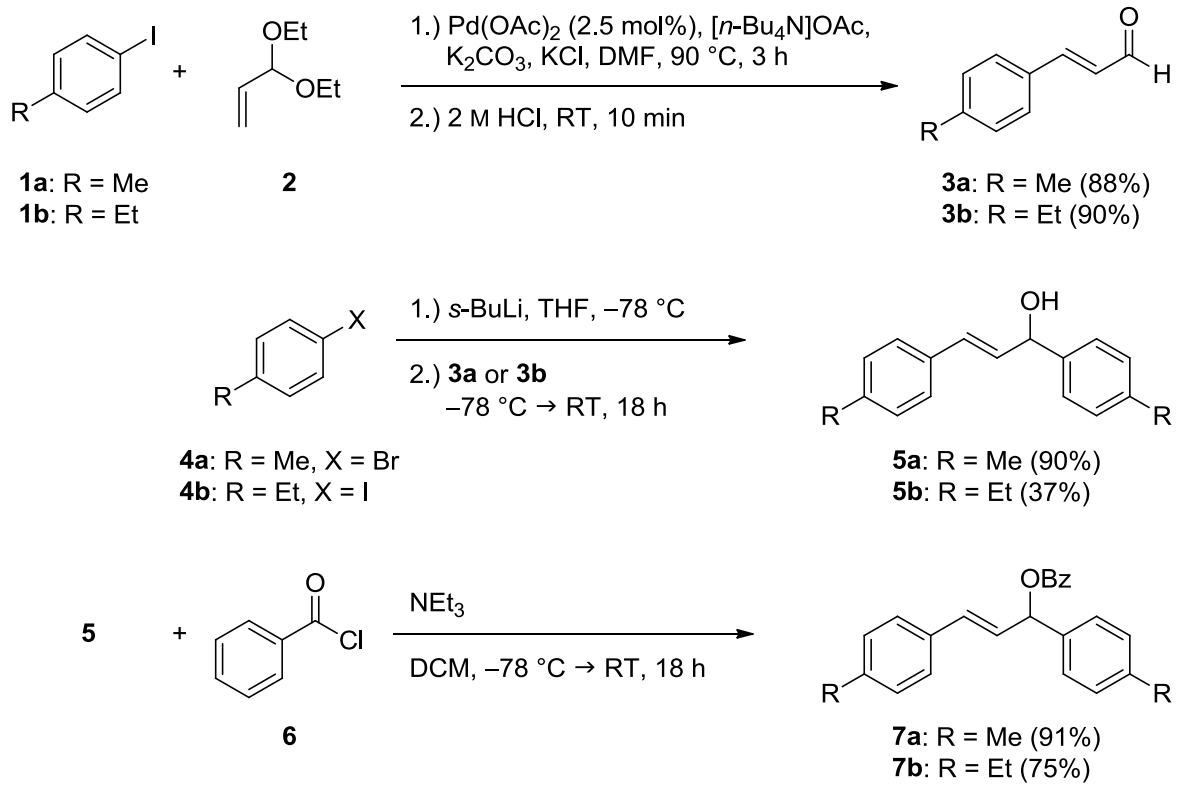
Figure 5. *Dependency of the enantiomeric excess/intermediate ratio on the substrate ratio which was applied (calculated graphs).*

Another property concerning the sensitivity can be found regarding the lower *ee* range. The curves shown in Figure 5 do not shown linear behavior in the entire detection range. For enantiomeric excesses lower than about 35% the curves show a higher slope than in the range above 35% *ee*. This is accompanied with lower sensitivity in this low selectivity range. However, since in a catalyst screening one searches for highly selective catalysts, lower sensitivity in this range is not really problematic.

1.3 Synthesis

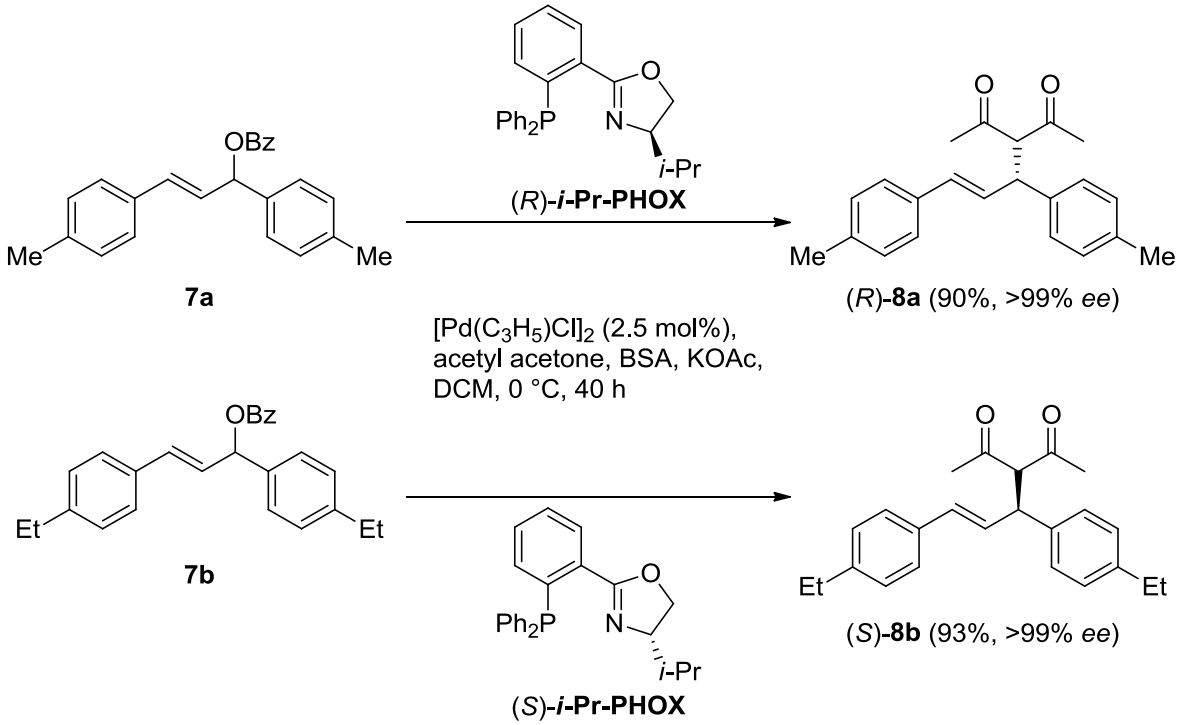
1.3.1 Substrate Synthesis

Mass-labeled quasi-enantiomeric substrates **8** had to be synthesized in an enantiomerically pure fashion. This was achieved according to a previously reported route.[20,27] The key step in the synthesis was the palladium catalyzed allylic substitution. Therefore the corresponding benzoate precursors **7** were prepared (scheme 7).



Scheme 7. *Synthesis of the benzoate precursors for the substrate preparation.*

This was accomplished starting from commercially available aryl iodides **1** which were treated with acrolein diethyl acetal (**2**) in a Heck reaction using of $Pd(OAc)_2$ followed by acidic workup to give acrylaldehydes **3** in high yields. These were then converted to the 1,3-diaryl allylic alcohols **5** by nucleophilic 1,2 addition of the aryl-lithium species to the corresponding aldehyde. After subsequent esterification with benzoylchloride (**6**) in the presence of NEt_3 the desired allylic benzoates **7** were obtained in good yield (overall yields: 72% for **7a**, 25% for **7b**).



Scheme 8. *Formation of enantiopure quasi-enantiomeric substrates by palladium catalyzed allylic substitution using* ***i-Pr-PHOX*** *ligands.*

Palladium-catalyzed allylic alkylation of the benzoates **7** by acetyl acetone using ***i*-Pr-PHOX** as chiral ligand yielded finally the desired quasi-enantiomeric mass-labeled substrates **8** in high yields (scheme 8). In both cases a perfect enantiomeric purity was obtained which is crucial for the planned ESI-MS screening-studies.

1.3.2 Catalyst Synthesis

1.3.2.1 Racemic Aryl-Dimethyl-PHOX Ligands

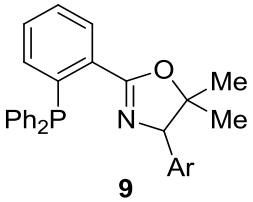


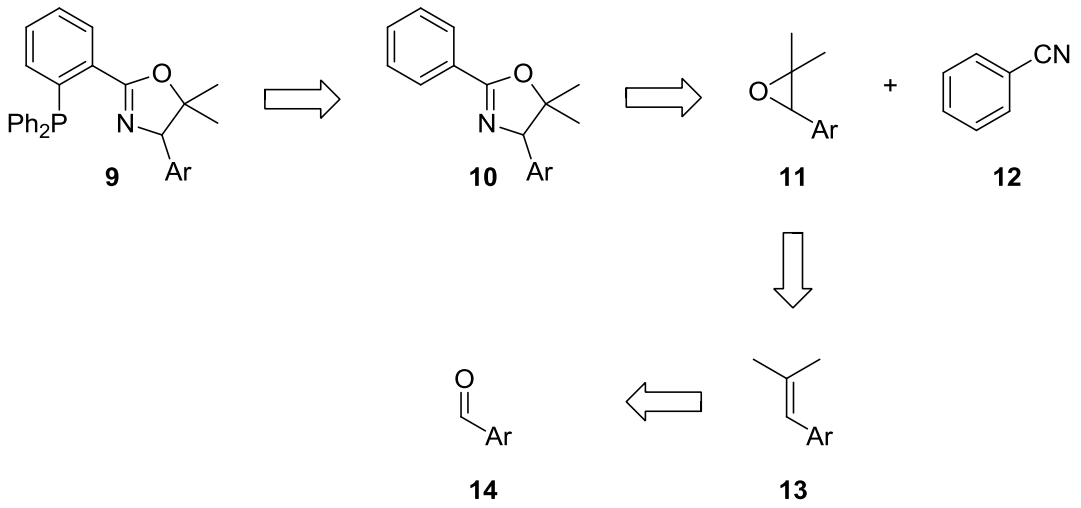
Figure 6. *Ar-dimethyl-PHOX ligands* ***9*** *to be tested.*

As described before the aim of the project was to evaluate the selectivity of novel aryl-PHOX derived catalysts in the allylic substitution. The first class of such ligands to be tested were Ar-PHOX ligands bearing an additional *gem*-dimethyl substitution on the oxazoline ring

(figure 6). It has been previously shown, that such a substitution can have a beneficial effect on the selectivity of a PHOX ligand in [3+2] cycloadditions of azomethine ylides with Ag(I)-PHOX catalysts[28] or in enantioselective Heck reactions of 2,3-dihydrofuranes and palladium-catalyzed allylation reactions of fluorinated silyl enol ethers.[29]

*Retrosynthetic analysis of aryl-dimethyl-PHOX ligands **9***

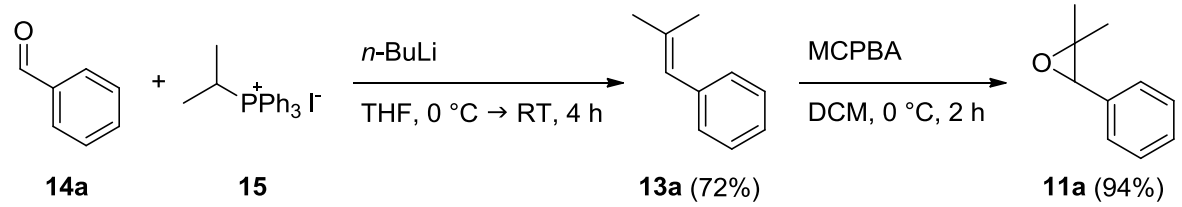
The synthesis of aryl-dimethyl-PHOX ligands **9** was accomplished by *ortho*-lithiation and treatment of the corresponding 1-phenyl oxazolines **10** with chloro diphenylphosphine (scheme 9) The key step in the synthesis should then be the formation of these oxazolines. It was planned to achieve this by a Ritter reaction between 1-aryl 2,2-dimethyl epoxides **11** and benzonitrile (**12**). Epoxide species **11** can be obtained by epoxidation of the corresponding alkenes **13**, which can be derived from the aryl-aldehydes **14** by Wittig olefination.



Scheme 9. *Retrosynthetic analysis of aryl-dimethyl-PHOX ligands **9**.*

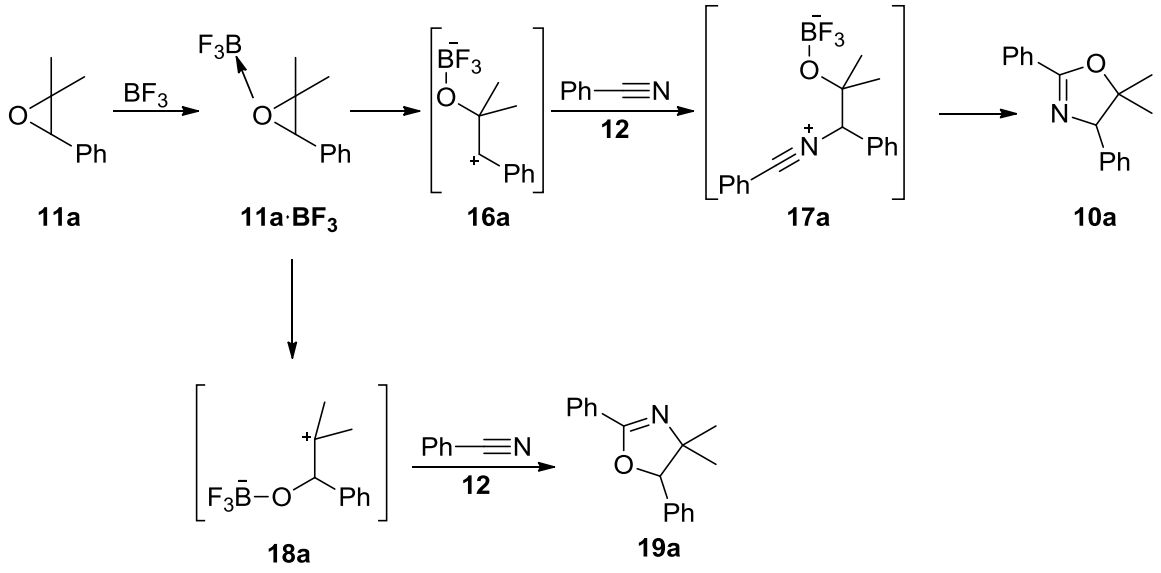
*Synthesis of phenyl-dimethyl-PHOX ligand **9a***

According to the retrosynthetic analysis shown in scheme 9, 2,2-dimethyl-3-phenyloxirane (**11a**) was obtained from commercial available benzaldehyde (**14a**) by Wittig reaction[30] with *iso*-propyltriphenylphosphonium iodide (**15**) followed by epoxidation using MCPBA[31] in 68% yield over two steps (scheme 10).



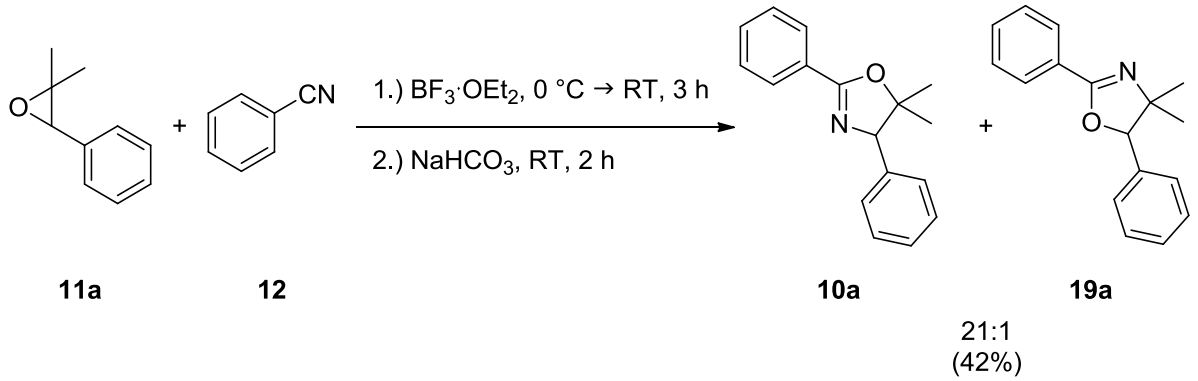
Scheme 10. *Synthesis of 1-phenyl 2,2-dimethyl epoxide **11a**.*

As mentioned above the key step in the synthesis was the Ritter reaction[32] between epoxide **11a** and benzonitrile (**12**). Mechanistically this reaction proceeds as shown in scheme 11. The epoxide **11a** gets activated by trifluoro borane. Thus, the epoxide opens to form the carbocationic species **16a** whose charge is in stabilized benzylic position. This carbocation gets then trapped by the nitrile group of **12** to form **17a**. Subsequent ring closure affords the oxazoline **10a**. However, if **11a** opens to form the tertiary carbocation **18a**, the following reaction with benzonitrile would afford the regioisomeric oxazoline **19a**.



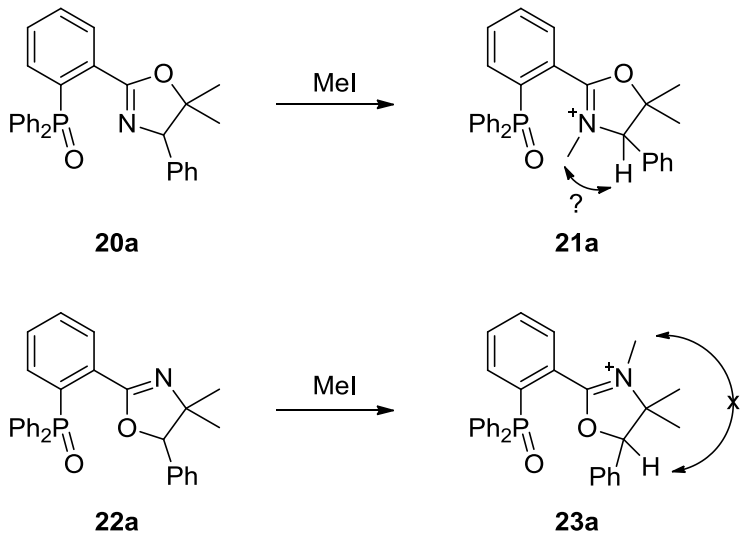
Scheme 11. *Proposed mechanism of the Ritter reaction.*

When the reaction was carried out, oxazoline formation occurred in acceptable 42% yield (scheme 12). It was found, that indeed two different oxazoline species have been formed in a ratio of 21:1. The major isomer could be isolated by column chromatography. However, determination of the constitution of this isomer proved to be very difficult by conventional analysis methods.



Scheme 12. *Ritter reaction to form 1-phenyl oxazoline* ***10a****.*

Thus, analysis had to be conducted after derivatization. During the course of the following synthesis towards the final ligand structure phosphine oxide **20a** (or the corresponding regioisomer **22a**) was obtained as a side product (see scheme scheme 14). As this was an undesired product from the first point of view, this was selected to be used for the derivatization. The idea to differentiate between the isomers has been *N*-methylation and subsequent NMR and NOESY analysis (scheme 13).



Scheme 13. *N-methylation for distinguishing between the oxazoline regioisomers.(Top: NOESY interaction between benzylic proton and N-Me should be present; bottom: the same interaction is not possible).*

The interaction of interest is the one between the benzylic proton and the protons of the *N*-Me group. If the desired regioisomer was formed, these protons should interact over space as the benzylic proton is adjacent to the nitrogen atom. If the other regioisomer is present, this interaction cannot be found due to the large distance in between. Furthermore *N*-methylation should have a higher influence on the group adjacent to the nitrogen atom. If the desired regioisomer was formed, there should be a significant low-field shift of the benzylic proton and a smaller low-field shift of the *gem*-dimethyl protons, while for the wrong regioisomer the influence should be on the same level as all of these protons would be in β-position relative to the nitrogen atom.

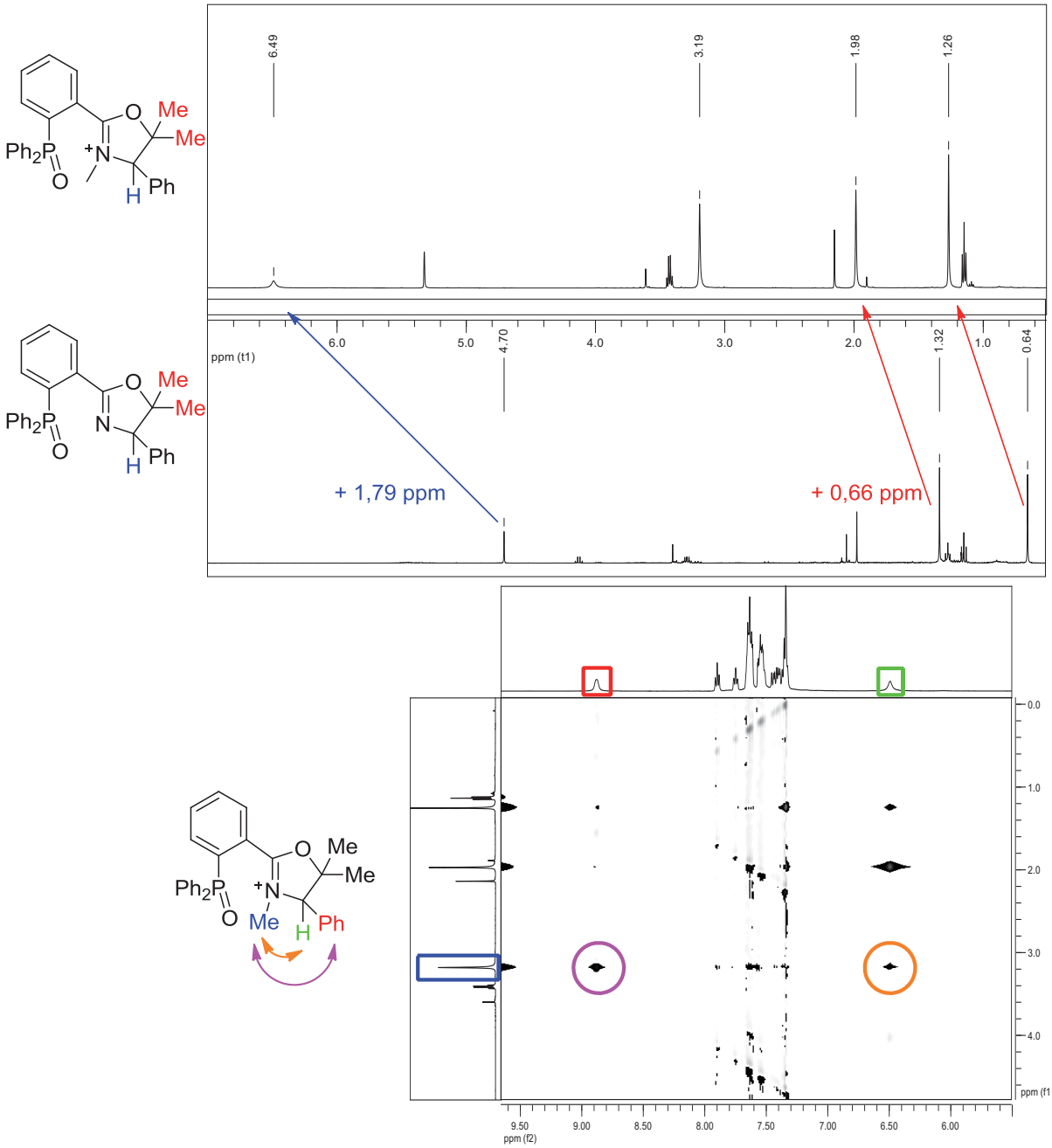
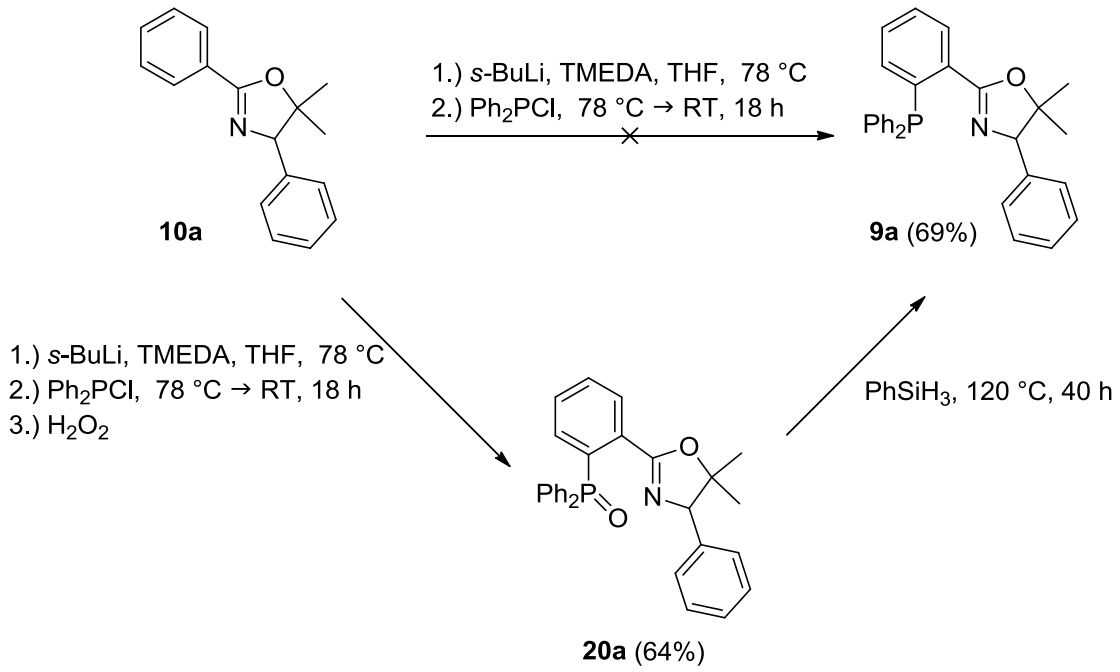


Figure 7. *Top: ^{1}H-NMR spectra after and before N-methylation; bottom: NOESY experiment.*

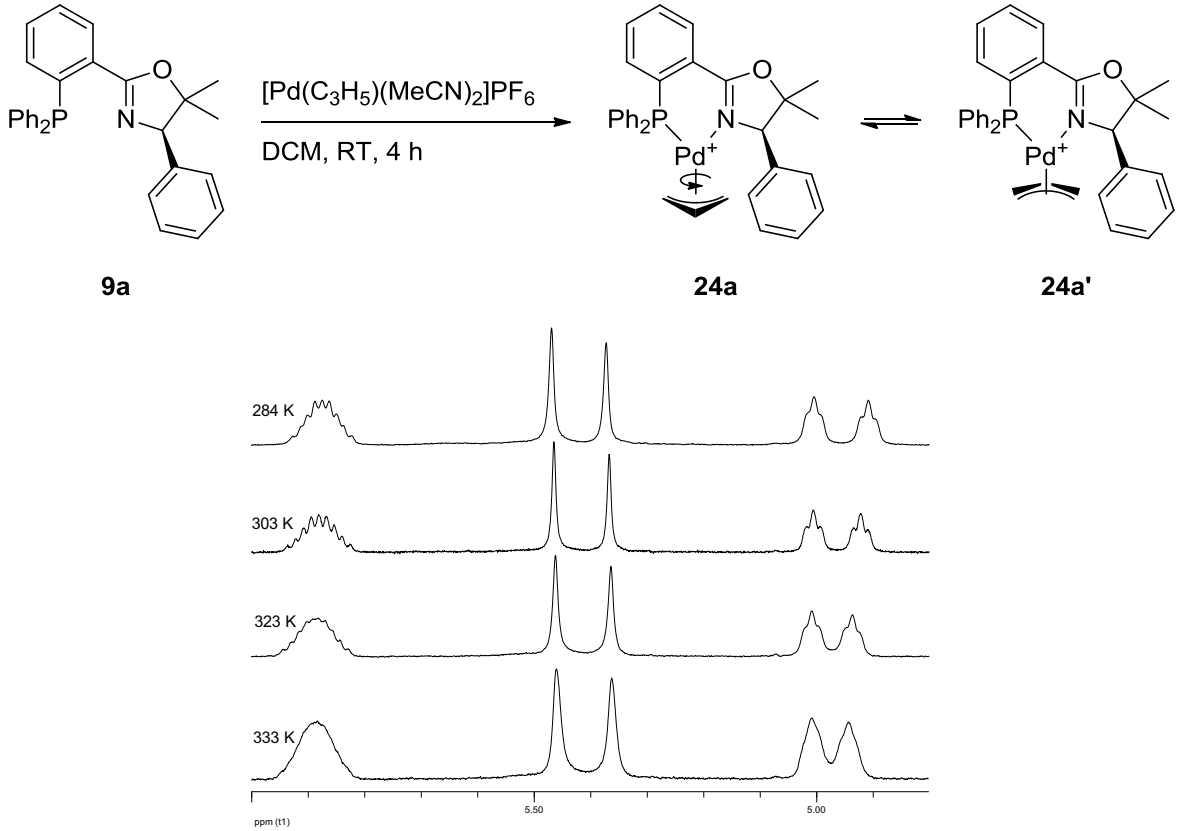
Comparison of the actual ^{1}H-NMR spectra before and after derivatization already gives a strong hint for the formation of the desired regioisomer. While the *gem*-dimethyl groups are low-field shifted by 0.66 ppm, the chemical shift of the benzylic proton changes by 1.79 ppm (Figure 7 top). This indicates that the two methyl groups are in γ-, the benzylic proton in α-position to the nitrogen atom. NOESY analysis of the *N*-methylated compound supports this observation as interaction between the *N*-methyl group and the benzylic proton has been observed (figure 7 bottom, orange circle). As described above this should only be possible if the desired regioisomer is present.

Next, the phosphine moiety had to be installed. First it was tested to achieve this aim by *ortho*-lithiation followed by reaction with chloro diphenylphosphine.[33] Although ^{31}P-NMR analysis of the crude mixture indicated formation of the desired compound, purification by column chromatography only gave the corresponding phosphine oxide **20a** in low amounts. Different purification attempts did not improve the outcome. Therefore **20a** was synthesized by treatment of the reaction mixture with H_2O_2. This species could be purified and isolated in 64% yield and subsequently reduced back to the desired phosphine species **9** using phenyl silane.[33] Thus, the synthesis of the final ligand structure could be accomplished in 12% overall yield (scheme 14).



Scheme 14. *Formation of phenyl-dimethyl-PHOX* ***9a****.*

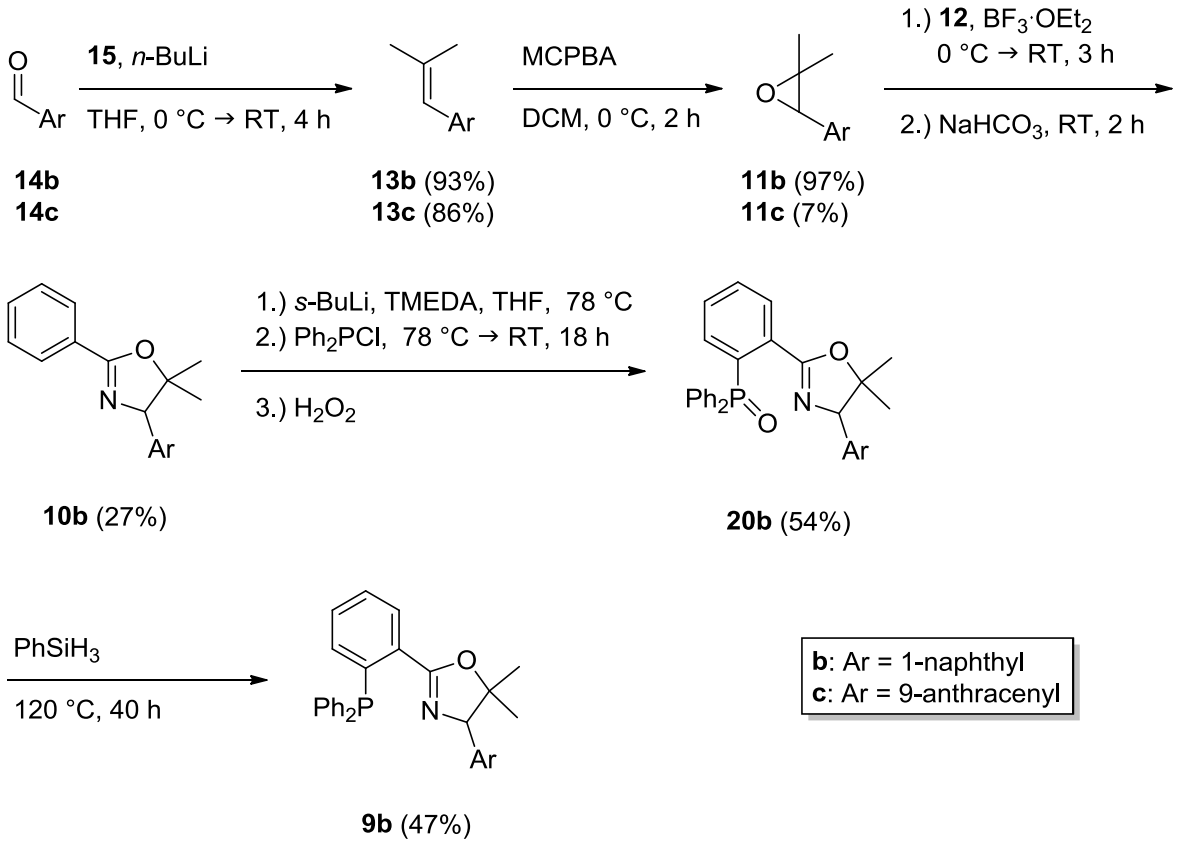
This ligand was then submitted to complexation with a palladium source to investigate its ability to form a palladium allyl species. For this purpose it was reacted with 1 equivalent of $[Pd(C_3H_5)(MeCN)_2]PF_6$ (scheme 15 top). When the resulting product was analyzed by ESI-MS the desired signal at *m*/*z* = 582 was observed. Interestingly NMR analysis of the formed complex showed different signals for the two possible diastereoisomers which can be formed (**24a** and **24a'**). This observation suggests that the additional *gem*-dimethyl substitution in the ligand backbone pushes the phenyl group on the stereogenic center more towards the palladium center and thus the allyl group, although unsubstituted, cannot rotate freely. When ^{1}H-NMR spectra were recorded at different temperatures sharper signals were found at lower temperature (scheme 15 bottom), which is in agreement with this proposal. A solvent dependence was observed as well. ^{31}P-NMR measurements gave two signals in $CDCl_3$ while only one signal was found in d_6-DMSO.



Scheme 15. *Top: synthesis of the palladium-allyl complex bearing ligand* ***9a****; bottom: ^{1}H-NMR spectra of the allyl protons of* ***24a*** *at varying temperatures (top: lowest temperature, bottom highest temperature).*

*Synthesis of further aryl-dimethyl-PHOX ligands **9***

According to the above described synthetic pathway further aryl-dimethyl PHOX derivatives were synthesized (scheme 16).



Scheme 16. *Synthesis of further aryl-dimethyl-PHOX ligands.*

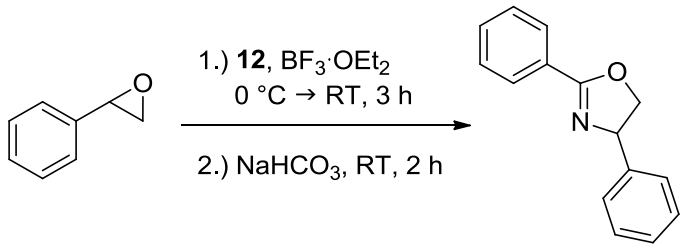
Synthesis of 1-naphthyl-dimethyl-PHOX **9b** was accomplished by the same route as for the phenyl equivalent **9a** giving an overall yield of 6%. However ligand **9c** bearing an anthracenyl substituent could not be accessed using this route. While the Wittig reaction did proceed in very good yield, the epoxide **11c** was obtained in only 7% yield. Therefore this ligand synthesis was be finished.

1.3.2.2 Racemic Ar-PHOX Ligands

*Synthesis of Ph-PHOX ligand **27a***

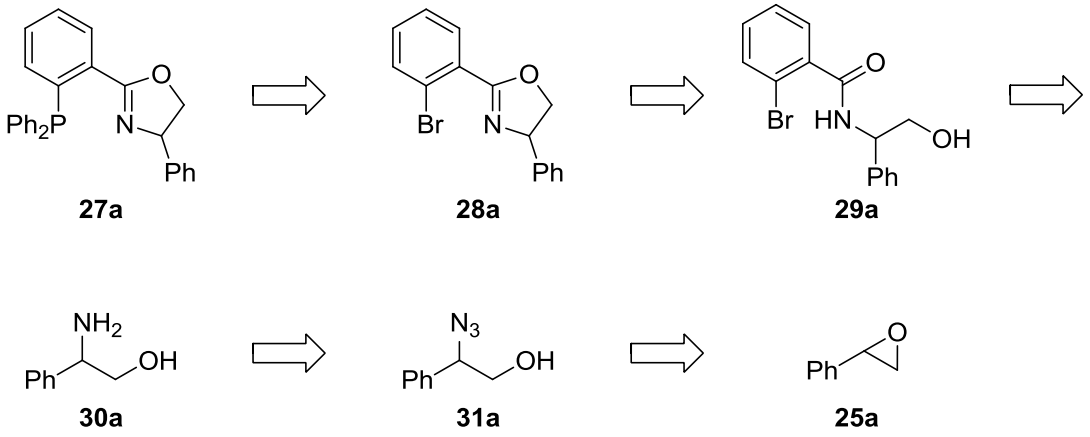
Besides the novel PHOX ligands which were planned to be tested by the ESI-MS screening method, literature-known Ph-PHOX[33] was supposed to be synthesized for comparison. In a first attempt the same synthetic pathway as for the Ar-dimethyl-PHOX ligands **9**, starting

from commercial available styrene oxide **25a**, was tested (scheme 17). Unfortunately the desired oxazoline could only be obtained in very poor yield and not be purified. Attempts to convert it into the PHOX ligand by *ortho*-lithiation failed, most likely due to the residual impurities. When the Ritter reaction was carried out using 2-bromo benzonitrile to facilitate the subsequent *ortho*-lithiation no product was formed at all. Changing the Lewis acid from BF_3 to BCl_3 yielded in no desired product formation as well.



Scheme 17. *Attempt to synthesize 2,4-diphenyl oxazoline via Ritter reaction.*

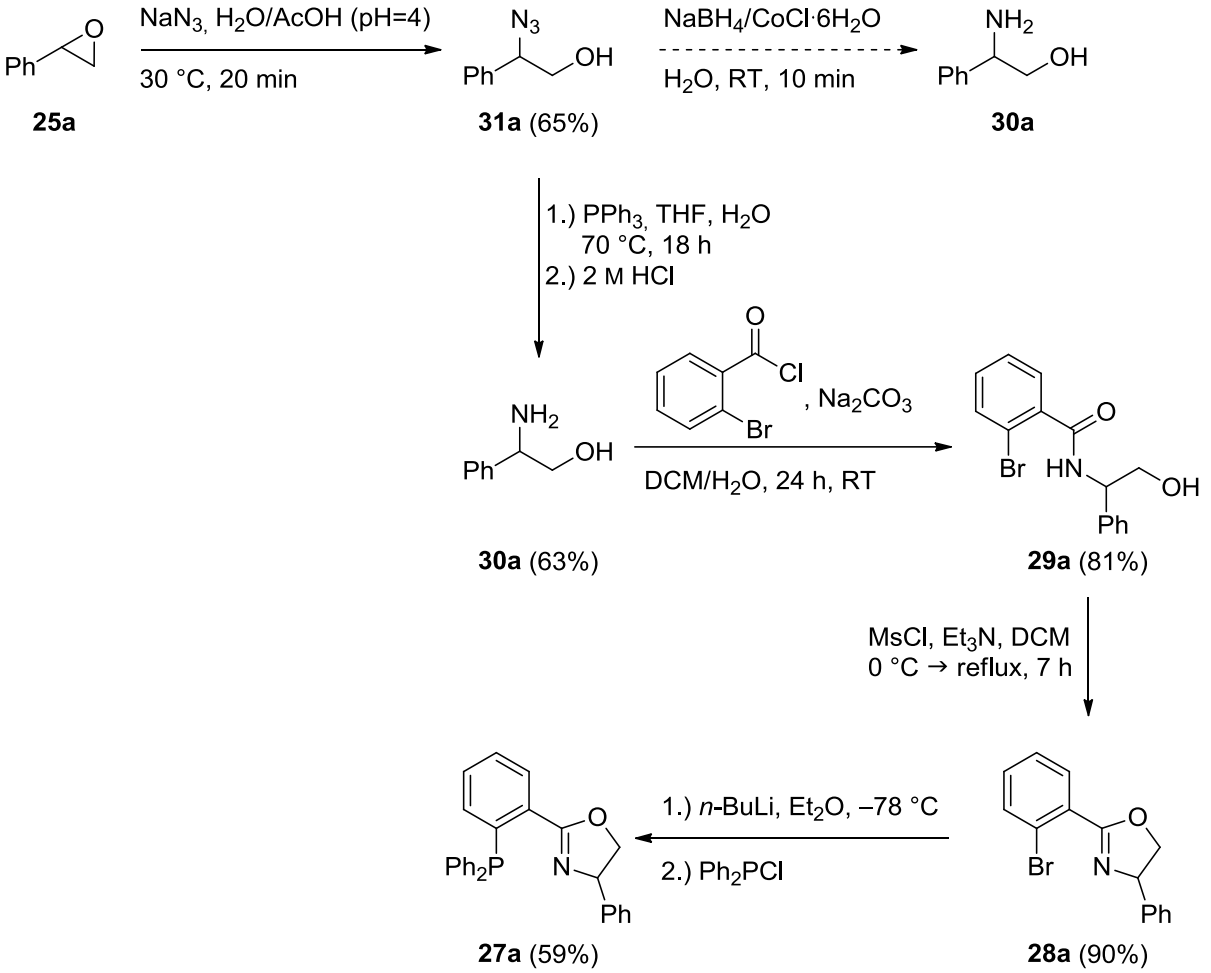
Thus, the synthetic route had to be changed. Common PHOX synthesis is very often performed starting from the corresponding amino alcohol.[26d,33-34] Therefore a synthetic route including the synthesis of racemic amino alcohol **30a** according to the retrosynthetic analysis shown in scheme 18 was tested.



Scheme 18. *Retrosynthetic analysis of Ph-PHOX (**27a**) via amino alcohol formation.*

Formation of the desired ligand **27a** was planned to be accomplished by lithium-halogen exchange and subsequent treatment with chloro diphenylphosphine. Oxazoline formation should be obtained starting from the corresponding benzamide (**29a**) which is available from 2-amino-2-phenylethanol (**30a**). The synthesis of the amino alcohol could be achieved by

reduction of the corresponding azido-alcohol which can be obtained by epoxide opening with sodium azide of compound **25a**.

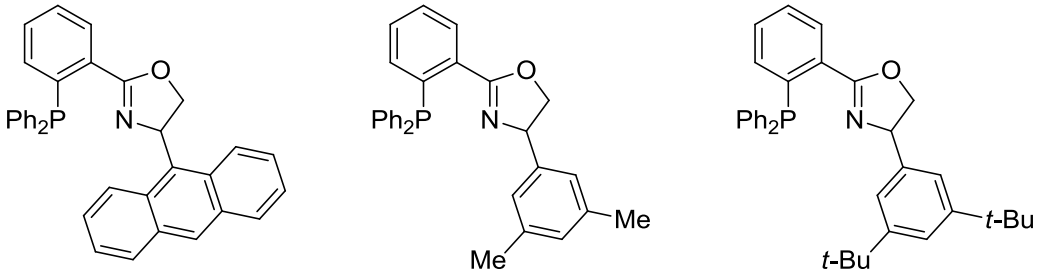


Scheme 19. *Synthesis of Ph-PHOX ligand* ***27a****.*

Starting from commercially available styrene oxide (**25a**) the formation of azido alcohol **31a** in aqueous acidic media proceeded in 65% yield.[35] Reduction of the azido functionality was first tried using $NaBH_4$ in the presence of CoCl.[36] Unfortunately the desired amino alcohol was only formed in low yields and the resulting crude mixture could not be purified. Therefore a Staudinger reaction was performed and the desired compound **30a** could be obtained.[37] It was found that upon acidic work-up an increased yield could be obtained since the formation of side-products during the work-up was suppressed.[38] According to a literature-known procedure,[34] oxazoline **28a** was formed via benzamide synthesis and subsequent cyclization upon use of MsCl in 73% yield over two steps. After *ortho*-lithiation and phosphine introduction racemic Ph-PHOX **27a** was obtained in an overall yield of 18% (scheme 19). In contrast to the dimethyl-PHOX ligands this time purification could be carried

out at the stage of the final ligand and no oxidation-purification-reduction sequence was necessary.

Furthermore it was planned to test PHOX ligands without a *gem*-dimethyl substitution in the backbone but bearing substituents on the aryl ring at the stereogenic center. This kind of ligands would be of particular interest since the corresponding enantiopure amino acids are not commercially available or very expensive. Thus, they seem to be well-suited to be evaluated in a racemate screening. As examples of such Ar-PHOX ligands 9-anthracenyl-PHOX and two 3,5-dialkyl substituted Ar-PHOX ligands were synthesized and tested (figure 8). Such catalysts, bearing additional substituents on the aryl-ring might show an increased selectivity due to the increased sterical demand close to the stereogenic center.

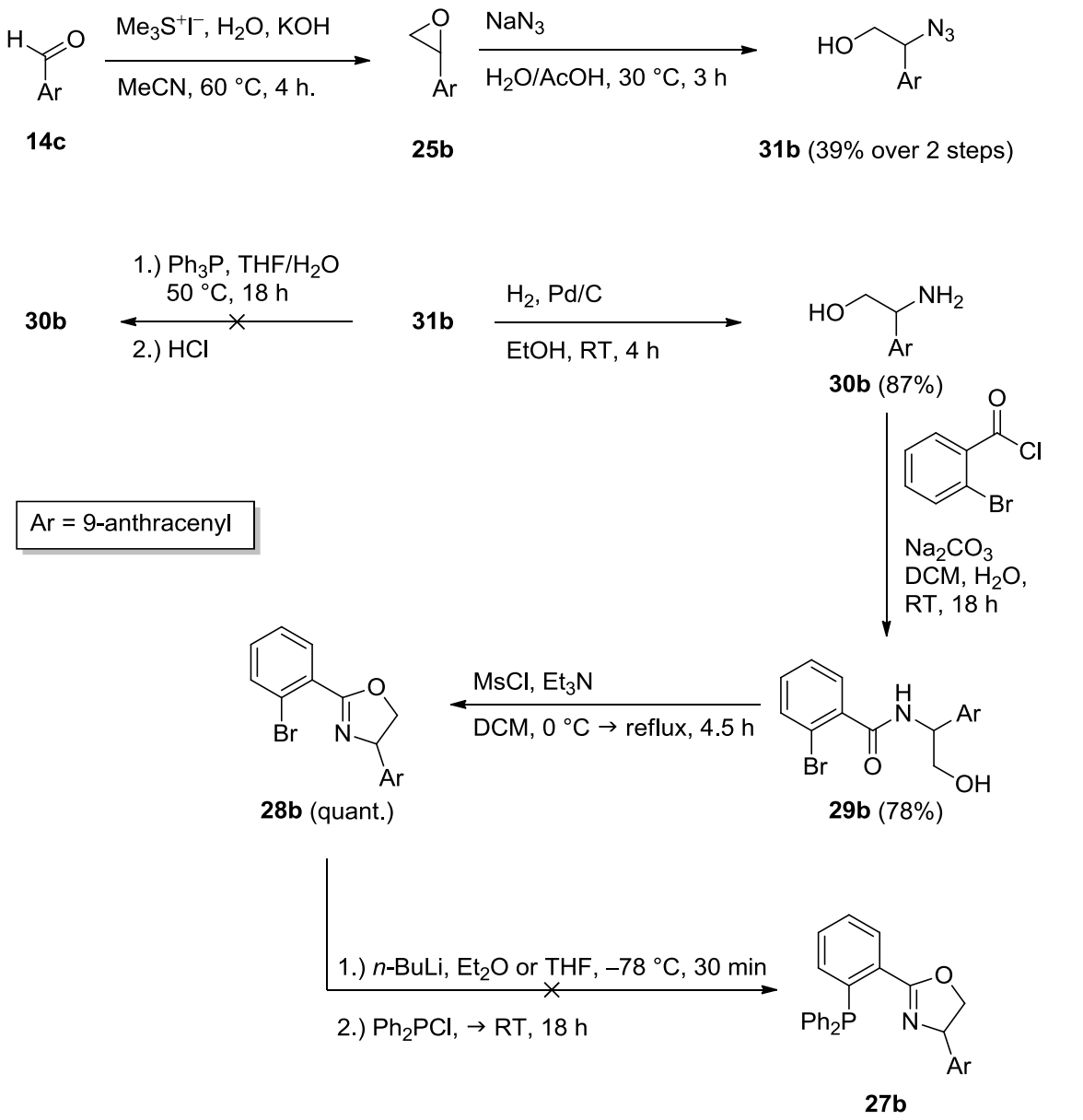


27b **27c** **27d**

Figure 8. *Ar-PHOX ligands with increased sterical demand on the aryl moiety.*

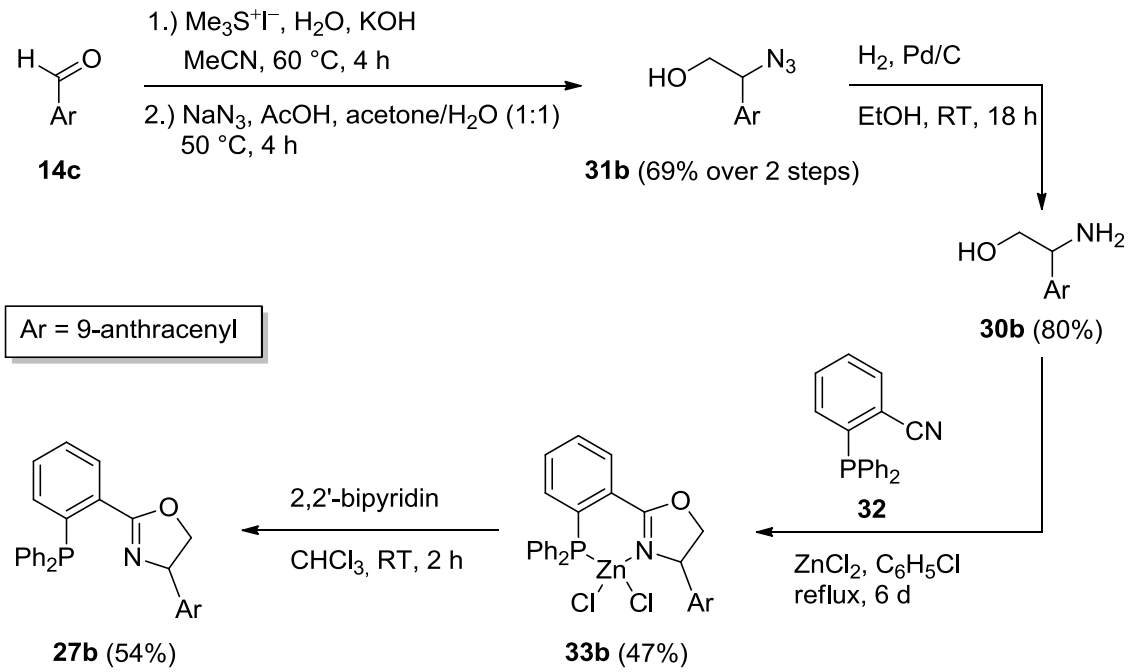
*Synthesis of 9-anhtracenyl-PHOX ligand **27b***

Following the same synthetic route as used for Ph-PHOX **27b**, 9-anthracenyl-PHOX **27b** was prepared (scheme 20). Starting point was the corresponding anthracene-9-carbaldehyde (**14c**). This was transformed into the epoxide **25b** by a Corey-Chaykovsky reaction[39] which was subsequently ring opened by NaN_3. The epoxidation did not proceed with full conversion and the epoxide could not be separated from the residual aldehyde. However, epoxide opening did work as well with unreacted aldehyde present in the reaction mixture and the azido alcohol could be easily separated from the aldehyde by column chromatography. When the reduction to the amino alcohol was carried out under Staudinger conditions no conversion towards the amino alcohol was observed. Reduction by hydrogenation with activated Pd/C[40] gave the desired compound **30b** in high yield. Benzamide formation was accomplished upon reaction with benzyl chloride and subsequent cyclization gave the oxazoline **28b** in quantitative yield. Unfortunately installation of the phosphine moiety by lithium-halogen exchange failed under various conditions tested.



Scheme 20. *Attempt to synthesize 9-anthracenyl-PHOX ligand* ***27b****.*

Consequently the synthetic route was changed. As described by PFALTZ and co-workers PHOX ligands can as well be obtained by reaction between an amino alcohol and 2-(diphenylphosphino)benzonitrile **32** in the presence of $ZnCl_2$.[33] Since the amino alcohol **30b** was already obtained, this approach was tested (scheme 21).

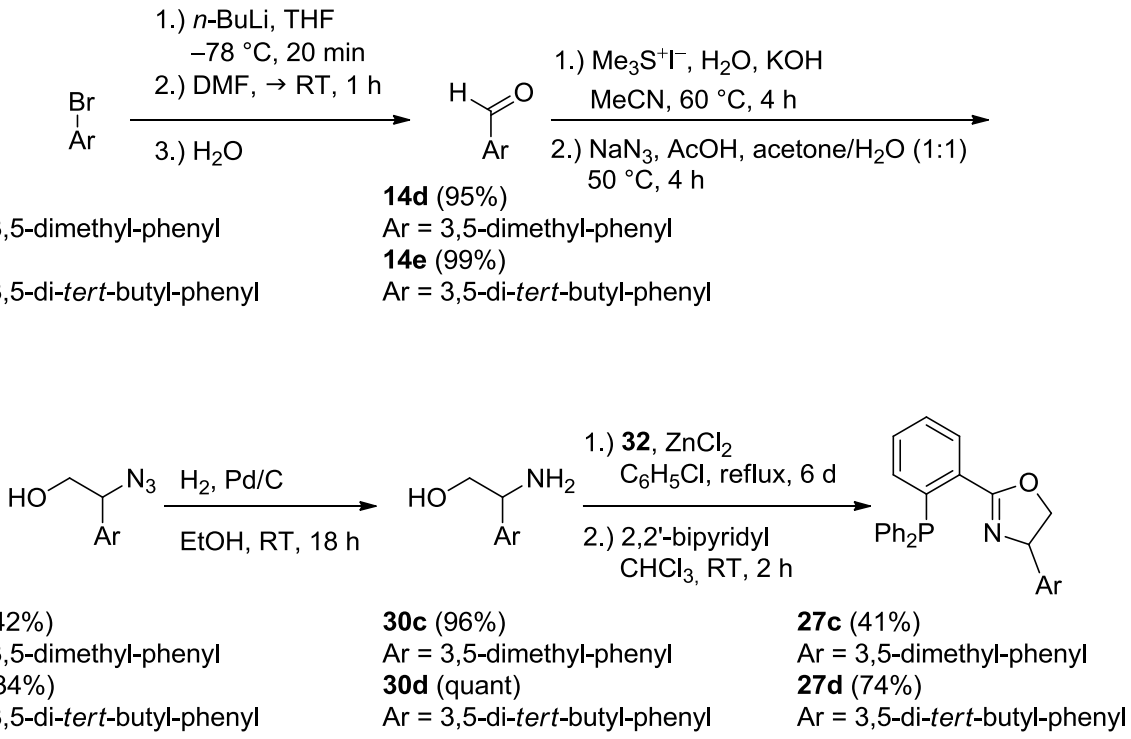


Scheme 21. *Synthesis of 9-anthracenyl-PHOX ligand* ***27b****.*

Since the synthesis of azido alcohol **31b** as shown in scheme 20 did only proceed in 39% yield over two steps, the reaction conditions for the epoxide opening were optimized. Here a 1:1 mixture of acetone and water was used as solvent and the reaction was carried out at elevated temperature. In this way the yield of **31b** was increased to 69% over two steps. Subsequent hydrogenation gave the amino alcohol **30b** as described above. Oxazoline formation according to the literature described protocol yielded the zinc-complex **33b**. 2-(diphenylphosphino)benzonitrile **32** was easily obtained from 2-bromobenzonitrile.[41] Removal of the zinc dichloride was achieved by reacting **33b** with bipy to give the 9-anthracenyl-PHOX **27b** ligand in 54% yield. Therefore the synthesis of **27b** succeeded with an overall yield of 14% starting from anthraldehyde (**14c**).

Synthesis of 3,5-dialkyl-phenyl-PHOX ligands ***27c*** *and* ***27d***

According to the synthesis shown in scheme 21, two 3,5dialkyl-phenyl-PHOX ligands were synthesized (scheme 22). Although the aldehydes **14c** and **14e** are commercially available they were synthesized as they are fairly expensive from commercial sources. These syntheses were accomplished by formylation of the corresponding aryl bromide species **34** in high yields. All following steps proceeded as described above allowing an easy access to the desired racemic PHOX ligands **27c** and **27d**.



34a
Ar = 3,5-dimethyl-phenyl
34b
Ar = 3,5-di-*tert*-butyl-phenyl

14d (95%)
Ar = 3,5-dimethyl-phenyl
14e (99%)
Ar = 3,5-di-*tert*-butyl-phenyl

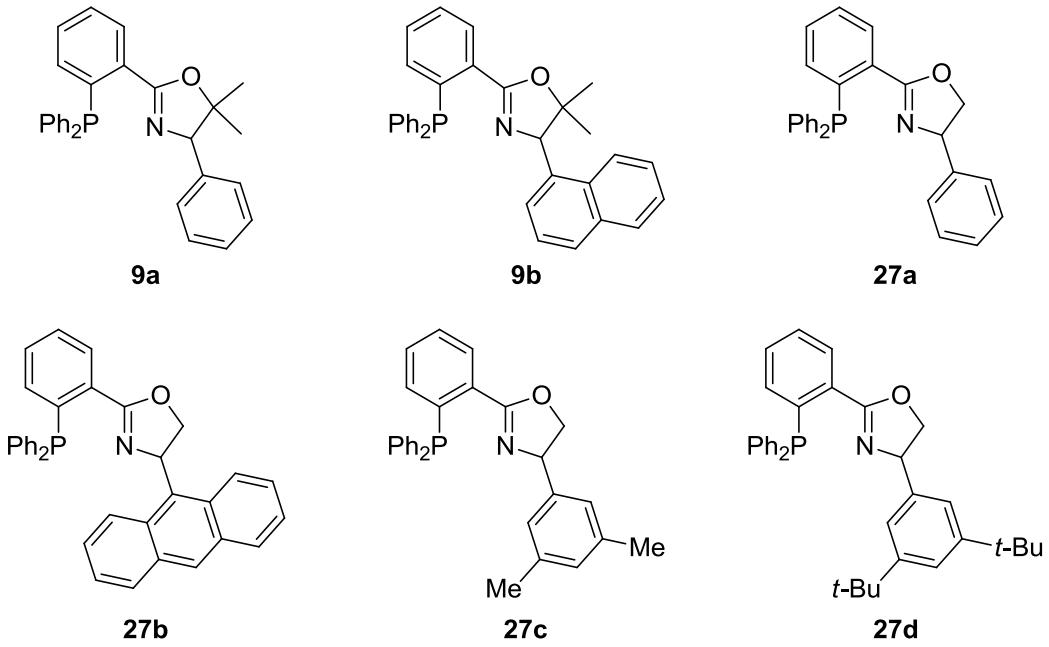
31c (42%)
Ar = 3,5-dimethyl-phenyl
31d (34%)
Ar = 3,5-di-*tert*-butyl-phenyl

30c (96%)
Ar = 3,5-dimethyl-phenyl
30d (quant)
Ar = 3,5-di-*tert*-butyl-phenyl

27c (41%)
Ar = 3,5-dimethyl-phenyl
27d (74%)
Ar = 3,5-di-*tert*-butyl-phenyl

Scheme 22. *Synthesis of aryl-PHOX ligands* ***27c*** *and* ***27d****.*

Figure 9 summarizes the different racemic PHOX ligands which were synthesized during these studies.



9a **9b** **27a**

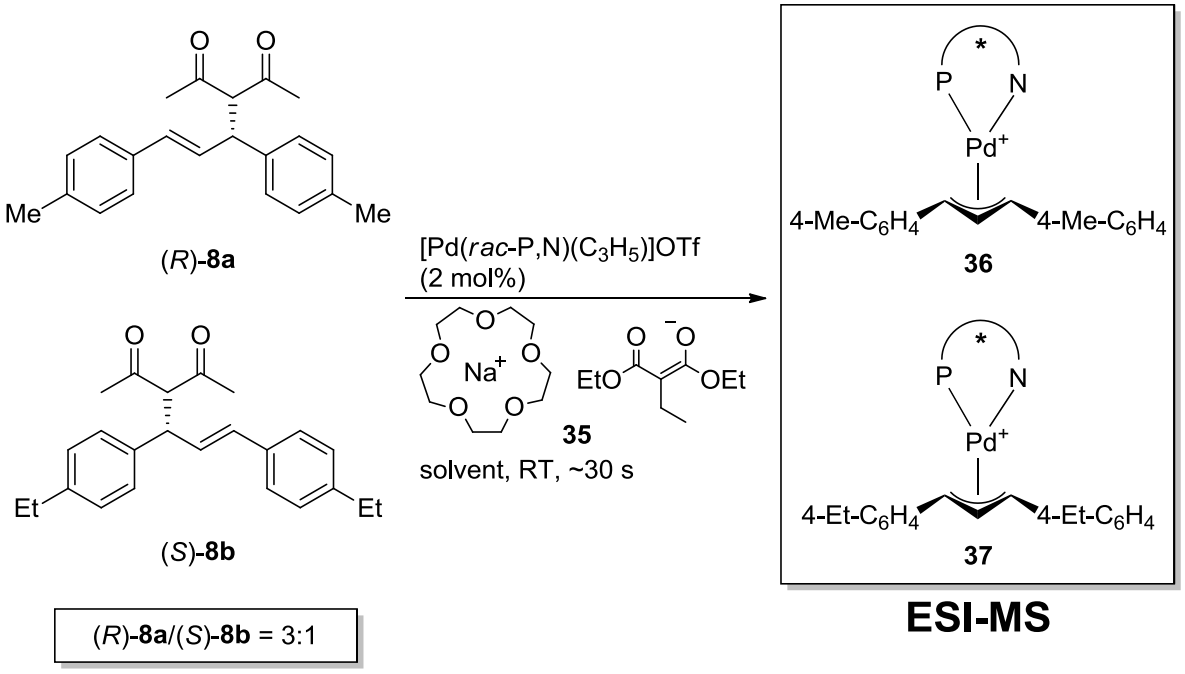
27b **27c** **27d**

Figure 9. *Summary of successfully synthesized PHOX ligands.*

1.4 Screening Results

1.4.1 Screening Conditions

The screening of racemic catalysts mixtures was carried out in analogy to the protocol of the ESI-MS screening of enantiopure catalysts for selectivity determination in the palladium catalyzed allylic substitution reaction (scheme 23).[20] The precatalyst was obtained from pre-complexation of the corresponding P,N-ligand with [Pd(C_3H_5)(MeCN)]OTf prior to the actual screening. A catalyst loading of 2 mol% was applied. To activate the precatalyst 5 mol% of [Na([15]crown-5)][CEt(CO_2Et)$_2$] (**35**) was added. The quasi-enantiomeric substrates were mixed in a ratio of approximately (*R*)-**8a**/(*S*)-**8b** = 3:1. The ratio did not have to be at exactly 3:1 as equation 1 for the calculation of the selectivity can be used for varying ratios. As well it was possible to use a substrate mixture with (*S*)-**8b** as the major quasi-enantiomer ((*R*)-**8a**/(*S*)-**8b** = 1:3). After a reaction time of about 30 seconds an aliquot of the reaction mixture was diluted 200-fold with the corresponding solvent to terminate the reaction. The selectivity was determined by analysis of the signals corresponding to the intermediates **36** and **37** and subjection of this ratio to equation 1.



Scheme 23. *Screening conditions.*

It has been reported previously that the counter ion of the precatalyst has an influence on the outcome of the reaction in terms of enantiomeric excess.[42] Use of an OTf^- counter ion for example leads to a higher catalyst selectivity compared to a Cl-anion. Not only the selectivity

was influenced but at the same time as well the detectability of the intermediates by ESI-MS was affected too. When for example ligand **9a** was applied to the screening conditions the desired intermediates **36a** and **37a** could be observed when the counter ion was OTf^- while no intermediates were detected for PF_6^- as counter ion (figure 10).

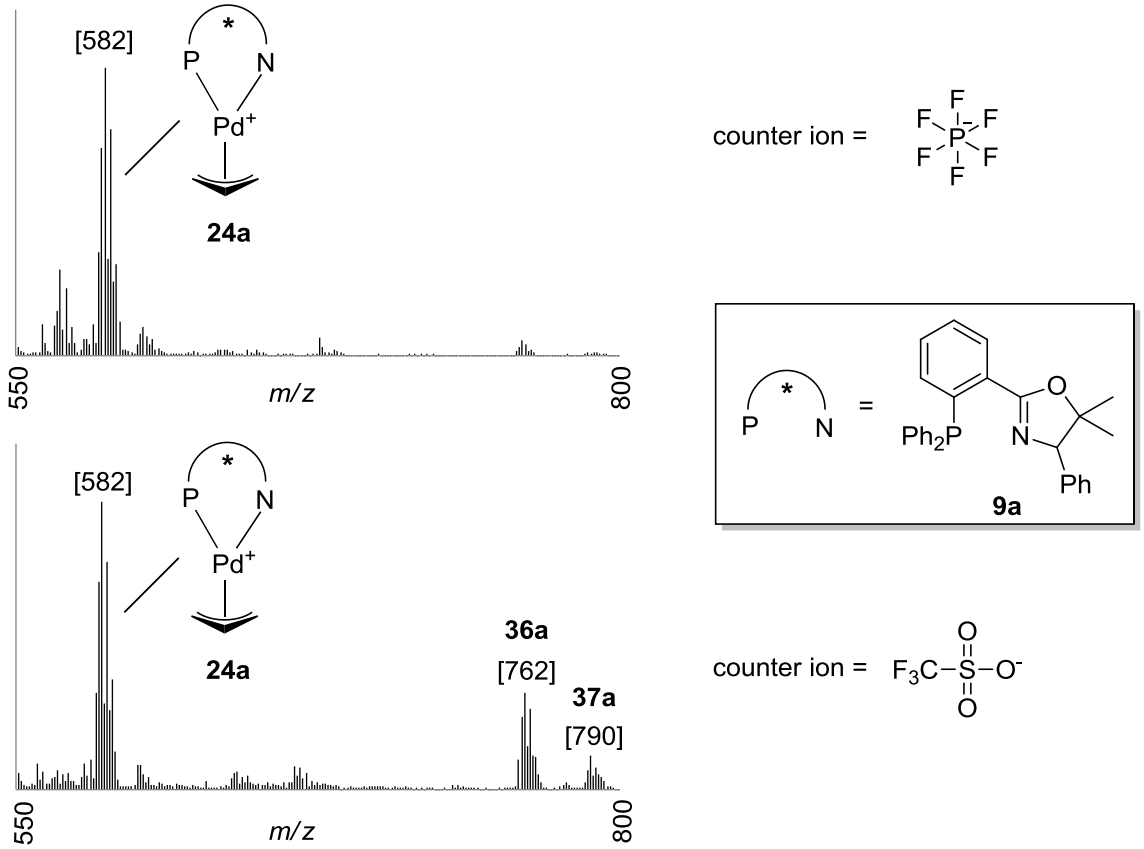
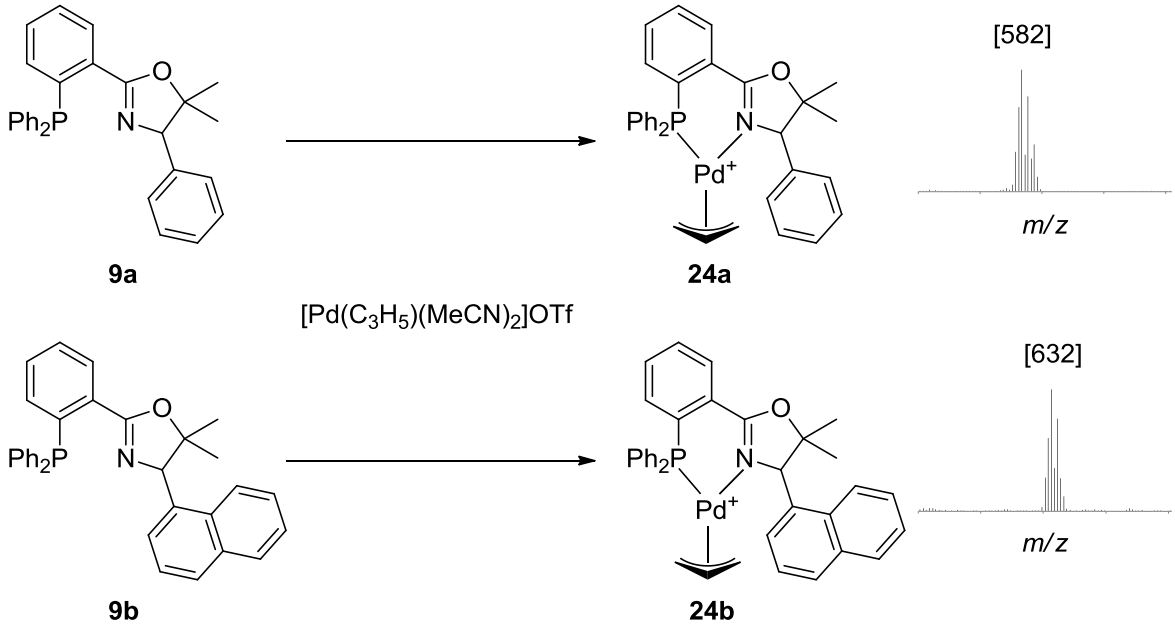


Figure 10. *Influence of the counter ion on the detectability of the reaction intermediates (top: counter ion = PF_6^-; bottom: counter ion = OTf^-.*

1.4.2 Screening of Racemic Aryl-Dimethyl-PHOX Ligands

The new aryl-dimethyl-PHOX ligands **9** were intended to be evaluated in the palladium-catalyzed allylic substitution. The additional *gem*-dimethyl substitution in the 5-position of the oxazoline backbone should force the aryl substituent in 4-position more towards the reactive center due to steric demand. As shown in chapter 1.3.2 (scheme 15) initial NMR experiments had already supported this assumption. The actual influence on the selectivity was evaluated by an ESI-MS racemate screening approach.

It was found that both ligands do form the desired precatalyst complex **24** upon reaction with $[Pd(C_3H_5)(MeCN)]OTf$. The desired mass-signals were observed by ESI-MS analysis of the precatalyst solution (scheme 24).

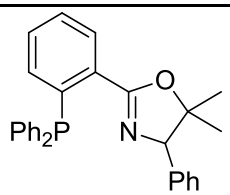
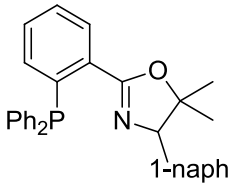
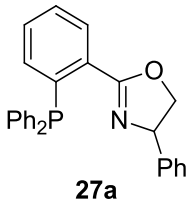
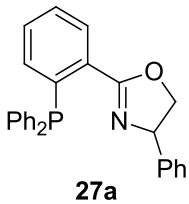


Scheme 24. *Precatalyst formation using aryl-dimethyl-PHOX ligands* ***24a*** *and* ***24b****.*

When the precatalysts were mixed with the quasi-enantiomeric substrates in DCM the desired intermediates **36a** and **37a** were observed. The theoretical *ee´*s induced by the catalysts were calculated according to eq. 1 (table 1, entries 1 and 2). It was found that the aryl-dimethyl-PHOX ligands show a very low selectivity in the allylic substitution reaction. For ligand **9a** an enantiomeric excess of 21% was calculated. For ligand **9b** an even lower selectivity was found (5% *ee*). Obviously, the two geminal methyl groups, which alter the conformation of the oxazoline ring by interaction with the adjacent aryl substituent, have a detrimental effect on the enantioselectivity. Furthermore it was observed that the ratio of intermediates detected by ESI-MS was not constant throughout multiple measurements. Thus, the calculated *ee* values given in table 1 are mean-values of four (for ligand **9b**) respectively five (for ligand **9a**) measurements (for the single screening results see chapter 8.2). These findings match the suggested low sensitivity of the screening method in the low *ee* region as described in chapter 1.2.2. For comparison the literature-known Ph-PHOX ligand **27a** was tested as well (entries 3 and 4). When the screening was carried out in DCM an enantiomeric excess of 56% was calculated, in toluene 72% *ee* was found. This shows that the screening method also allows evaluation of solvent effects. The observation that higher selectivities can be obtained in toluene compared to DCM was already reported previously.[42b] However it was shown as well that significantly shorter reaction times can be achieved in DCM compared to toluene,[43] which makes the reaction more viable. Therefore the catalyst screenings in this work were carried out in DCM as solvent. The screening results obtained for ligand **27a** were constant

throughout multiple runs. Again this is in agreement with the in chapter 1.2.2 postulated sensitivity of the method. For more selective catalysts the screening seems to be significantly more robust than for less selective catalysts.

Table 1. *ESI-MS screening results of rac-**9a,b** and rac-**27a**.*

Entry	Ligand	Solvent	$ee^{[a]}$ [%]	$s^{[a]}$
1	 **9a**	DCM	5	1.11
2	 **9b**	DCM	21	1.53
3	 **27a**	DCM	56	3.55
4	 **27a**	toluene	72	6.14

[a]: Calculated from eq. 1.

1.4.3 Verification of the Results Obtained for Racemic Ph-PHOX and Aryl-Dimethyl-PHOX Ligands

Having obtained the results from the racemate screening as described in table 1, the *ee* values had to be verified. For this purpose an ESI-MS screening of the enantiopure catalysts was performed.[20] The corresponding enantiomerically pure ligands were obtained by semi-preparative HPLC purification of the corresponding phosphine oxides and subsequent reduction using $PhSiH_3$ to the desired enantiopure ligands. The results from this screening are shown in figure 11 (red bars) and compared to the values obtained from the racemate screening (blue bars).

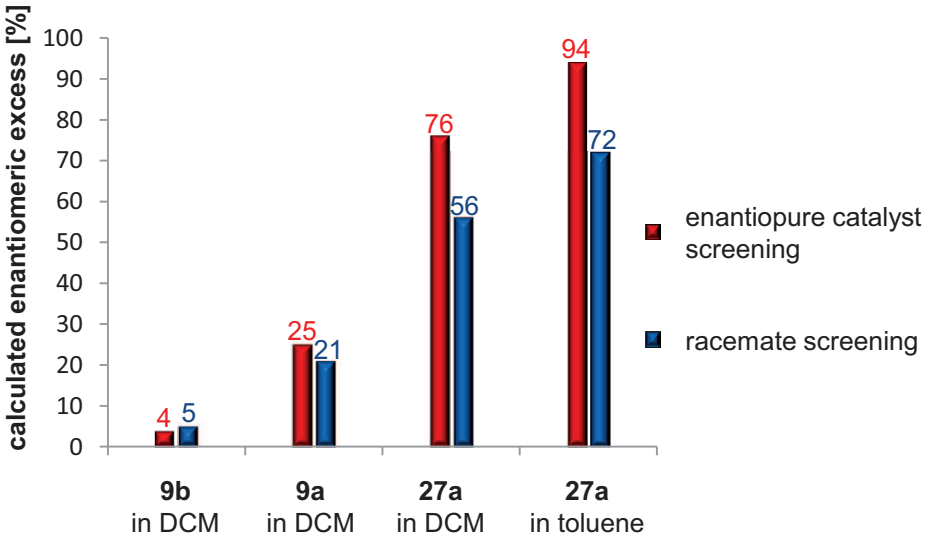


Figure 11. *Comparison of the screening results.*

Evidently, the enantioselectivities obtained with the enantiopure catalysts deviated significantly from the values calculated for the racemic catalysts. However, the enantioselectivity order was the same, demonstrating that the most selective catalysts and the best conditions (e.g., choice of solvent) can be readily identified by screening racemic catalysts. Both methods have shown that the PHOX derivative **27a** induces the highest selectivity from the ligands tested. As well the same solvent effect was observed by both screening methods. Interestingly the difference between the *ee*-values increases with increasing selectivity of the corresponding catalyst. When the actual *ee* values, obtained from the screening of enantiopure catalysts, were plotted against the values from the racemate screening, surprisingly a perfect linear correlation between the two data sets was found (figure 12).

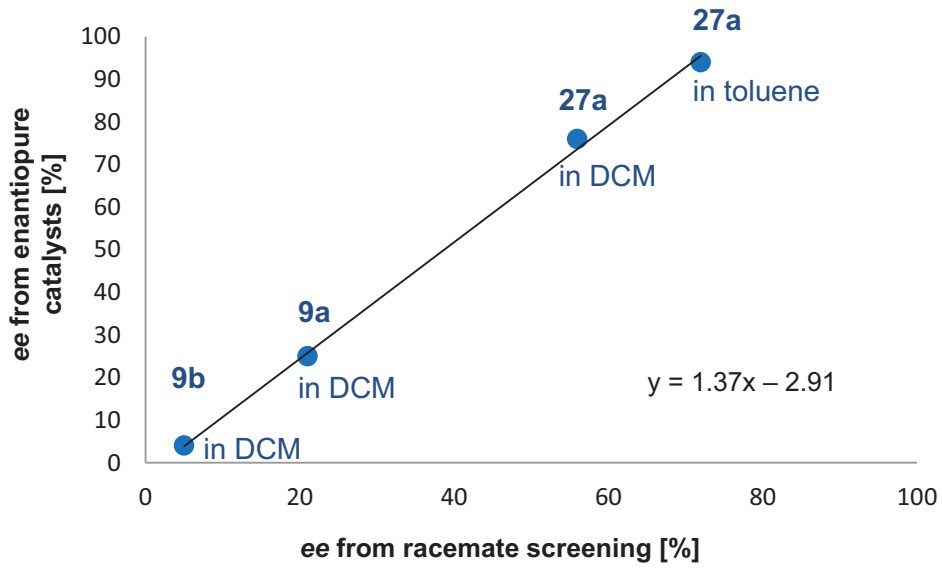


Figure 12. *Correlation between the enantiomeric excesses obtained by the two screening methods.*

The linear relation between the values was of excellent accuracy (R^2 = 0.998). Thus, it should be possible to determine the actual enantioselectivity of a chiral catalyst from its racemic form by applying the correction function obtained by linear regression. When the selectivity values obtained by the two methods were compared, an exponential relation was found (figure 13). The goodness of fit was slightly lower than the one shown above but still in a very good range (R^2 = 0.993). However, as the linear relation shown in figure 12 is more easy to handle and of slightly better accuracy, the equation obtained from this regression was chosen as correction function.

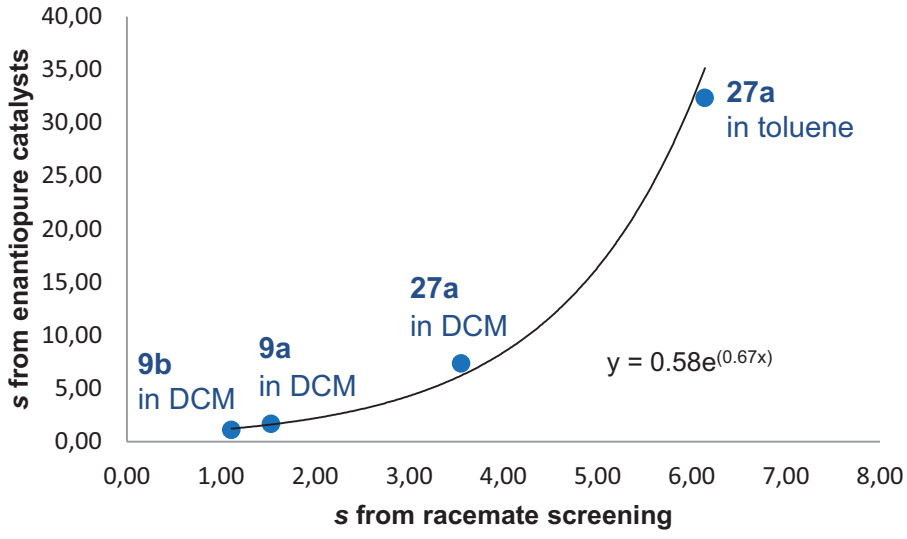


Figure 13. *Correlation between the selectivities obtained by the two screening methods.*

1.4.4 Screening of Racemic Aryl-PHOX Ligands

Having established a reliable ESI-MS screening method for the determination of a catalyst´s selectivity by testing its racemic form, further ligands were evaluated in the palladium-catalyzed allylic substitution reaction. As *gem*-dimethyl substitution in the 5-position of the oxazoline backbone of the ligands shown in chapter 1.4.2 has a deleterious effect on the selectivity of the resulting catalysts it was decided to test Ar-PHOX ligands with an increased sterical demand on the aryl ring on the stereogenic center. Three ligands of that kind were chosen for the ESI-MS racemate screening (**27b**-**c**, figure 14).

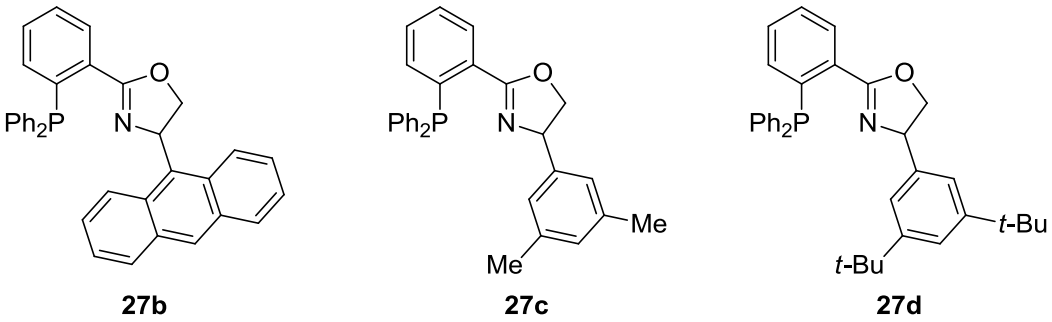
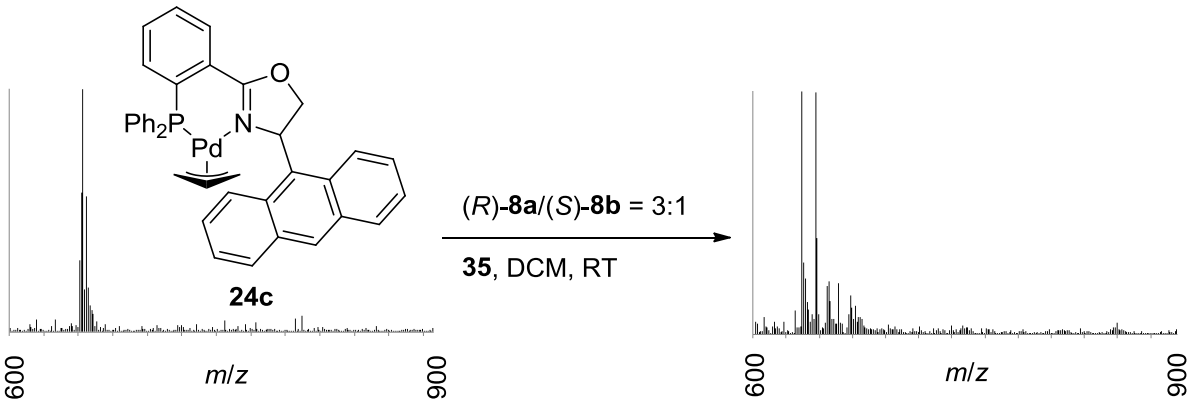


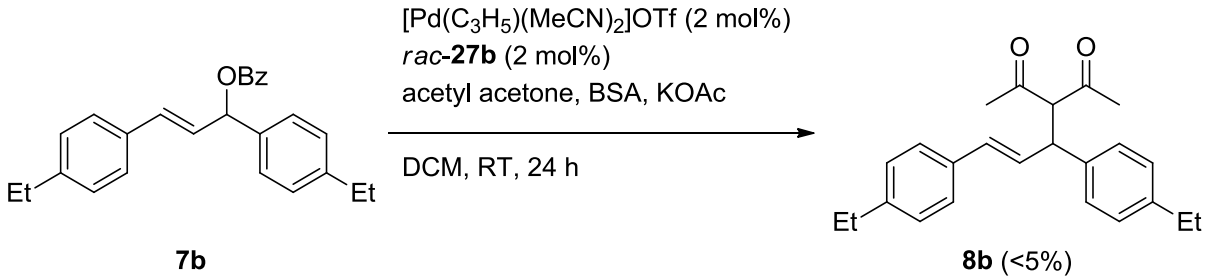
Figure 14. *Ar-PHOX ligands to be evaluated by ESI-MS screening of their racemic forms.*

The first ligand which was tested was the 9-anthracenyl PHOX **27b**. Upon complexation with $[Pd(C_3H_5)(MeCN)_2]OTf$ formation of the desired precatalyst **24c** was observed by ESI-MS. However, when the quasi-enantiomeric substrate mixture was added, the desired catalysis intermediates could not be detected but only decay of the precatalyst was observed (scheme 25).



Scheme 25. *ESI-MS screening of rac-**24c**.*

When a preparative reaction using racemic ligand **27c** was carried out to evaluate the activity of the resulting catalyst, less than 5% product had formed even after 24 h (scheme 26). Apparently, the sterically demanding anthracenyl-substituted ligand does not form an active catalyst.



7b **8b** (<5%)

Scheme 26. *Preparative allylic alkylation using rac-**27c**.*

Although this result did not lead to the finding of a selective catalyst it shows that an inactive catalyst does not give any misleading signals in the screening. Furthermore it proves that the detected signals exclusively correspond to the desired reaction intermediates and not to any kind of undesired background reaction which could affect the intermediate ratio.

The two other ligands which were evaluated are the ones bearing a 3-5-dialkyl substitution on the aryl ring in the 4-position of the oxazoline moiety. PREGOSIN and co-workers previously reported a beneficial effect of *meta*-substituents on aryl groups in enantioselective hydrogenations, allylic substitutions and Heck reactions.[44] Ligands **27c** and **27d** were therefore screened in DCM under the conditions described above. The results of this screening are summarized in table 2. For comparison the result for Ph-PHOX **27a** is listed as well (entry 3).

Table 2. *ESI-MS screening results of rac-**27c** and rac-**27d**.*

Entry	Ligand	*ee*[a] [%]	*s*[a] [%]	Corrected *ee*[b] [%]
1	3,5-dimethyl-phenyl PHOX **27c**	56	3.55	74
2	3,5-di-*tert*-butyl-phenyl PHOX **27d**	61	4.13	81
3	phenyl PHOX **27a**	56	3.55	74

[a]: Calculated from eq. 1; [b]: calculated from the correction function shown in figure 12.

As shown table 2, ligand **27c** did induce the same enantioselectivity as the corresponding Ph-PHOX. This indicates that a relatively small methyl-substitution in the *meta*-position of the phenyl ring does not have an influence on the selectivity of the catalyst. However when ligand **27d** was tested in the screening a slightly increased *ee* was calculated. The bulky *meta tert*-butyl substituents apparently have a small but distinct positive effect on the enantioselectivity of the catalyst. The 61% *ee* found correspond to a corrected value of 81% *ee* (calculated from the correction function shown in figure12). To verify this finding the enantiopure catalyst was tested as well in an ESI-MS screening. And indeed an enantiomeric excess induced by the catalyst of 82% was found. When the correction function for the selectivity factor shown in figure 13 was applied to the *s*-value shown in table 2 a selectivity factor of $s = 9.23$ was calculated. Comparison with the result from the ESI-MS screening of the enantiopure catalyst ($s = 10.11$) again showed very good agreement.

1.4.5 Elucidation of the Reason for the Difference Between the Results Obtained from Racemic and Enantiopure Catalyst Screening

The findings described above show that due to the correction function, especially the one found by linear regression (see figure 12), the screening method indeed allows for the exact determination of the *ee* induced by a catalyst in the preparative reaction by testing its racemic form. However there is still one question unanswered: why do the *ee* values obtained from the racemate screening differ from the values determined from the enantiopure catalyst?

As described in chapter 1.2.1, equation 1 for the calculation of the selectivity of a catalyst was derived under the assumption of pseudo zeroth-order conditions.[5] It was assumed that the *ee* difference results from a deviation from these ideal conditions. If the turnover rates of the two catalyst enantiomers show some dependence on the substrate concentration, the amount of intermediate **36** derived from the more abundant quasi-enantiomer **8a** should be higher than that under pseudo-zeroth-order conditions, resulting in a lower predicted selectivity when equation 1 is applied. In this case, the observed linear correlation would imply that the deviation from pseudo-zeroth-order conditions affects the *ee* values of the different catalysts by the same degree. To verify this assumption the racemate screening of ligand **27d** was carried out at different substrate-to-catalyst (S/C) ratios (table 3).

Table 3. *ESI-MS screening at varying catalyst loadings.*

Entry	S/C	Intermediate ratio 36:37	Calculated *ee* [%]
1	25:1	2.13	58
2[a]	50:1	2.04	61
3[b]	100:1	1.87	68
4[b]	200:1	1.64	76

[a]: Standard screening conditions as shown in scheme23; [b]: low signal intensity.

Indeed the assumed dependence of the screening results on the catalyst loadings has been observed. When the S/C-ratio was raised from 25:1 to 200:1 the calculated enantiomeric excess increased from 58% *ee* to 76% *ee* indicating that for lower catalyst loadings the difference between the two screening methods is smaller. However, due to the low signal intensity observed with S/C-ratios of ≥100:1 (the standard 2 mol% catalyst loading used in this work (entry 2)), which gives more reliable results, is preferred. These findings show that even under conditions that deviate from an ideal zeroth-order regime, the screening method allows for the determination of reliable *ee* values.

1.5 Summary and Outlook

In summary it was shown that by combination of the concept of racemate screening reported by LLOYD-JONES[4] and the ESI-MS back reaction screening methodology developed by PFALTZ,[7,20] the enantioselectivity of a chiral catalyst can be determined from its racemic form by mass spectrometric screening of a non-equal mixture of two quasi-enantiomeric substrates. This allows for a very easy and fast screening of a catalyst library as, on the one side, synthesis of the individual library members is no more needed to be carried out in an enantioselective fashion, and on the other hand, the screening itself does not require workup or product isolation. Although the results obtained from this racemate screening deviated from the actual *ee* in a preparative reaction, the determination of the true selectivity of the catalyst was possible due to the finding of a linear correlation between these values which could be used as a correction function.

This methodology seems to be a valuable addition to existing screening methods, especially for the evaluation of catalysts which are not readily available in enantiomerically pure form. In this context the behavior of new PHOX ligand derived catalysts in the palladium-catalyzed allylic substitution reaction could be analyzed, which had not been tested before. While an asymmetric synthesis of these ligands would be very challenging, it was shown that the racemic ligands could be synthesized by a short sequence starting from readily available starting materials. During this work five new racemic PHOX catalysts were synthesized. By subjecting the corresponding catalysts to the ESI-MS racemate screening an aryl-PHOX ligand, bearing a sterical demanding 3,5-di-*tert*-butyl-phenyl substituent on the stereogenic center, was found which showed an increased selectivity compared to the previously reported Ph-PHOX ligand. Furthermore it was found that additional *gem*-dimethyl substitution on the oxazoline back-bone had an deleterious influence on the performance of such aryl-PHOX derived catalysts.

Future work might be dedicated to the development of a parallel screening approach of multiple catalysts in analogy of the previously reported work for the enantiopure catalyst by PFALTZ and co-workers.[24]

Chapter 2

New PHOX Containing Catalysts for the Iridium-Catalyzed Asymmetric Hydrogenation

2.1 Introduction

2.1.1 Historical Overview

The homogeneous metal-catalyzed asymmetric hydrogenation of unsaturated compounds is a very powerful tool in organic synthesis as such reactions commonly proceed under very mild reaction conditions, with low catalyst loadings, mostly quantitative yields, perfect atom economy and with high enantioselectivities,[45] demonstrated for example in the well-known L-DOPA process developed by MONSANTO.[46]

While the asymmetric hydrogenation of functionalized olefins, bearing a coordinating group in the close proximity of the double bond, has been already achieved in the late 1960s and in the 1970s using rhodium or ruthenium catalysts,[1b,47] the asymmetric hydrogenation of unfunctionalized olefins remained a big challenge for several years. Inspired by the work of CRABTREE and co-workers,[48] in 1998 PFALTZ and co-workers achieved a break-through in this field by using an cationic iridium complex bearing a bidentate chiral phosphino-oxazoline (PHOX) ligand for the hydrogenation of such substrates.[49] In the following years several related catalysts have been developed, such as SimplePHOX,[50] ThrePHOX,[51] NeoPHOX[52] and others[53] (figure 15), which have been applied in the asymmetric hydrogenation with great success.

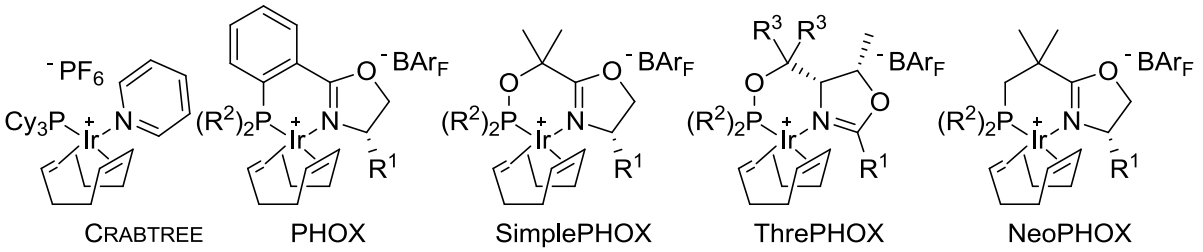


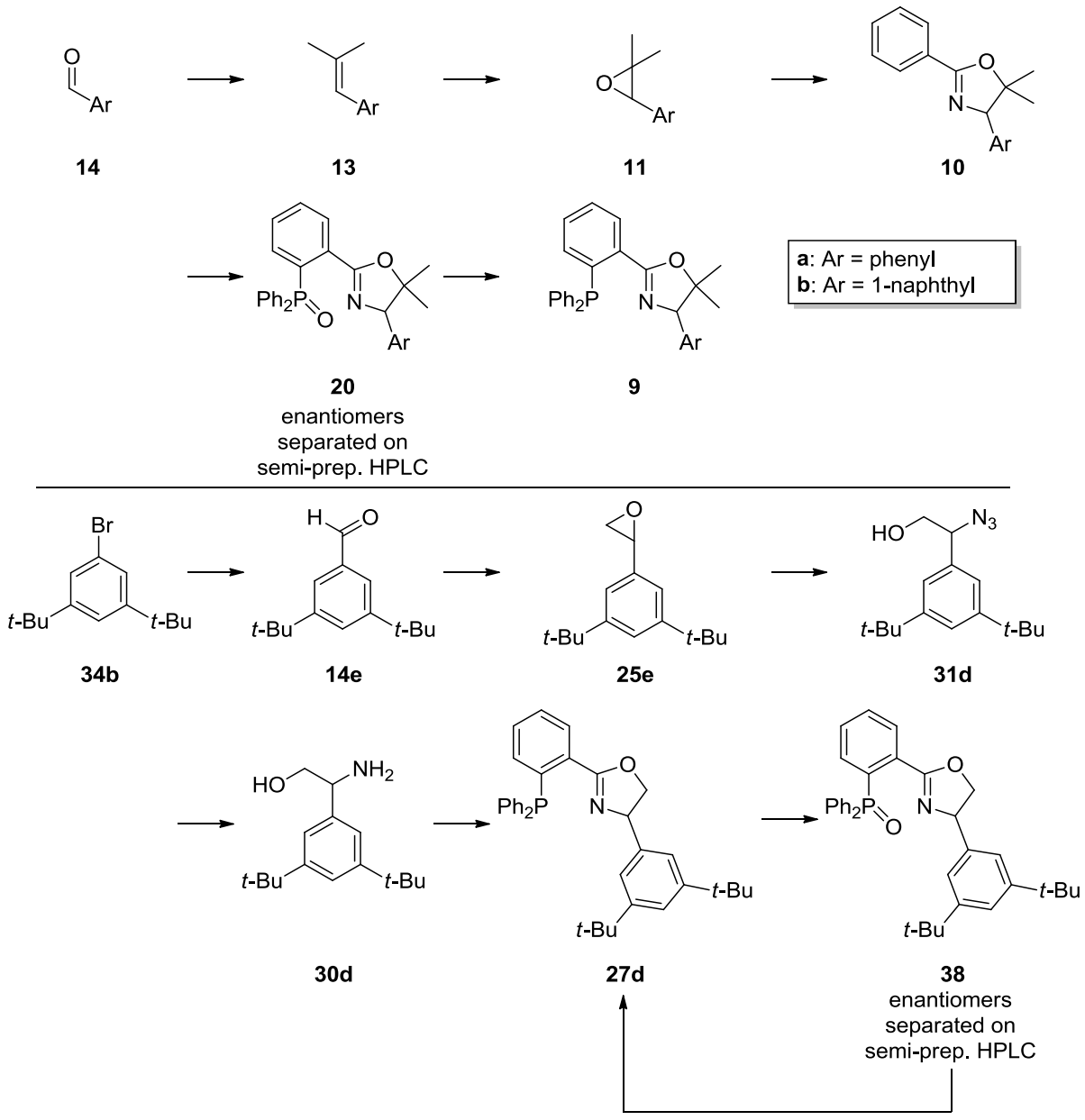
Figure 15. *P,N-Ligand derived complexes for the asymmetric iridium-catalyzed hydrogenation.*

2.1.2 Objectives of This Work

As described in chapter 1, new members of the PHOX ligand family have been synthesized during this work. Since PHOX derived complexes are known to be very effective hydrogenation pre-catalysts,[26c,49,54] these novel PHOX derivatives were aimed to be converted to the corresponding iridium complexes and their behavior in the asymmetric hydrogenation of various olefins to be evaluated.

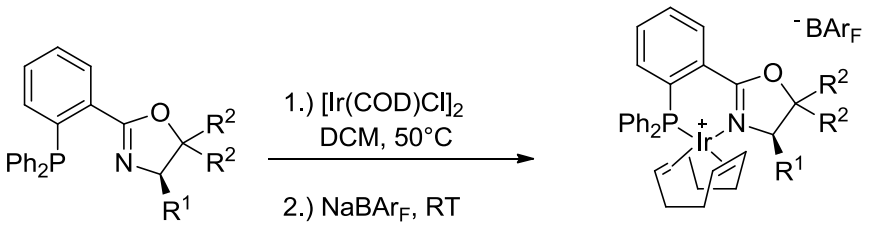
2.2 Catalyst Synthesis

The synthesis of PHOX ligands **9a**, **9b** and **27d** has been described in chapter 1 (for summary see scheme 27). Enantiomerically pure catalysts were obtained by semi-preparative HPCL resolution of the corresponding phosphine oxides **20a**, **20b** and **38** and subsequent reduction to the desired PHOX derivatives.



Scheme 27. *Synthesis of PHOX ligands as described in chapter 1.*

These enantiopure ligands were transformed into the corresponding iridium-complexes by reaction with $[Ir(COD)Cl]_2$ in DCM and subsequent anion exchange with $NaBAr_F$ (scheme 28).[55]



(*R*)-**9** or (*R*)-**27d**

(*R*)-**39a** (39%)
R^1 = Ph, R^2 = Me
(*R*)-**39b** (33%)
R^1 = 1-naphthyl, R^2 = Me
(*R*)-**39c** (66%)
R^1 = 3,5-di-*tert*-butyl-phenyl, R^2 = H

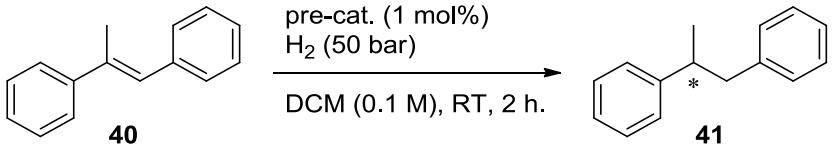
Scheme 28. *Complexation towards the iridium-precatalysts* ***39****.*

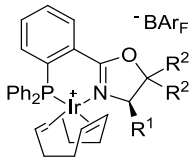
The formation of the precatalysts for the iridium-catalyzed asymmetric hydrogenation derived from the three different PHOX derivatives did proceed in all cases. The lower yields for **39a** and **39b** compared to **39c** together with the hydrogenation results shown in the tables below indicate that in the case of dimethyl substitution in the backbone the substituent R^1 is more pushed into the direction of the coordination-side and therefore complexation becomes more difficult due to sterical hindrance.

2.3 Hydrogenation Results

The hydrogenation of different model-substrates using the above described novel PHOX-iridium complexes are summarized in the following tables.

Table 4. *Hydrogenation of (E)-prop-1-ene-1,2-diyldibenzene (**40**).*

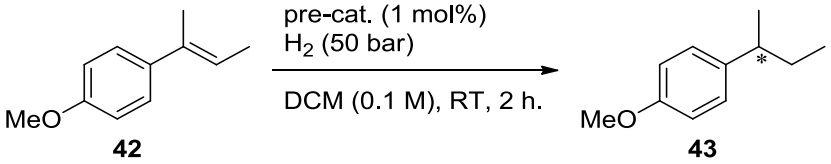


Entry	Precatalyst		R^1	R^2	Conv.[a] [%]	*ee*[b] [%] (Config.)
1		(*R*)-**39a**	Ph	Me	11	4 (*R*)
2		(*R*)-**39b**	1-naphthyl	Me	14	4 (*S*)
3		(*R*)-**39c**	3,5-di-*tert*-butyl phenyl	H	45	58 (*R*)

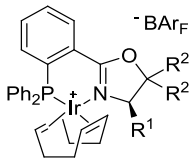
[a]: Determined by GC analysis; [b]: determined by HPLC analysis on a chiral stationary phase.

In the hydrogenation of *trans*-methyl stilbene (table 4) only low conversions were achieved. Especially the *gem*-dimethyl PHOX containing pre-catalysts showed very low activity (entry 1 and 2). As well in terms of selectivity they were inferior to complex **39c**. However, this catalyst achieved only 58% *ee* at 45% conversion.

Table 5. *Hydrogenation of (E)-1-(but-2-en-2-yl)-4-methoxybenzene (**42**).*



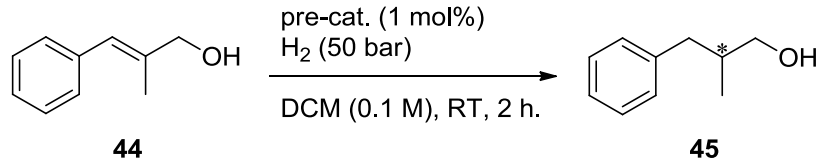
42 **43**

Entry	Precatalyst		R^1	R^2	Conv.[a] [%]	*ee*[b] [%] (Config.)
1		(*R*)-**39a**	Ph	Me	43	15 (*S*)
2		(*R*)-**39b**	1-naphthyl	Me	43	16 (*S*)
3		(*R*)-**39c**	3,5-di-*tert*-butyl phenyl	H	55[c]	35 (*R*)

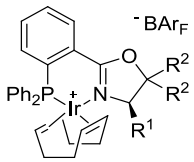
[a]: Determined by GC analysis; [b]: determined by GC analysis on a chiral stationary phase; [c]: 2% isomerization towards the (Z)-substrate was observed.

The hydrogenation of olefin **42** was achieved with slightly better results (table 5). The pre-catalysts **39a** and **39b** showed comparable performance, both converting the hydrogenation substrate **42** with 43% giving the hydrogenation product **43** with low enantiomeric excess (15% *ee* respectively 16% *ee*, entries 1 and 2). Again complex **39c** was slightly superior but still not very satisfying behavior (entry 3).

Table 6. *Hydrogenation (E)-2-methyl-3-phenylprop-2-en-1-ol (**44**).*



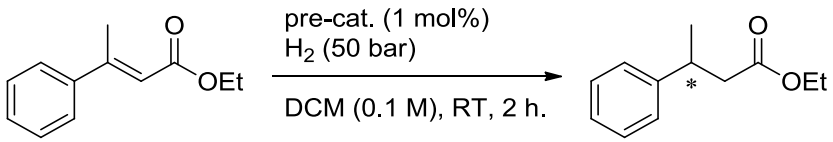
44 **45**

Entry	Precatalyst		R^1	R^2	Conv.[a] [%]	*ee*[b] [%] (Config.)
1		(*R*)-**39a**	Ph	Me	n.d.[c]	n.d.
2		(*R*)-**39b**	1-naphthyl	Me	n.d.[c]	n.d.
3		(*R*)-**39c**	3,5-di-*tert*-butyl phenyl	H	>99[d]	78 (*R*)

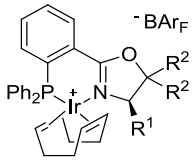
[a]: Determined by GC analysis; [b]: determined by HPLC analysis on a chiral stationary phase; [c]: a mixture of different products was formed; [d]: 10% of side products were formed.

In the hydrogenation of the allylic alcohol **44** (table 6) the different complexes showed significantly different behavior. While the dimethyl-PHOX containing pre-catalysts **39a** and **39b** only led to a complex mixture of unidentified side-products, complex **39c** fully converted the olefin with acceptable 10% of undesired by-product formed. The enantiomeric excess was found to be relatively good 78%.

Table 7. *Hydrogenation of (E)-ethyl 3-phenylbut-2-enoate (**46**).*



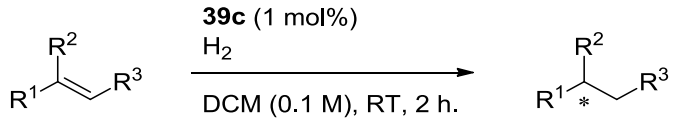
46 **47**

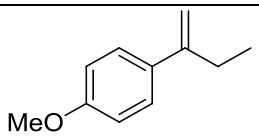
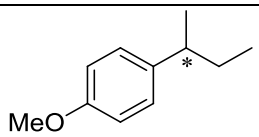
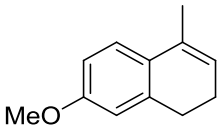
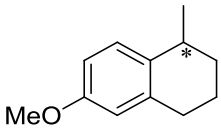
Entry	Precatalyst	R^1	R^2	Conv.[a] [%]	*ee*[b] [%] (Config.)
1	(*R*)-**39a**	Ph	Me	3	n.d.
2	 (*R*)-**39b**	1-naphthyl	Me	3	n.d.
3	(*R*)-**39c**	3,5-di-*tert*-butyl phenyl	H	21	39 (*R*)

[a]: Determined by GC analysis; [b]: determined by GC analysis on a chiral stationary phase.

In the hydrogenation of the acryl ester **46** (table 7) low conversions were observed. Best results were obtained again using complex **39c** although only 21% conversion and 39% *ee* were found.

Table 8. *Hydrogenation of 1-(but-1-en-2-yl)-4-methoxybenzene (**28**) and 7-methoxy-4-methyl-1,2-dihydronaphthalene (**50**).*

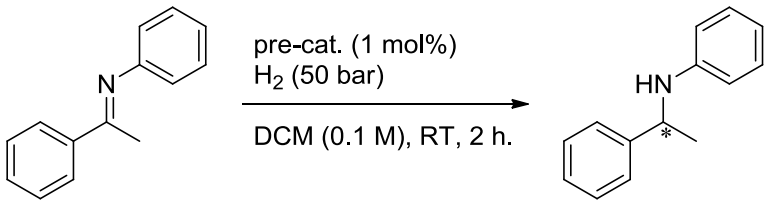


Entry	Substrate	Product	H_2-Pressure [bar]	Conv[a] [%]	*ee* [%] (Config.)
1	 **48**	 **49**	1	90[b]	66 (*S*)[c]
2	 **50**	 **51**	50	87[d]	23 (*R*)[e]

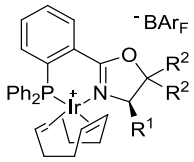
[a]: Determined by GC analysis; [b]: 5% of isomerization products were formed; [c]: determined by GC analysis on a chiral stationary phase; [d]: 13% of oxidation product was formed; [e]: determined by HPLC analysis on a chiral stationary phase.

In previous studies the terminal olefin **48** and the cyclic olefin **50** have shown to be very challenging substrates. Therefore the most active and selective complex **39c** of the three prepared was tested in the hydrogenation of these two substrates (table 8). Acceptable conversions were found for both olefins (90% respectively 87%), although in both cases undesired side-product formation was observed. The hydrogenation product **49** was obtained in moderate 66% *ee* while for the reduction of the cyclic substrate **50** low selectivity was found.

Table 9. *Hydrogenation of (E)-N-(1-phenylethylidene)aniline (**48**).*



52 **53**

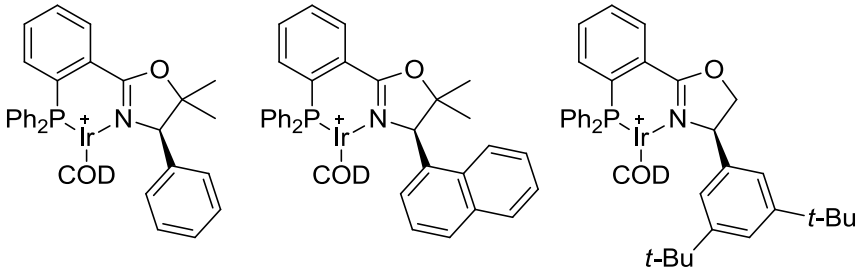
Entry	Precatalyst		R^1	R^2	Conv.[a] [%]	*ee*[b] [%] (Config.)
1		(*R*)-**39a**	Ph	Me	>99	10 (*S*)
2		(*R*)-**39b**	1-naphthyl	Me	>99	24 (*S*)
3		(*R*)-**39c**	3,5-di-*tert*-butyl phenyl	H	>99	74 (*S*)

[a]: Determined by GC analysis; [b]: determined by HPLC analysis on a chiral stationary phase.

When imine substrate **52** was hydrogenated using the novel pre-catalyst complexes **39** a different behavior compared to the above described reduction of alkenes was found (table 9). While the activities of catalysts **39a** and **39b** were poor in the hydrogenation of all olefins described above, full conversion of substrate **52** to the hydrogenation product **53**, was found. This matches the suggestion, that the iridium-catalyzed hydrogenation of imines proceeds via a different mechanistical pathway than the iridium-catalyzed hydrogenation of alkenes.[56] Nevertheless again the best result was obtained using complex **39c** (entry 3) where full conversion and 74% *ee* was found.

2.4 Summary

In summary, the synthesis of three novel PHOX containing iridium complexes was achieved (figure 16). These have shown to be active pre-catalysts for the asymmetric iridium catalyzed hydrogenation of alkenes and imines. In general low conversions were obtained in the hydrogenation of olefins. Especially the complexes **39a** and **39b** proved to be not very suitable catalysts. The *gem*-dimethyl substitution in the 5-position of the oxazoline backbone, which alter the conformation of the oxazoline ring, seem to have a deleterious effect by pushing the aryl-moiety towards the reactive center. By this the environment of the iridium center might become more occupied and due to the resulting sterical repulsion the hydrogenation substrates can no more easily access the metal-center.



39a **39b** **39c**

Figure 16. *Synthesized PHOX containing iridium complexes.*

On the other hand, in the hydrogenation of an imine all three complexes showed very high activities, which is in agreement with the suggestion of different mechanisms for those two substrate classes. For all substrates tested, complex **39c** shows clearly superior behavior in terms of activity and selectivity. Especially for the hydrogenation of allylic alcohols and imines with this pre-catalyst, some promising results (70-80% *ee*) were found.

Chapter 3

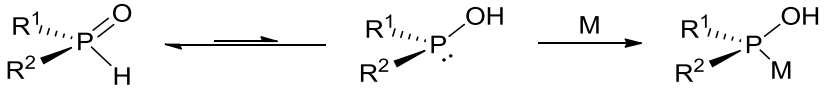
Secondary Phosphinoxide Containing Ligands in the Palladium Catalyzed Allylic Substitution

3.1 Introduction

Chiral catalysts bearing a trivalent phosphorus containing ligand are very common in asymmetric catalysis.[57] However, a drawback of such ligands can often be found in the low stability against air or moisture, especially when alkyl substituted.[58] Secondary phosphine oxides (SPO) have sown to be a promising alternative to circumvent these issues.[59]

3.1.1 Properties of Secondary Phosphine Oxides

Secondary phosphine oxides exist in an equilibrium between their oxo- and hydroxy-form (scheme 29).[60] At room-temperature the pentavalent oxo-tautomer predominates, resulting in an air-, moisture- and temperature-stable compound.[61] The equilibrium can be shifted towards the hydroxy-tautomer by either the presence of electronegative substituents on the phosphorus[62] or by coordination with a transition-metal.[63]

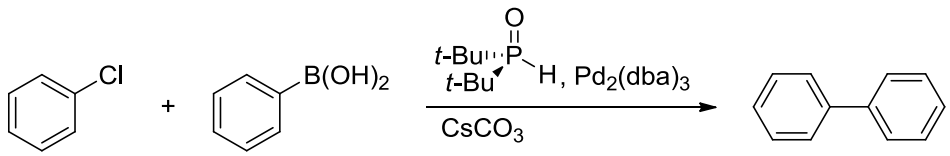


Scheme 29. *Equilibrium between the oxo- and the hydroxy-form of secondary phosphine oxides.*

Bearing two different substituents (R^1 and R^2), secondary phosphines become chiral on the phosphorus atom. The individual enantiomers are configurationally stable in solution and the chiral information is retained upon coordination with a metal center.[61a,64]

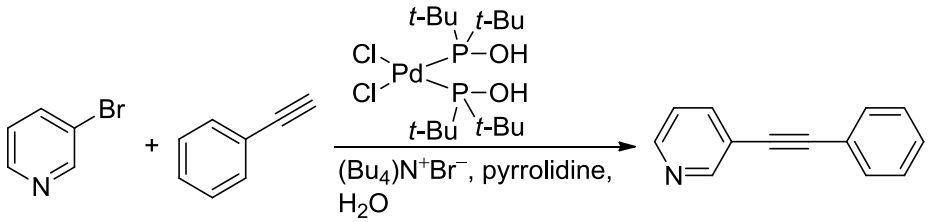
3.1.2 Application of Secondary Phosphine Oxides in Catalysis

A great variety of applications of such secondary phosphine oxides in catalysis has been found.[59] One reaction-type where different examples using SPO ligands have been reported was the field of cross-coupling reactions. In 2001 LI was the first to report the catalytic activity of a palladium-SPO complex in a Suzuki cross-coupling reaction (scheme 30).[65]



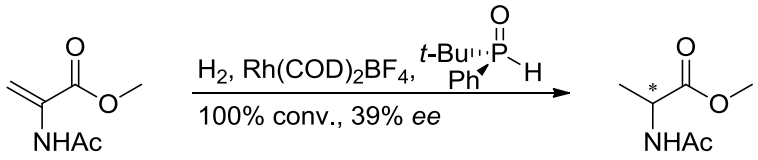
Scheme 30. *Suzuki cross-coupling using a palladium-SPO complex as catalyst.*[65]

Other cross-coupling reactions have been reported as well. The stability of the palladium-SPO complexes even allowed for the performance of Sonogashira-reactions under air and in water, as reported by WOLF and LEREBOURS (scheme 31).[66]



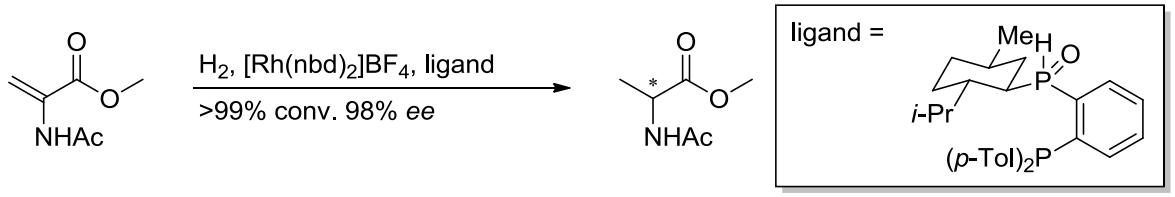
Scheme 31. *Sonogashira reaction in water.*[66]

The suitability of SPO-ligands in metal-catalyzed asymmetric transformations has been investigated too. MINNAARD, FERINGA and DE VRIES for example reported the asymmetric rhodium-catalyzed hydrogenation of *N*-acyl dehydroamino acids and esters using *P*-chiral SPO ligands (scheme 32), although they could not achieve very high enantioselectivities.[67]



Scheme 32. *Rhodium-catalyzed hydrogenation.*[67]

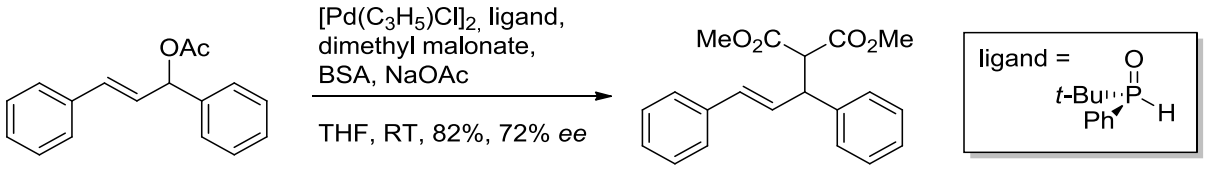
Later, PUGIN and PFALTZ showed that a bidentate SPO,P-ligand bearing an additional chiral information in the backbone is able to induce very high selectivity in the hydrogenation of the same substrate (scheme 33).[68]



Scheme 33. *Highly selective rhodium-catalyzed hydrogenation.*[68]

The iridium-catalyzed hydrogenation of imines has also been reported by MINAARD, FERINGA and DE VRIES.[69]

Furthermore *P*-chiral SPO-ligands have been proven to form active palladium-catalysts for the asymmetric allylic alkylation reaction by DAI and co-workers (scheme 34).[64] Respectable 72% *ee* have been reported.



Scheme 34. *Pd-SPO catalyzed asymmetric allylic alkylation.*[64]

3.1.3 Objectives of This Work

As shown above secondary phosphine oxide containing catalysts show very promising behavior in asymmetric catalysis. Furthermore it was previously shown that bidentate SPO-containing ligands are active in a variety of different catalytic transformations.[70] Thus the aim of the project was the evaluation of such catalysts in the palladium catalyzed allylic substitution in order to find novel, air- and moisture-stable ligands with improved selectivities in this reaction compared to the ones described for example in scheme 34. The idea was to test both phosphine,SPO and as well nitrogen,SPO containing bidentate ligands (figure17).

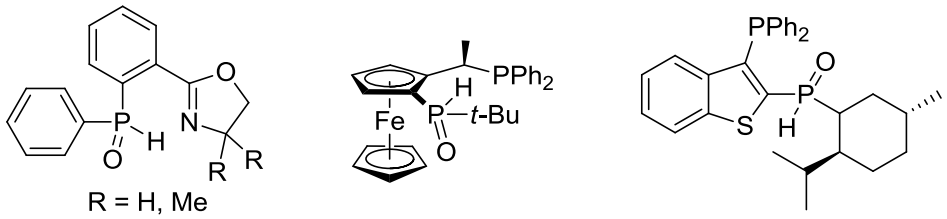


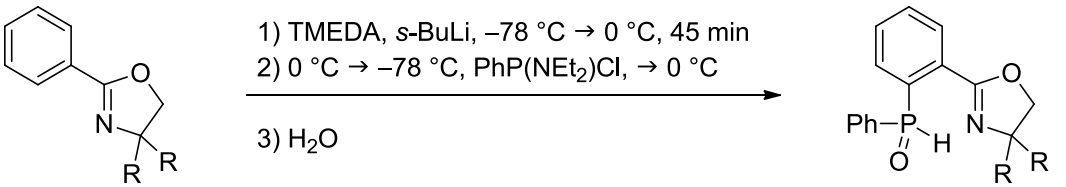
Figure 17. *SPO containing ligands to be tested in the asymmetric palladium-catalyzed allylic substitution reaction.*

The N,SPO-ligands[27] to be tested were based on the PHOX-ligand core-structure as PHOX ligands are known to form active palladium-catalysts for this reaction.[26c] P,SPO-ligands were based on systems which have previously used in highly selective iridium-catalyzed hydrogenations.[68,71]

3.2 Secondary Phosphine Oxide, Nitrogen Based Ligands

3.2.1 Synthesis

Secondary phosphine oxide containing PHOX ligands were obtained in a one-pot reaction starting from the corresponding phenyl oxazolines by *ortho*-lithiation, subsequent reaction with 1-chloro-*N*,*N*-diethyl-1-phenylphosphinamine and final quenching with water in medium yields (scheme35).[27] In a first attempt racemic ligands have been synthesized in order to evaluate their activity in the palladium catalyzed alkylation.

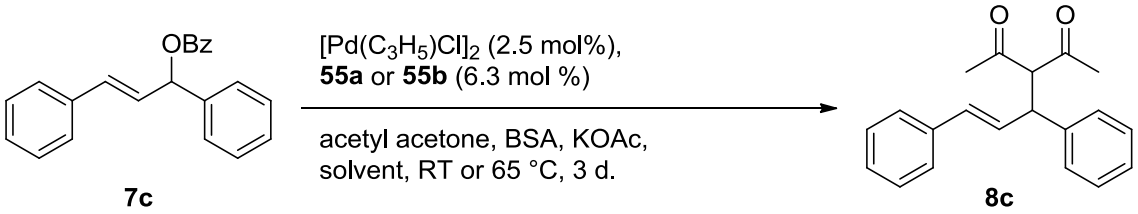


Scheme 35. *Synthesis of SPO-PHOX ligands.*

3.2.2 Catalysis Results

These novel N,SPO-ligands have been tested in the palladium-catalyzed allylic alkylation (table 10).[27] All reaction listed were carried out at both room temperature and 65 °C for 3 d giving the same results under both conditions.

Table 10. *Catalysis results.*



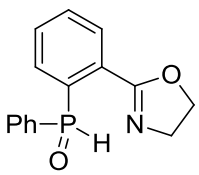
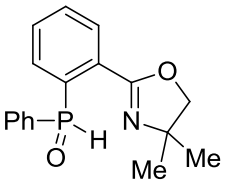
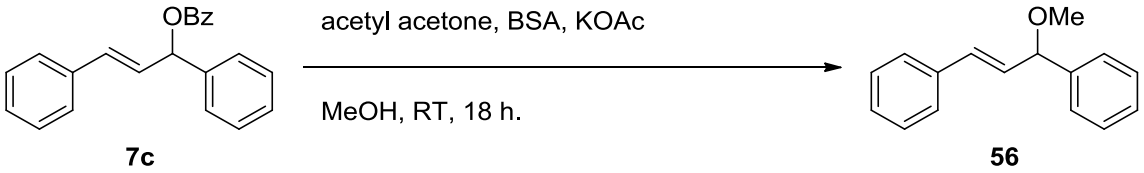
Entry	Ligand	Solvent	Result
1		DCM	no conversion
2		THF	no conversion
3		DMF	no conversion
4	**55a**	MeOH	only side-product formed

Table 10. *Continued.*

Entry	Ligand	Solvent	Result
5		DCM	no conversion
6		DMF	no conversion
7	**55b**	MeOH	only side-product formed

As shown in table 10 no desired product was formed in all solvents tested. Only when the reactions were carried out in MeOH, the formation of a new product was observed. It was proven that this product was (*E*)-(3-methoxyprop-1-ene-1,3-diyl)dibenzene (**56**), resulting from the substitution of the benzoate function by methanol. The same reaction was again carried out without the addition the palladium catalyst and it was demonstrated, that this reaction proceeded without the need of the catalyst (scheme 36).



Scheme 36. *Observed formation of side-product* ***56*** *in MeOH in the absence of a Pd-catalyst.*

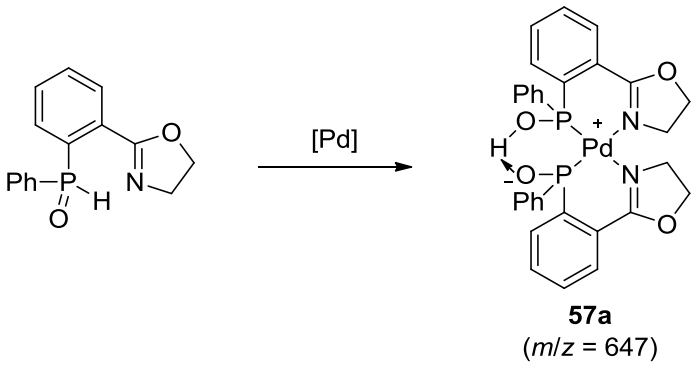
3.2.3 Complexation Behavior

As the N,SPO-ligand derived catalysts did not show any activity in the palladium-catalyzed allylic alkylation, the complexation behavior of these ligands was investigated in order to find reasons for the lack of activity. For that purpose the N,SPO-ligands were reacted with different palladium-precursors and the resulting complexes were analyzed by ESI-MS.[27]

Table 10. *Complexation behavior of ligand* ***55a****.*

Entry	Palladium source	Solvent	Observed mass [*m/z*]
1	$[Pd(C_3H_5)(MeCN)_2]OTf$	toluene	647
2	$[Pd(C_3H_5)(MeCN)_2]OTf$	DCM	647
4	$[Pd(C_3H_5)Cl]_2$	DCM	647
5	$[Pd(C_3H_5)(MeCN)_2]OTf$	MeOH	647
6	$[Pd(C_3H_5)Cl]_2$	MeOH	647
8	$[Pd(C_3H_5)Cl]_2$	THF	647
9	$[Pd(C_3H_5)(MeCN)_2]OTf$	DMF	647
10	$[Pd(C_3H_5)Cl]_2$	DMF	647

First, the complexation behavior of ligand **55a** was evaluated (table 10). Throughout all conditions tested, a complex with the mass of *m*/*z* = 647 was found. This finding was independent of the solvent, the palladium-precursor and the palladium/ligand-ration used. The observed mass corresponds to a palladium-complex bearing two N,SPO-ligands, one of them being deprotonated. Thus, hydrogen bonding between the two ligands was proposed (scheme 37) as it was observed previously for other systems already.[61a]



57a
(*m*/*z* = 647)

Scheme 37. *Formation of a bis-N,SPO palladium complex.*

Crystallization from DCM afforded crystals suitable for X-ray analysis (figure18). The resolved structure verified the above mentioned proposal. The position of the acidic proton was found by differential-fourier transformation and refined. Its distance to the two phosphorus atoms of 1.00 Å respectively 1.44 Å as well as the O,H,O angle of 166 ° confirm

the existence of a hydrogen-bonding. Furthermore it was proven that coordination takes place via the phosphorus atom rather than vie the oxygen of the SPO moiety which is in agreement with other previously described examples of SPO-transition metal complexes.[61b]

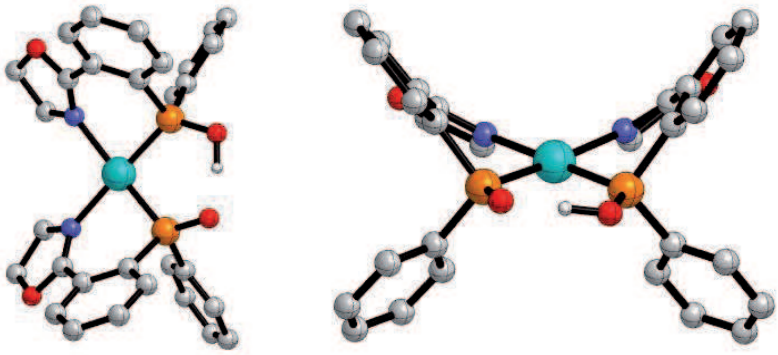
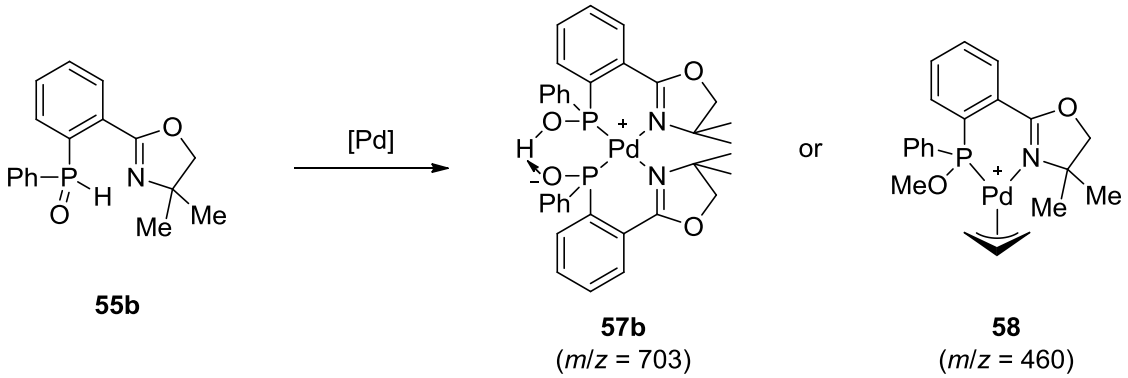


Figure 18. *X-ray structure of complex* ***57a*** *(left: top-view; right: front-view; co-crystallized* PF_6 *and DCM are omitted for clarity).*

Next, the complexation behavior of ligand **55b** was evaluated (table 11). Again, the corresponding mass of a bis-SPO,N palladium complex **57b** was found under most conditions tested (entries 1-5). Only in MeOH a different result was achieved (entries 6 and 7). Here, reaction of the ligand with the solvent seemed to have taken place. Thus, the corresponding methoxy-phosphino species was formed which then was converted to the P,N palladium allyl complex **58** (scheme 38). Notably, when this complex was used in the preparative reaction no conversion was observed.

Table 11. *Complexation behavior of ligand* ***55b****.*

Entry	Palladium source	Solvent	Observed mass [*m/z*]
1	$[Pd(C_3H_5)(MeCN)_2]OTf$	toluene	703
2	$[Pd(C_3H_5)Cl]_2$	DCM	703
3	$[Pd(C_3H_5)Cl]_2$	THF	703
4	$[Pd(C_3H_5)(MeCN)_2]OTf$	DMF	703
5	$[Pd(C_3H_5)Cl]_2$	DMF	703
6	$[Pd(C_3H_5)(MeCN)_2]OTf$	MeOH	460
7	$[Pd(C_3H_5)Cl]_2$	MeOH	460

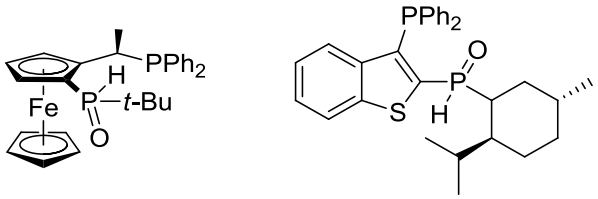


Scheme 38. *Complexation behavior of ligand* ***55b****.*

The above described complexation behavior of both ligands with a palladium-source explains the lack of activity in the palladium-catalyzed allylic alkylation found. As all coordination-sides of the palladium center are occupied and due to the hydrogen-bonding between the individual ligands they are bound very strongly, the allyl substrate can no more access the palladium center to then undergo the desired reaction.

3.3 Secondary Phosphine Oxide, Phosphine Based Ligands

The SPO,P-ligands **59**, **59'** and **60** (figure19) were kindly provided by SOLVIAS AG, Switzerland. Ligand **59** and **59'** are epimers with, at the beginning of this project, unknown configuration of the *P*-stereogenic center.



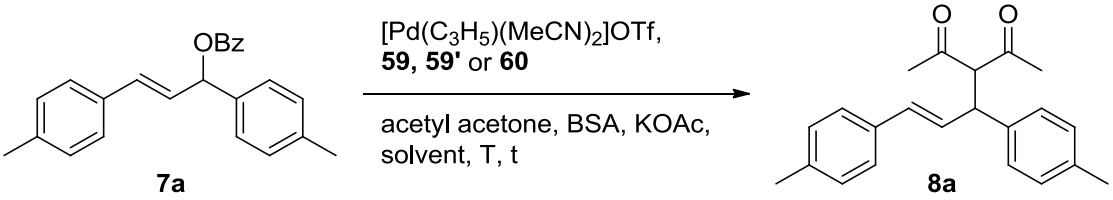
59 **60**

Figure 19. *P,SPO-ligands provided by SOLVIAS AG.*

3.3.1 Catalysis Results

The results obtained in the palladium-catalyzed allylic alkylation with these P,SPO-ligands are summarized in table 12. It was clearly shown that the ferrocenyl-based P,SPO-ligands **59** (entries 1-6) were superior to the benzothiophene based ligand **60**. Furthermore a clear match/mismatch situation was observed for the two epimers **59**, where ligand **59'** proved to be both more active and selective. However, for all ligands tested low yields were obtained. Best conditions were found using ligand **59'** in toluene at room temperature yielding the desired product **8a** in only 14% with 95% *ee* (entry 5). When the reaction temperature was increased to 110 °C the yield could be improved (42%) but upon significant loss of selectivity (25% *ee*). Notably, no undesired side-products were formed but the unreacted staring material could be recovered almost completely.

Table 12. *Catalysis results.*

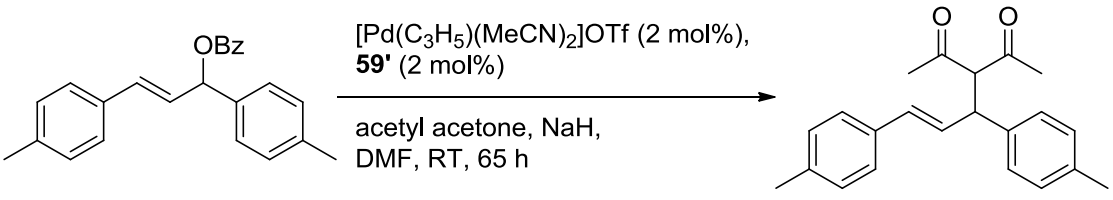


7a **8a**

Entry	Ligand	Catalyst loading [mol%]	T [°C]	Solvent	t [h]	Recovered 7a[a] [%]	Yield[a] [%]	*ee* [b] [%] (Config.)
1	**59**	2	25	DCM	44	78	18	60 (*S*)
2	**59**	5	25	DCM	42	n.d.	44	52 (*S*)
3	**59**	2	50	DCM	44	63	36	64 (*S*)
4	**59'**	2	25	DCM	41	n.d.	31	88 (*S*)
5	**59'**	2	25	toluene	41	84	14	95 (*S*)
6	**59'**	2	110	toluene	43	50	42	25 (*S*)
7	**60**	2	25	DCM	69	89	10	16 (*S*)

[a]: Isolated yield; [b]: analyzed by HPLC on a chiral stationary phase.

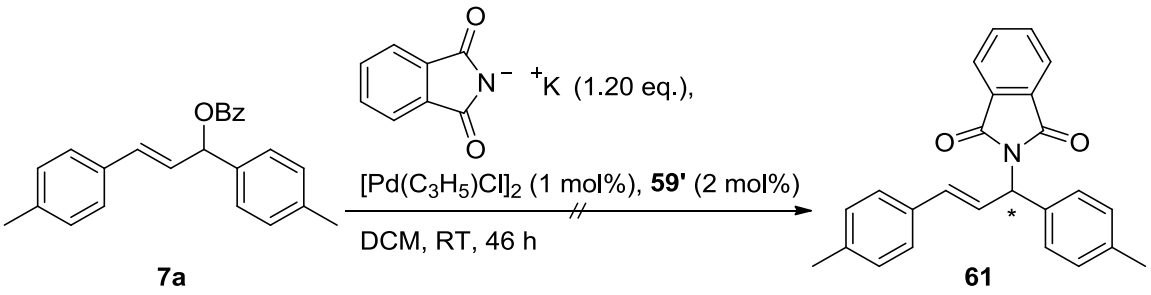
As the catalyst derived from ligand **59'** showed high selectivity but only low activity in the allylic alkylation, further reaction conditions were examined. It was previously shown by VON MATT, that, dealing with less reactive substrates, higher yields can be obtained upon use of an excess of NaH as base in DMF.[43] These conditions were applied testing ligand **59** (scheme 39). Unfortunately an even lower yield was obtained. Furthermore as well the *ee* dropped to 27%.



7a **8a** (5%, 27% *ee* (*S*))

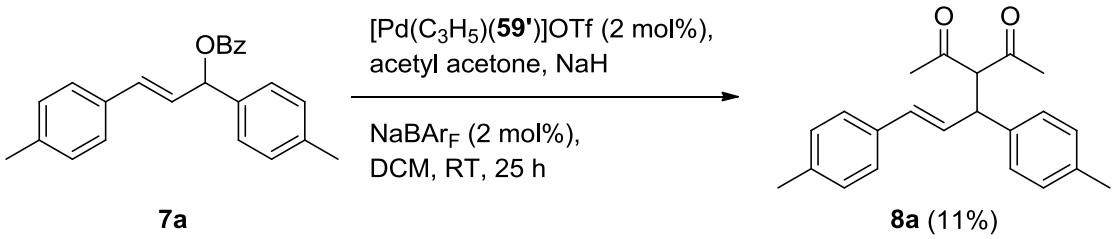
Scheme 39. *Changing reaction-conditions towards use of NaH as base.*

A more reactive nucleophile was tested as well. MÜLLER reported that phthalimide, according to its lower pK_a value compared to acetyl acetone, shows increased reactivity in the allylic substitution reaction.[42b] However, when this nucleophile was tested no desired product was formed but only unreacted starting material was fully recovered (scheme 40).



Scheme 40. *Testing ligand **59'** in the allylic amination reaction.*

Another attempt to increase the activity of the catalyst derived from ligand **59'** based on the findings reported by LLOYD-JONES and co-workers. They showed that addition of catalytic amounts of $NaBAr_F$ to reaction mixture increases the turnover rates in the Tsuji-Trost allylation.[42a] These conditions were applied to the system described herein (scheme 41). Again the yield did not increase but dropped to 11%.



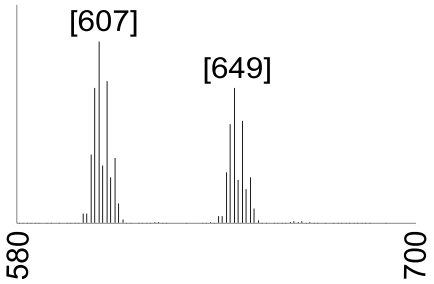
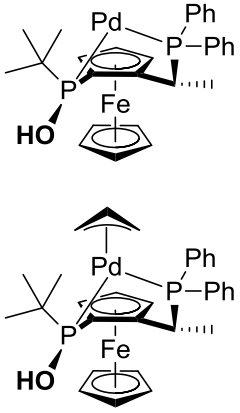
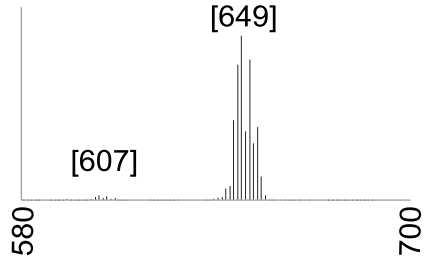
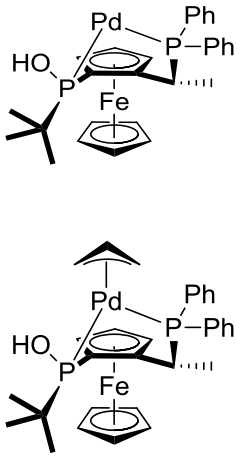
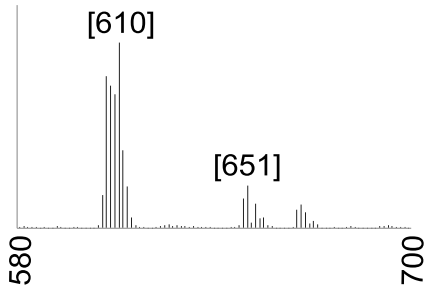
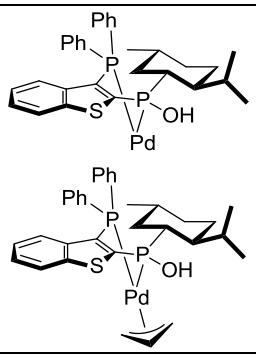
Scheme 41. *Testing $NaBAr_F$ as additive to increase the activity of the catalyst.*

3.3.2 Complexation Behavior

In order to examine the complexation behavior of the P,SPO-ligands they were reacted with $[Pd(C_3H_5)(MeCN)_2]OTf$ in DCM for 1 h at room temperature and the resulting complexes were analyzed by ESI-MS (table 13). It was found, that in all cases the corresponding ligand did bind to the palladium center. For ligand **59** two mass-signals were observed. One corresponded to the desired P,SPO-palladium allyl complex, the other one was assigned to the species without the coordinating allyl moiety, in a ratio of 1.3:1 favoring the complex without the allyl moiety (entry 1). A comparable result was found for ligand **60**, where again the

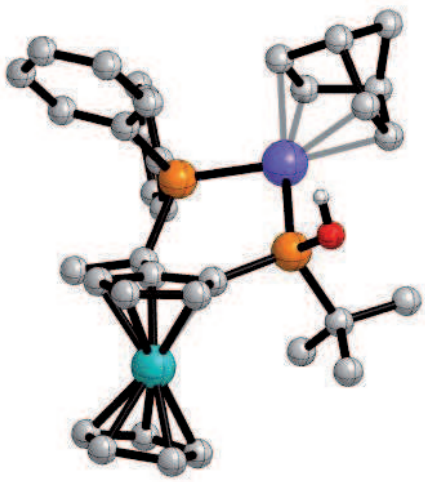
complex without the allyl moiety was formed as the major product (4.4:1, entry 3). These findings could explain the low activity of especially those catalysts, derived from these two ligands.

Table 13. *Complexation behavior of the P,SPO-ligands.*

Entry	Ligand	ESI-MS spectrum	Observed mass	Correlating structure
1	**59**		607 649	
2	**59'**		607 649	
3	**60**		610 651	

When the complexation behavior of ligand **59'** was tested (entry 2), the desired P,SPO-palladium allyl complex was the major product formed (38.4:1). This explains why the highest activity was observed for the catalyst derived from ligand **59'**. It was suggested that the reason for the observation of the complexes without the allyl moiety can be found in the sterical demand of the ligands. They seem to be too bulky to allow the allyl species entering the coordination sphere of the palladium-center. As the test substrate was a 1,3-diphenyl allyl species which is more bulky than the simple allyl moiety of the pre-catalysts, this is again a possible explanation for the low activities described above.

Having observed that ligand **59'** seems to allow for an easier access of the allyl species to the palladium-center compared to ligand **59**, it was suggested the *tert*-butyl substituent on the SPO center is pointing away from the coordination center as shown in table 13, entry 2. Thus, the *P*-chiral stereogenic center was proposed to be in (*S*)-configuration for ligand **59'** and in (*R*)-configuration for the epimeric ligand **59**. This suggestion was later confirmed when researchers at SOLVIAS AG were able to obtain an X-ray structure of the corresponding P,SPO-rhodium norbornadiene complex **62** (figure20). As it was proposed based on the complexation behavior of the ligands, the *tert*-butyl substituent on the SPO-center of **59'** was indeed pointing away from the coordination center and the configuration of the phosphorus atom was assigned as the (*S*) form.



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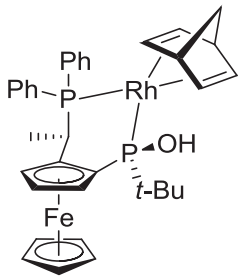


62

Figure 20. *X-ray structure of rhodium complex* ***62*** *derived from ligand* ***59'*** *(the counter ion BF_4 is omitted for clarity).*

3.4 Summary

In summary it was shown that Pd-catalysts derived from *P*-chiral bidentate N,SPO-ligands bearing a phenyl oxazoline backbone are not active in the allylic substitution reaction.[27] The reason for this was found in the tendency of such ligands to form a stable bis-N,SPO palladium complex with the two individual ligands bridged via hydrogen bonding. This was demonstrated by ESI-MS studies as well as by X-ray analysis of such a complex.

Furthermore the properties of P,SPO-ligands in the allylic alkylation reaction were investigated. During these studies a very selective catalyst derived from a ligand bearing a ferrocenyl backbone was found. This catalyst however showed only low activity in the test reactions which could not be improved by various optimization attempts. ESI-MS studies on the complexation behavior of these P,SPO-ligands have been carried out and elucidated the reason for the low activities observed. The ligands which were tested seemed to be too sterically demanding and hence shielded the palladium-center. Therefore the substrate allyl species could no more coordinate to the metal-center and the reaction could not proceed.

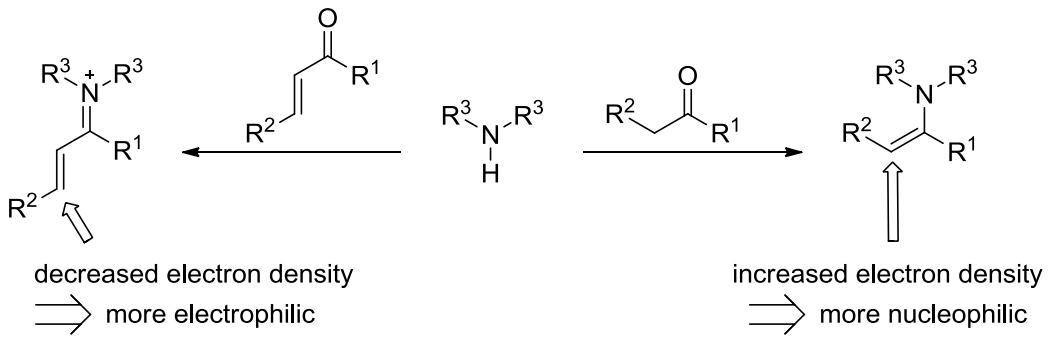
Chapter 4

Organo-Catalyzed Transfer-Hydrogenation of α,β-Unsaturated Carbonyl Compounds

4.1 Introduction

4.1.1 Organo Catalysis

Organocatalysis is a very fast growing field in organic chemistry providing remarkably robust and divers protocols for asymmetric reactions.[72] Small molecules bearing a secondary amine functionality are an important class of organo-catalysts. Such compounds can act as enamine or iminium catalyst depending on the nature of the substrate which is applied (scheme 42).[72b]



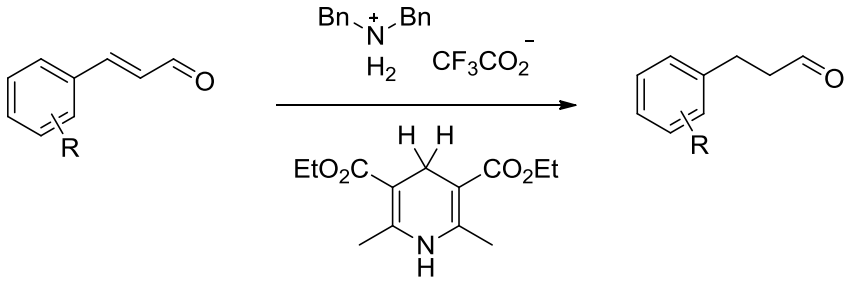
Scheme 42. *Activation of carbonyl compounds by iminium- (left) and enamine- (right) catalysis.*

Upon iminium formation by reaction of an α,β-unsaturated carbonyl compound with a secondary amine, the energy level of the LUMO is decreased and thus reaction with a nucleophile is facilitated. Reaction of a secondary amine with an enolizable carbonyl compound leads to formation of an enamine and therefore the reaction with an electrophile is enabled.

Despite the early reports by KNOEVENAGEL in the late 18th century that amines are able to catalyze reactions on carbonyl compounds[73] and the remarkable enantioselectivities, which were achieved using L-proline as organo-catalyst in aldol reactions by the industrial groups of WIECHERT and HAJOS in the early 1970s,[74] the potential of small molecule catalysis has not been recognized until the beginning of the 21st century. Starting with the reports of LIST and BARBAS on the asymmetric aldol-reaction via enamine-catalysis[75] and of MACMILLAN on asymmetric Diels-Alder reactions via iminium-catalysis,[76] this research field came into the focus of the scientific community and started to grow.[77]

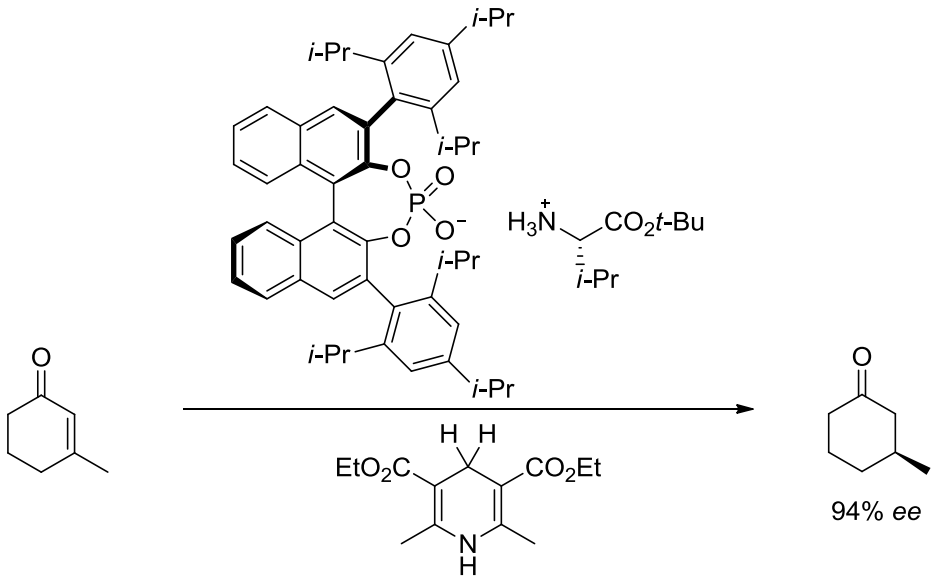
4.1.2 Organo Catalyzed Transfer-Hydrogenation

Among a great variety of different organo-catalyzed reactions, the transfer-hydrogenation of α,β-unsaturated carbonyl compounds has been discovered recently by LIST and co-workers.[78] They reported the reduction of acryl aldehydes catalyzed by a secondary amine upon the use of Hantzsch ester as the hydride source (scheme 43). Thus, this method mimics enzymatic reductions by replacing the enzyme by the organo-catalyst and the cofactor NADH or $FADH_2$ by the Hantzsch ester.



Scheme 43. *First report of an organo-catalyzed transfer-hydrogenation of acryl aldehydes.*[78]

Especially in the conjugate reduction of α,β-unsaturated aldehydes this method proved to be of great value since metal catalyzed reductions often lead to the corresponding alcohols rather than to the saturated aldehydes.[79] There is only one report found in literature where a asymmetric metal-catalyzed approach was successfully applied in the reduction of acryl aldehydes preserving the aldehyde function.[80] KANAZAWA and NISHIYAMA described the rhodium-catalyzed hydrosilylation of such substrates. However, this methodology was only applicable to a very limited substrate scope and the products were obtained mostly in moderate yield or selectivity. Furthermore formation of allylic alcohols as side product was observed in significant quantities. Already in their first report LIST and co-workers described as well an asymmetric variant of this reaction using an imidazolidinone catalyst with highly promising results. This was later improved and a variety of β-aryl,β-alkyl acrylaldehydes were reduced with high selectivities.[81] In the same time MACMILLAN and co-workers independently reported the same reaction as well catalyzed by an imidazolidinones compound.[82] They slightly broadened the substrate-scope by reducing β,β-dialkyl acryl aldehydes. In 2006 both LIST and MACMILLAN individually reported on the reduction of α,β-unsaturated ketones. While MACMILLAN applied the previously used imidazolidinone catalysts,[83] LIST described an asymmetric counter ion directed catalysis (ACDC)[84] approach (scheme 44).[85]



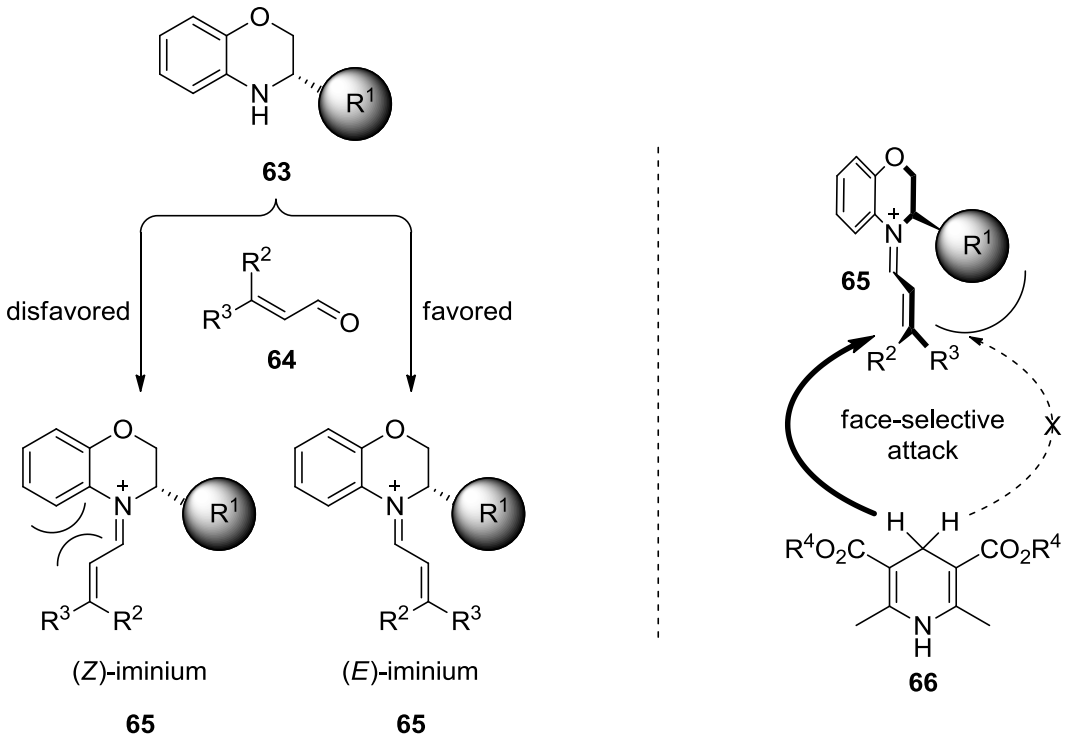
Scheme 44. *ACDC approach reported by LIST and co-workers.*[85]

Inspired by these early works, COSSY and co-workers described the reduction of β-alkyl, β-heteroaryl acryl aldehydes using imidazolidinone catalysts.[86] ZHAO and CORDOVA reported the asymmetric reduction of acryl aldehydes using the well-known Hayashi-Jørgenson catalyst.[87] Finally KUDO and co-workers described the use of a resin-bound proline catalyst for this reaction.[88]

4.1.3 Objectives of This Work

During the studies on the palladium-enamine tandem-catalyzed α-allylation of carbonyl compounds (see chapter 6), chiral 2,3-dihydrobenzo[1,4]oxazines were envisioned to be applicable as organo catalysts. As shown above there is a very limited number of catalysts known in literature for the organo-catalyzed transfer-hydrogenation of α,β-unsaturated carbonyl compounds. Thus, the aim of this project was the use of such 2,3-dihydrobenzo[1,4]oxazine systems as catalysts for this transformation. If this could be achieved, the substrate scope of the reaction was supposed to be extended. So far only the reduction of β-alkyl,β-aryl- or β,β-dialkyl acryl aldehydes has been described in literature. Thus it was planned to examine as well β,β-diaryl compounds with the potential new organo-catalyst.

4.2 Chiral Dihydrobenzo[1,4]oxazines as New Organo-Catalysts



Scheme 45. *Chiral 2,3-dihydro-benzo[1,4]oxazines as new organo-catalysts: mode of stereoinduction (left: (E)-selective iminium formation; right: face-selective hydride transfer).*

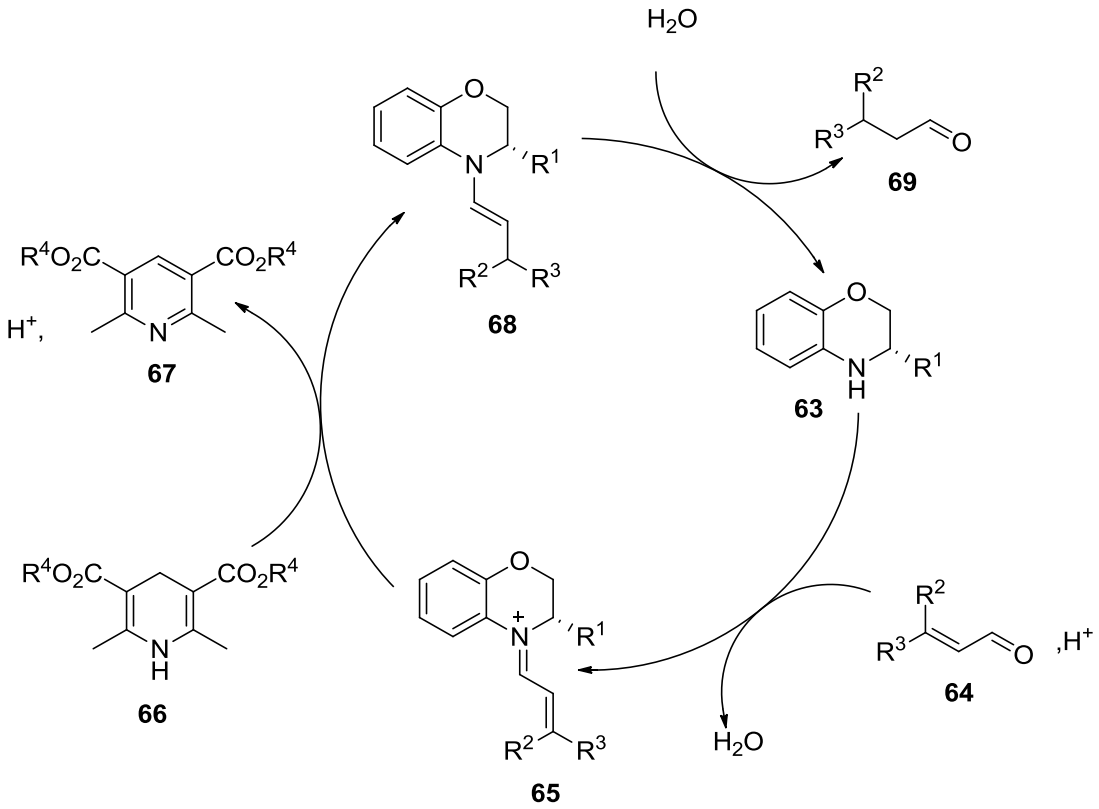
Based on the generally accepted mechanism of asymmetric transfer hydrogenation[89] it was thought that chiral 2,3-dihydrobenzo[1,4]oxazines **63** (scheme 45) could be a useful extension to the known catalysts for this reaction.

Upon reaction between the catalyst **63** and the acryl aldehyde **64** an iminium species **65** should be formed. This intermediate **65** can adopt a *cis*- or a *trans*-conformation. Discrimination between these two isomers by the catalyst is crucial in order to achieve high selectivity in the transformation, because in the (*E*)- and (*Z*)-isomer the opposite faces of the π-system are shielded. As the hydride attack occurs from the unshielded face, opposite enantiomers are formed from the two possible iminium isomers. The new organo-catalyst structure **63** should be able to selectively form the (*E*)-iminium species of **65** due to the planar conformation of the system. The benzene moiety of the catalyst is in conjugation with the α,β unsaturated iminium and due to sp^2-hybridization, all atoms involved should be in the same plane. Thus, (*E*)-iminium formation is expected to be strongly favored because of steric repulsion of the olefinic proton and the benzene ring (scheme 45, left). The stereogenic center is sp^3-hybridized and by this its substituent is not coplanar with the iminium moiety. Therefore less sterical interaction between the substituent on the stereogenic center and the

iminium moiety is present and thus this substituent does not destabilize the planar conformation. Once the enal-system is activated due to the iminium formation the hydride attack can occur. This will proceed face selectively as the substituent on the stereogenic center of the catalyst is shielding one face of the π-system and the hydride approaches the molecule from the less hindered face (scheme 45, right).

As initial experiment to prove the general applicability of benzoxazines as organo-catalyst for the transfer-hydrogenation the ability of this catalyst to form the desired iminium-species **65** was tested. For this purpose cinnamaldehyde was reacted with catalyst **63a** (R^1 = Bn) under acidic conditions and the resulting mixture was analyzed by ESI-MS. Indeed the desired signal corresponding to **65** was observed. Furthermore, it was shown that Hantzsch ester **67** acts as the hydride source, as pyridine species **67**, resulting from oxidation of the Hantzsch ester, was isolated from the reaction mixture.

After this hydride attack, enamine species **68** is formed which, after hydrolysis, sets free the desired hydrogenation product **69** and the regenerated organo-catalyst **63** (scheme 46).[89]

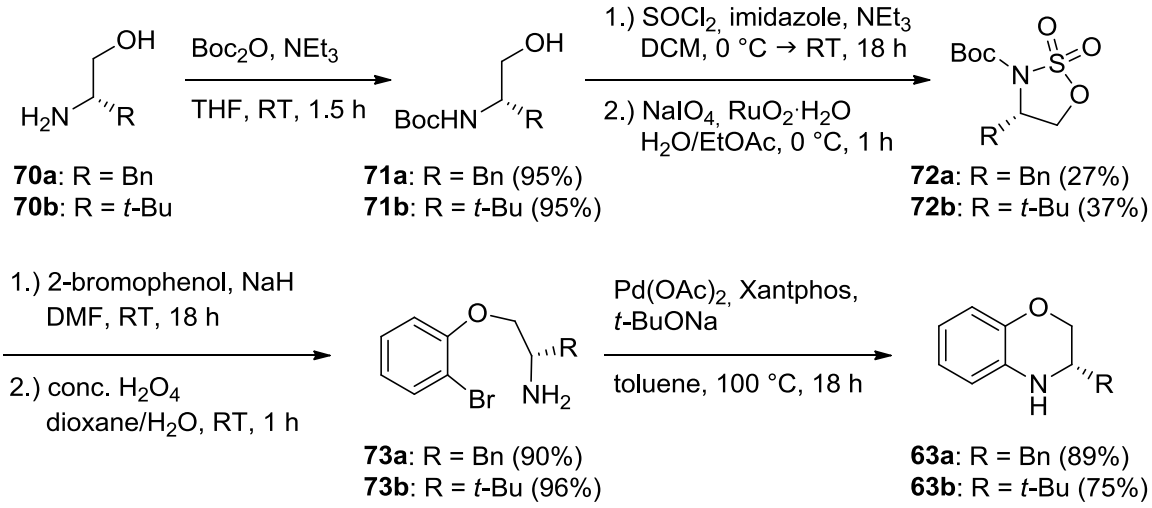


Scheme 46. *Proposed mechanistic cycle.*

4.3 Synthesis

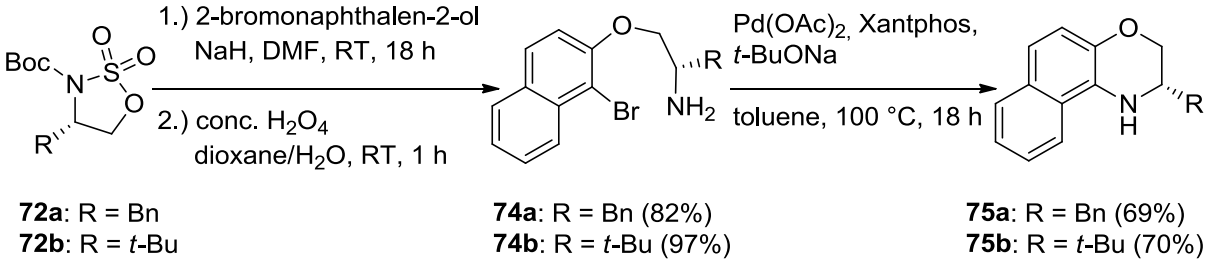
4.3.1 Catalyst Synthesis

Catalyst synthesis was achieved according to a literature-known protocol starting from commercially available aminoalcohols **70** (scheme 47).[90] The aminoalcohols were first *N*-Boc protected and subsequently transformed into the cyclic sulfamidates **72** by reaction of **71** with $SOCl_2$ followed by oxidation with RuO_2. This electrophilic species was then reacted with 2-bromophenol under basic conditions and deprotection under acidic conditions afforded the free amine **73**. These catalyst precursors were then cyclized to the desired benzoxazines **63** by Buchwald-Hartwig amination.[91]



Scheme 47. *Synthesis of benzoxazine catalysts* ***63****.*

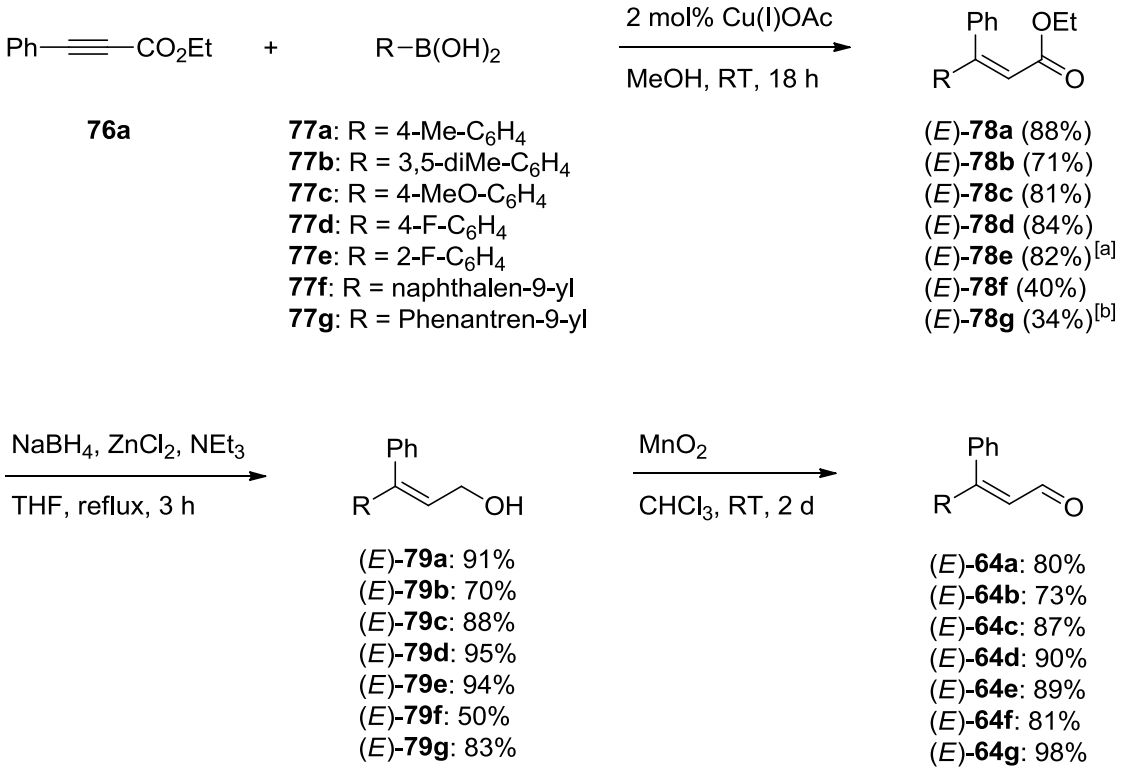
Following the same strategy the corresponding naphthyl derivatives **75** were obtained upon reaction of **72** with 2-bromonaphthalen-2-ol and subsequent palladium-catalyzed ring closure (scheme 48).



Scheme 48. *Synthesis of naphthoxazine catalysts* ***75****.*

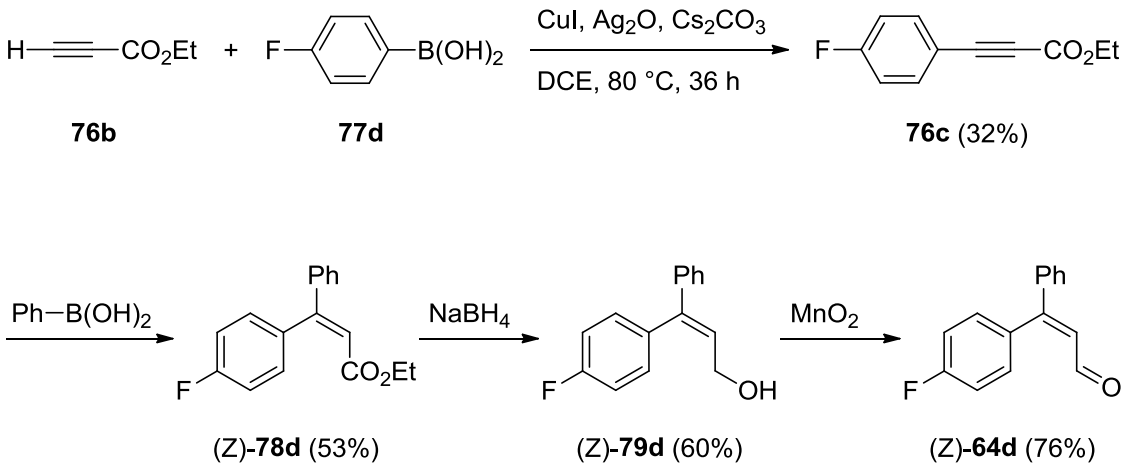
4.3.2 Substrate Synthesis

As mentioned in the introduction one aim of this project was the hydrogenation of β,β-diaryl acryl aldehydes. For this purpose these compounds had to be synthesized in perfect (*E*)/(*Z*)-selectivity. This was achieved according to a literature described protocol (scheme 49).[92] Starting from commercially available 3-phenylpropiolate (**76a**), ethyl acrylates (*E*)-**78** were obtained by copper-catalyzed conjugate addition of the corresponding arylboronic acids **77** with perfect (*E*)-selectivity according to GC analysis. Reduction to the allylic alcohols (*E*)-**79** with $NaBH_4$ and subsequent mild oxidation with MnO_2 afforded the desired acryl aldehydes (*E*)-**64**.



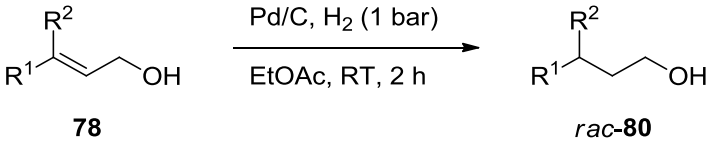
Scheme 49. *(E)-Selective synthesis of β,β-diaryl acryl aldehydes ([a]: carried out using 10 mol% CuOAc for 3 h; [b]: carried out in MeOH/DCM = 2:1).*

In a similar fashion substrate (*Z*)-**64c** was obtained. After transformation of ethyl propiolate (**76b**) into 3-(4-fluorophenyl)-propiolate (**76c**) by a ligand-free copper(I)-catalyzed Sonogashira-type coupling[93] with (4-fluorophenyl)boronic acid (**77c**) the same conditions as described above could be applied in order to obtain the desired (*Z*)-acryl aldehyde in perfect selectivity (scheme 50).



Scheme 50. *(Z)-Selective synthesis of acryl aldehyde* ***64c*** *(conditions for the transformation of* ***76*** *to* ***64*** *as shown in scheme 49).*

As the analysis of the enantiomeric excess after the transfer hydrogenation was carried out after reduction to the corresponding alcohol, racemic samples of the alcohol derived from the hydrogenation products **69** were obtained by hydrogenation of the allyl alcohols **79** using palladium on charcoal (scheme 51).



Scheme 51. *Preparation of racemic samples for HPLC references.*

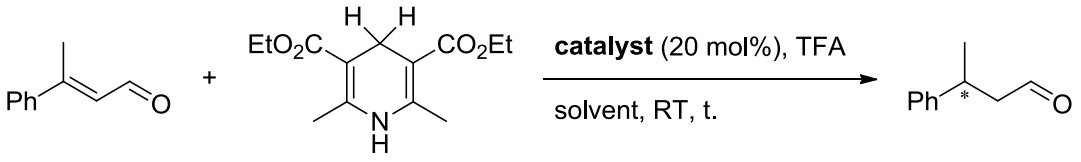
During this work (*E*)-3-(pentadeuterophenyl)-3-phenylacrylaldehyde was prepared as well according to the protocol described above. Unfortunately no GC or HPLC separation conditions were found to analyze the enantiomeric excess of the corresponding hydrogenation product neither of the saturated aldehyde, alcohol nor of various derivatization products.

4.4 Hydrogenation Results

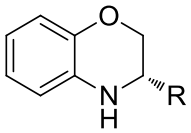
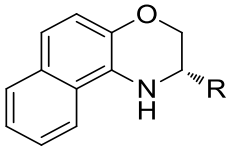
4.4.1 Hydrogenation of β-Methyl Cinnamaldehyde

For initial experiments β-methyl cinnamaldehyde ((*E*)-**64h**) was chosen as model substrate. First the different new organo-catalysts **63** and **75** were investigated (table14).

Table 14. *Catalyst screening for substrate (E)-**64h**.*



64h **66a** **69h**

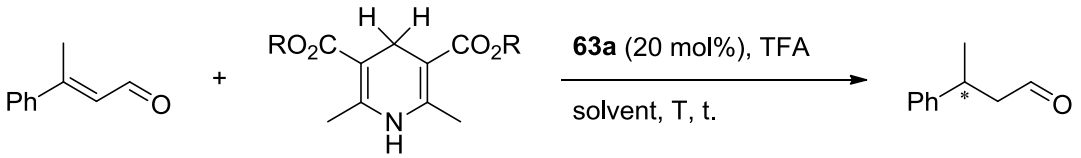
Entry	Catalyst		Solvent	t [h]	Conversion[a] [%]	*ee*[b] [%] (Config.)
1		**63a** (R = Bn)	$CHCl_3$	0.25	>99	61 (*R*)
2		**63b** (R = *t*-Bu)	CH_2Cl_2	0.75	>99	40 (*R*)
3		**75a** (R = Bn)	$CHCl_3$	0.5	>99	59 (*R*)
4		**75b** (R = *t*-Bu)	$CHCl_3$	4	<10	26 (*R*)
5		**75b** (R = *t*-Bu)	$CHCl_3$	24	<10	25 (*R*)

[a]: determined by GC analysis; [b]: determined by GC analysis on a chiral stationary phase.

When catalyst **63a** was applied at room temperature in chloroform a very high activity of the catalyst was found. Under these conditions full conversion to the desired hydrogenation product **69** was found already after 15 min of reaction time (entry 1). Furthermore a promising enantiomeric excess of 61% favoring the (*R*)-enantiomer was found. When other catalyst derivatives were examined it was shown that benzyl-substitution on the stereogenic center of the catalyst leads to higher enantioselectivities compared to *tert*-butyl substituents. A possible explanation for this observation could be π-π interaction between the benzyl group of the catalyst and the conjugated system of the iminium moiety.[94] Due to this stabilizing interaction the benzyl group would be aligned above the iminium system leading to a better

sterical shielding of one face. Furthermore it was found that catalyst **75b**, bearing a naphthyl- and a *tert*-butyl moiety seemed to be too sterically demanding. Thus, the "binding pocket" of the catalyst is too sterically encumbered and the acryl aldehyde cannot access the amine in order to undergo iminium formation resulting in very low conversion to the product even after 24 h. By comparison of the results obtained with the two benzyl-bearing catalysts **63a** and **75a** (entry 1 versus entry 3) it was found that a benzene moiety on the catalyst is already sufficiently sterically demanding in order to form selectively the (*E*)-iminium species. Otherwise the selectivity induced by catalyst **75a** should be higher than the one obtained with **63a** as (*Z*)-iminium formation seems to be impossible with a catalyst bearing a naphthyl moiety.

Table 15. *Optimization studies.*



64h **66** **69h**

Entry	Solvent	T [°C]	t [h]	R	Conversion[a] [%]	*ee*[b] [%] (Config.)[c]
1	$CHCl_3$	25	0.25	Et	>99	61 (*R*)
2	CH_2Cl_2	25	0.25	Et	>99	57 (*R*)
3	Toluene	25	0.25	Et	>99	56 (*R*)
4	Et_2O	25	0.5	Et	>99	69 (*R*)
5	Dioxane	25	1.25	Et	>99	63 (*R*)
6	$CHCl_3$	–25	15[d]	Et	>99	66 (*R*)
7	$CHCl_3$	–50	3	Et	>99	67 (*R*)
8	$CHCl_3$	25	1	*t*-Bu	>99	59 (*R*)

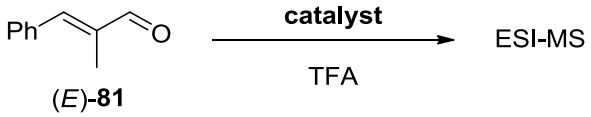
[a]: determined by GC analysis; [b]: determined by chiral GC; [c]: absolute configuration determined by optical rotation and comparison with literature data ((–) = (R))[95]; [d]: conversion was not tested before the given reaction time.

Having identified catalyst **63a** as the best choice, different reaction conditions were tested (table 15). It was shown that the nature of the solvent had only a small influence on the enantiomeric excess found (entries 1-5). The best result was obtained in Et_2O yielding (*R*)-**69h** in full conversion after 30 min with 69% *ee* (entry 4). However, when the reaction was carried out at decreased temperature it did not reach completion anymore. As the reaction proceeded faster in chloroform it could be carried out at low temperature. By this it was found that the selectivity increased with decreasing temperature (entries 6 and 7). The sterical demand of the Hantzsch-ester had essentially no effect on the *ee* as shown in the reaction with the di-*tert*-butyl ester (entry 8). Although full conversions were observed in most cases in less than one hour, the catalyst loading could not be lowered. When this was tried already with 10 mol% catalyst loading the reaction did no more reach completion. These results show that dihydro-benzoxazine derivatives are very reactive catalysts yielding the desired hydrogenation product in remarkably short reaction times. However, in terms of selectivity previously reported catalysts are clearly superior to the ones described herein.

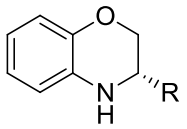
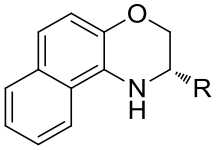
4.4.2 Hydrogenation of α-Methyl Cinnamaldehyde

Next α-substituted acryl aldehydes were tested as potential substrates. For this, α-methyl cinnamaldehyde ((*E*)-**81**) was chosen as model substrate. First, the ability of the different catalysts to form the desired iminium species upon reaction with the substrate was evaluated. For this reason the corresponding catalyst was reacted with (*E*)-**81** under acidic conditions and the resulting mixture was analyzed by ESI-MS (table 16). In all cases tested the desired signal corresponding to the iminium species was observed although always in low intensity. To compare the individual tendencies to form the desired iminium species the observed catalyst/iminium ratio was determined. By this it was found that the largest fraction of iminium ion was formed upon use of catalyst **75a** (catalyst/iminium = 24:1). Surprisingly it was found that the benzoxazine catalysts **63** led to a lower fraction of iminium ion than the naphthoxazines **75**. Again the *tert*-butyl substituted catalysts were too sterically demanding and consequently catalyst **63b** showed the lowest tendency to form the desired iminium species (catalyst/iminium = 250:1). When for comparison cinammaldehyde was mixed with catalyst **63a** in the presence of TFA, a catalyst/iminium signal ratio of 2.3:1 was found by ESI-MS analysis.

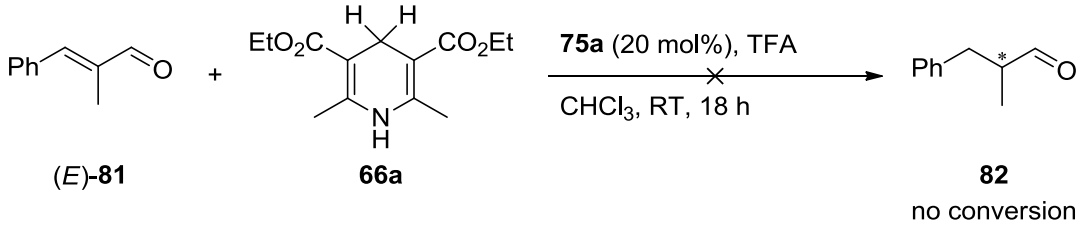
Table 16. *Testing for the ability of the catalysts to form iminium species.*



(*E*)-**81**

Entry	Catalyst		*m/z* calc. (cat. + H^+)	*m/z* Calc. (iminium)	*m/z* Obs.	Cat./iminium ratio
1		**63a** (R = Bn)	226	354	226 354	29:1
2		**63b** (R = *t*-Bu)	192	320	192 320	250:1
3		**75a** (R = Bn)	276	404	279 404	24:1
4		**(75b)** (R = *t*-Bu)	242	370	242 370	53:1

In agreement with the observation that no sufficient enamine formation is obtained, no conversion to the desired saturated aldehyde was observed when catalyst **75a** was then tested in the transfer-hydrogenation of substrate (*E*)-**81** (scheme 52) even after 18 h. Thus, α-substituted aldehydes were not further investigated.

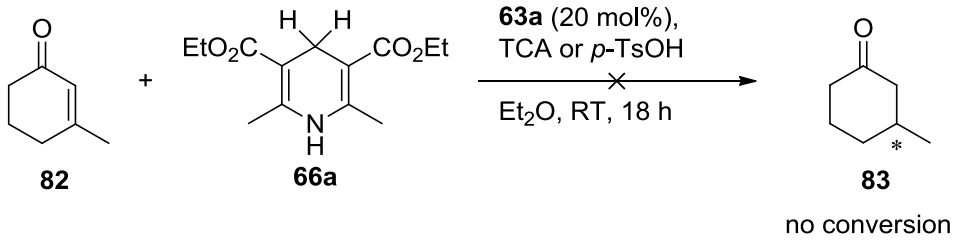


(*E*)-**81** **66a** **82**
no conversion

Scheme 52. *Attempted transfer-hydrogenation of α-methyl cinnamaldehyde ((E)-**81**).*

4.4.3 Hydrogenation of α,β-Unsaturated Ketones

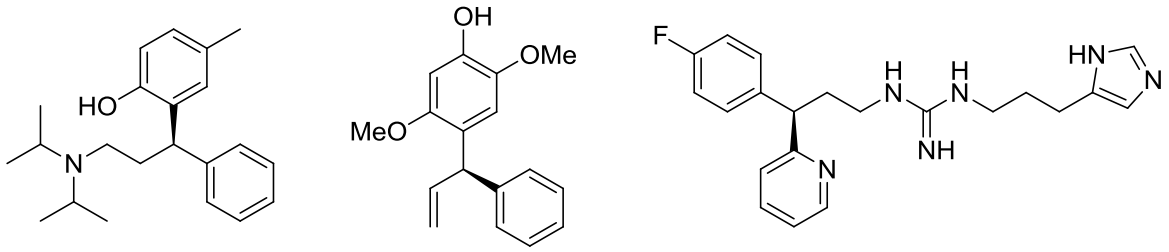
Next, the attention was turned towards the transfer-hydrogenation of α,β-unsaturated ketones. As model substrate for this reaction β-methyl cyclohexenone (**82**) was selected and catalyst **63a** was tested under the same conditions as reported in literature for such substrates.[83] Again no conversion to the desired saturated ketone **83** could be observed using different acids (scheme 53). As expected, when the ability of the catalyst to form the desired iminium species was tested by ESI-MS studies no iminium signals could be observed in this case.



Scheme 53. *Attempted transfer-hydrogenation of β-methyl cyclohexenone (**82**).*

4.4.4 Hydrogenation of β,β-Diaryl Acryl Aldehydes

The hydrogenation of β,β-diaryl acryl aldehydes would lead to saturated aldehydes with a diaryl-substituted stereogenic center in the β position. Such compounds would be very valuable as potential precursors for the synthesis of bioactive natural products or drugs such as tolteridine (**84**),[96] mimosifoliol (**85**)[97] or arpromidine (**86**)[98] (figure 21).



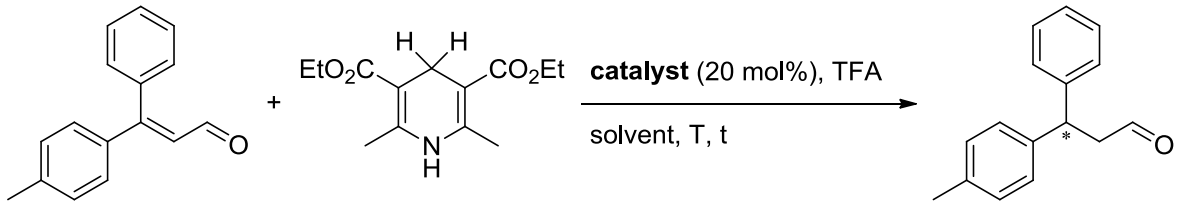
84 tolteridine | **85** mimosifoliol | **86** arpromidine

Figure 21. *Natural products or drugs which could be accessible from saturated aldehydes with a diaryl-substituted stereogenic center in the β position*

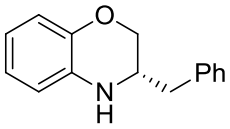
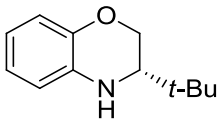
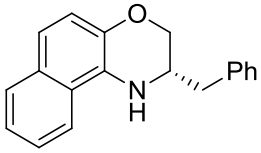
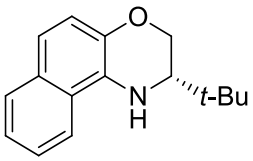
There are only very few examples on the enantioselective conjugate reduction of 1-acceptor-substituted 2,2-diarylalkenes found in literature. ANDERSSON and co-workers reported on the iridium-catalyzed asymmetric hydrogenation of α,β-unsaturated esters, allylic alcohols and allylic acetates of that kind.[99] YUN and co-workers described previously the copper-catalyzed asymmetric reduction of 3,3-diaryl-acrylonitriles.[98] In the asymmetric hydrogenation of terminal diarylalkenes, WANG and co-workers showed the applicability of chiral rhodium catalysts.[100] However, no such reactions of β,β-diaryl-acrylaldehydes have been reported yet.

For initial experiments with this class of substrates (*E*)-3-phenyl-3-(*p*-tolyl)acrylaldehyde (*E*)-**64a** was chosen as test substrate (table17).

Table 17. *Optimization studies on the transfer-hydrogenation of β,β-diaryl acryl aldehydes.*



64a **66a** **69a**

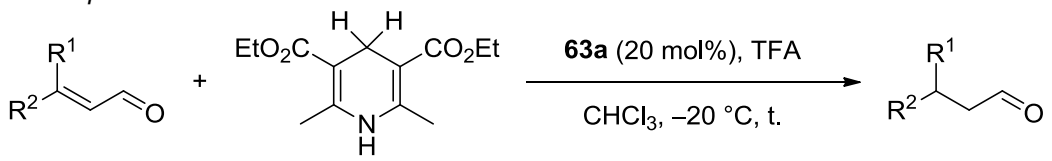
Entry	Catalyst	Solvent	T [°C]	t [min]	Conversion[a] [%]	*ee*[b] [%] (Config.)
1	 **63a**	$CHCl_3$	25	15	>99	76 (+)
2	 **63b**	$CHCl_3$	25	60	75	79 (+)
3	 **75a**	$CHCl_3$	25	120	40	73 (+)
4	 **75b**	$CHCl_3$	25	300	<10	n.d.
5	**63a**	Et_2O	25	30	>99	63 (+)
6	**63a**	CH_2Cl_2	25	60	>99	72 (+)
7	**63a**	$CHCl_3$	–20	45	>99	78 (+)
8	**63a**	$CHCl_3$	–40	210	50	n.d.

[a]: Determined by GC analysis; [b]: determined by HPLC analysis on a chiral stationary phase of the corresponding saturated alcohol after reduction with $NaBH_4$.

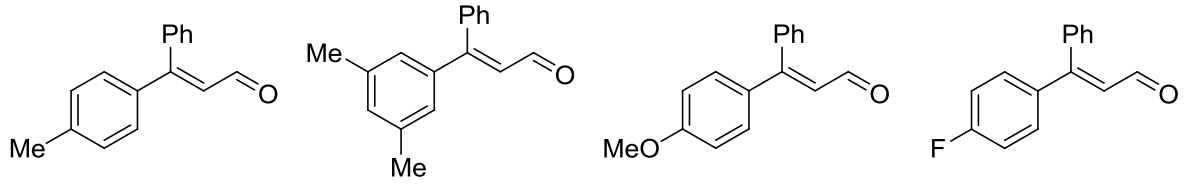
A brief catalyst screening (entries 1-4) revealed again catalyst **63a** as the best choice giving full conversion in remarkably short reaction time. Generally significantly higher activities were found for the benzoxazine catalysts **63** compared to the naphthoxazines **75**. Catalyst **63a** emerged as the catalyst of choice for this reaction yielding the hydrogenation product **69a** in full conversion with 76% *ee* (entry 1). Although the *tert*-butyl analogue **63b** was slightly more

selective it was less practical as only 75% conversion was found even after prolonged reaction time of 60 min (entry 2). Furthermore it was found that again the nature of the solvent had only a small influence on the selectivity of the catalyst (entries 1, 5 and 6). While for β-methyl cinnamaldehyde (**64h**) Et_2O led to the highest selectivity now chloroform was the solvent of choice. Taking advantage of the high activity of the catalyst it was possible to perform the reaction at lower temperatures. At –20 °C still full conversion was found after only 45 min (entry 7). When the temperature was further decreased to –40 °C the reaction did not reach completion anymore (entry 8). Having found the optimal reaction conditions (entry 7), the scope of the reaction was examined (table 18).

Table 18. *Scope of the reaction.*[a]



64 **66a** **69**

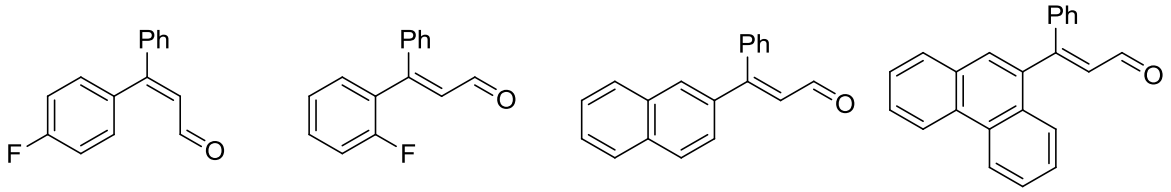


(*E*)-**64a**
t = 1 h.
>99% conv.
78% *ee* (+)

(*E*)-**64b**
t = 3.5 h.
90% conv.
82% *ee* (*S*)

(*E*)-**64c**
t = 23 h.
>99% conv.
87% *ee* (*S*)

(*E*)-**64d**
t = 2 h.
>99% conv.
91% *ee* (*S*)



(*Z*)-**64d**
t = 3 h.
>99% conv.
80% *ee* (*R*)

(*E*)-**64e**
t = 3 h.
>99% conv.
91% *ee* (+)

(*E*)-**64f**
t = 4.5 h.
83% conv.
87% *ee* (*S*)

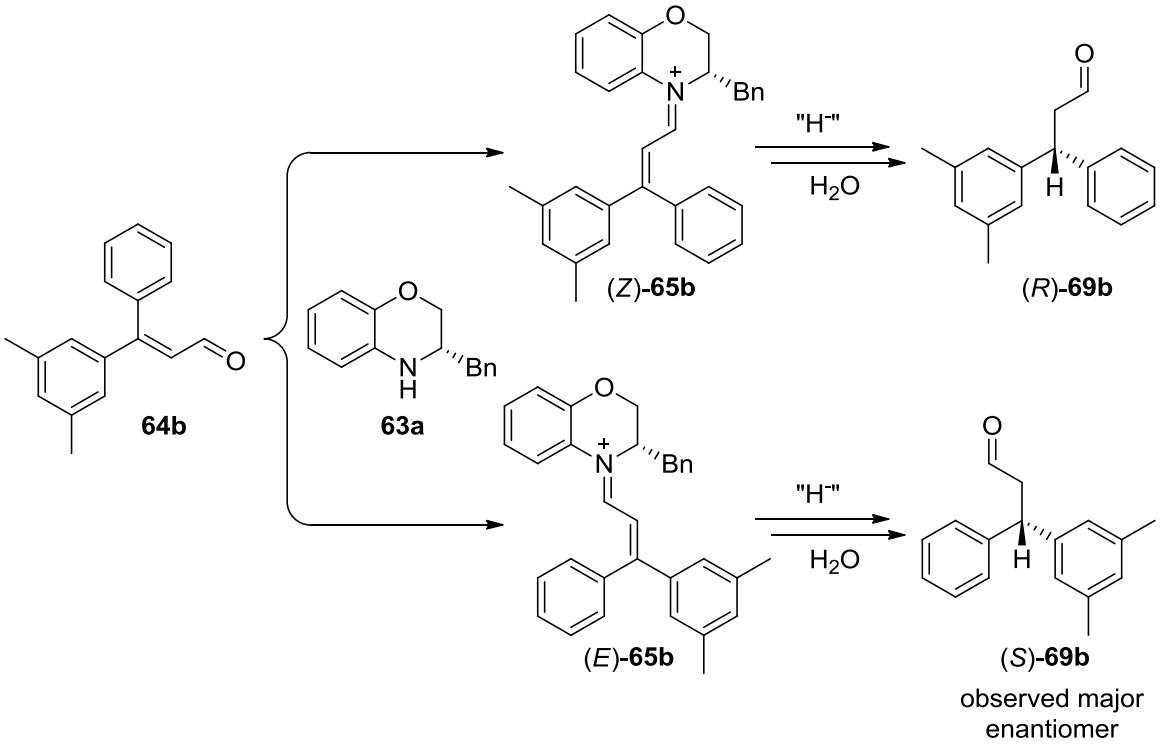
(*E*)-**64g**
t = 6 h (at RT).
<5% conv.
***ee* n.d.**

[a]: Conversion determined by GC analysis of the reaction mixture; the ee was determined by HPLC analysis of the corresponding alcohol on a chiral stationary phase after reduction with $NaBH_4$. When given, the absolute configuration was determined by comparison of the sign of optical rotation of the saturated aldehyde with literature data.[101]

Catalyst **63a** showed both high activity and selectivity in the hydrogenation of the substrates tested. Enantiomeric excesses from 78%-91% were found. Electron-donating (**64c**) as well as as electron-withdrawing (**64d**-**64e**) substituents on the aryl moiety of the substrate were tolerated. The sterical demand of the substrate seemed to be the limiting factor. When

substituents in *meta*-position of the aryl ring were present in the substrate (**64b** and **64f**) incomplete conversions were observed. The enantioselectivities in these examples however, remained at a high level. Substrate **64g** bearing a substitution in the *ortho*-position of the aryl-moiety proved to be unreactive. Apparently, the phenanthrenyl group induced too much steric hindrance and thus only traces of product were formed.

The absolute configuration of the major enantiomers formed in this reaction is in agreement with the proposed model of stereoinduction shown in scheme 45. For example in the reduction of substrate **54b** both, the *cis*- and the *trans*-isomers could be formed while according to the proposed mode of action of the catalyst the iminium species (*E*)-**65b** should be favored. If the reaction proceed via this intermediate the hydride delivered from the Hantzsch ester would approach the conjugate system in a *Re*-facial attack and after hydrolysis lead to the formation of (*S*)-**69b**. Reaction via iminium species (*Z*)-**65b** would lead to the (*R*)-enantiomer of the hydrogenation product should be formed (scheme 54). As shown in table 18, substrate **64b** was converted to (*S*)-**69b** with 82% *ee* which is in accordance with the proposed mode of stereoinduction.

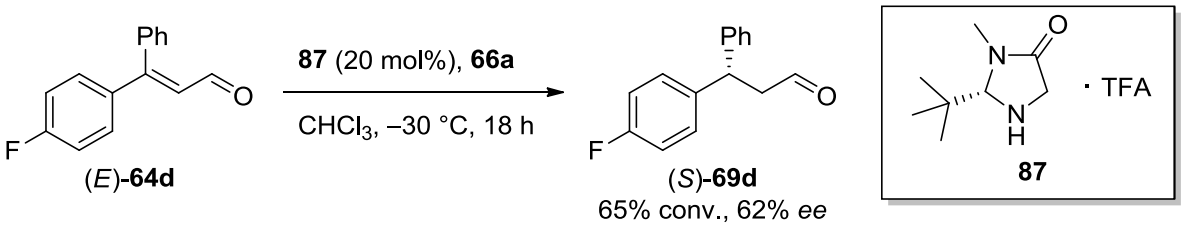


Scheme 54. *Verification of the proposed mode of stereoinduction.*

For substrate **64d** both the *cis* and the *trans* isomer were applied in the transfer-hydrogenation. It was found that the sense of chiral induction depends on the configuration of the C-C double bond of the substrate. While the reduction of (*E*)-**64d** resulted in formation of

(*S*)-**69d** (91% *ee*), the use of substrate (*Z*)-**64d** led to the other enantiomer (*R*)-**69d** (80% *ee*). In this respect the hydrogenation of β,β-diaryl acryl aldehydes differs from the previously reported reduction of β-alkyl derivatives were a stereoconvergent pathway was observed, leading to the same product enantiomer starting from either the (*E*)- or the (*Z*)-substrate. This has been rationalized by rapid *cis/trans* isomerization via a dienamine intermediate under the reaction conditions.[81] As such an isomerization is obviously not possible for β,β-diaryl compounds, the different (*E*)- and (*Z*)-substrates are converted to opposite enantiomers. As described above enantiocontrol is obtained due to sterical repulsion between the benzene moiety of the catalyst and the less substituted α-C atom of the substrate rather than by interaction with the prochiral β-CAr^1Ar^2 unit. Consequently, it is possible to achieve high enantioselectivity even with sterically and electronically very similar aryl substituents, provided that the substrate is available as pure (*E*)- or (*Z*)- isomer.

For comparison the literature described (*S*)-2-(*tert*-butyl)-3-methylimidazolidin-4-one catalyst[102] **87** was tested in the hydrogenation of substrate (*E*)-**64d** under the reported reaction conditions[82] (scheme 55).

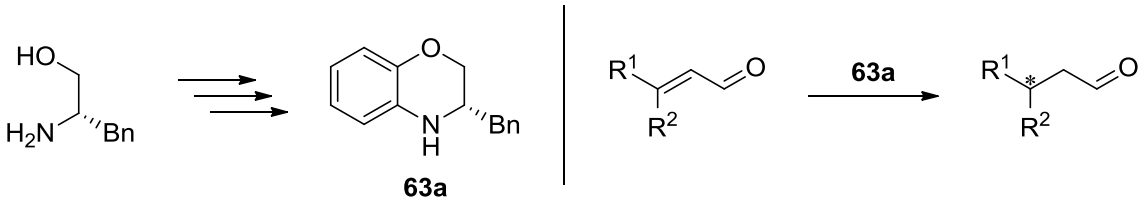


Scheme 55. *Comparison with the literature described imidazolidinone-catalyst* ***87****.*

When this experiment was carried out a significantly lower activity of catalyst **87** was found. Even after 18 h the conversion did not reach more than 65% and did not further increase from there on. After 2 h, during which time full conversion was achieved using benzoxazine catalyst **63a**, the conversion was found to be at only 26%. As well in terms of enantioselectivity catalyst **87** performed clearly inferior compared to catalyst **63a**. The enantiomeric excess of the hydrogenation product **69d** was found to be at 62% while, as shown in table18, upon use of catalyst **63a** 91% *ee* were obtained.

4.5 Summary and Outlook

In summary it was shown that chiral 2,3-dihydro-benzo[1,4]oxazines are efficient catalysts for the enantioselective organo-catalyzed transfer-hydrogenation of acryl aldehydes, a reaction for which only a very limited set of catalysts has been reported in literature so far. Synthesis of these new catalysts has been achieved by a short and reliable pathway starting from readily available starting materials (scheme 56). Especially the benzyl substituted derivative **63a** showed both high activity and selectivity in this reaction, possibly due to π,π-interactions of the catalyst with the conjugated system of the substrate.



Scheme 56. *Benzyl-substituted chiral benzoxazine as efficient catalyst for organo-catalyzed transfer-hydrogenations of acryl aldehydes.*

While conjugate reduction of α-substituted acrylaldehydes and of α,β-unsaturated ketones gave unsatisfying results, this catalyst class appears to be particularly effective for the transfer-hydrogenation of β,β-diaryl-substituted acrylaldehydes, a reaction which has not been reported for other organocatalysts yet, yielding potential precursors for the synthesis of various bioactive natural products or drugs. Synthesis of such substrates has been achieved in perfect (*E*)/(*Z*)-selectivity. Comparison with the previously established catalyst for this substrate class indicated superior performance of the benzoxazine catalyst and thus making it a valuable extension to the previously known catalysts.

Future work on this project might be dedicated to further optimization of the catalyst. Especially the installation of other aryl-moiety bearing substituents on the stereogenic center might be interesting in order to tune both the ability of sterical shielding of one substrate face and the tendency to undergo π,π-interactions between the catalyst and the substrate. Furthermore changing the electronic properties of the benzene moiety of the catalyst by installation of electron-donating or withdrawing groups could lead to improved properties of this catalyst.

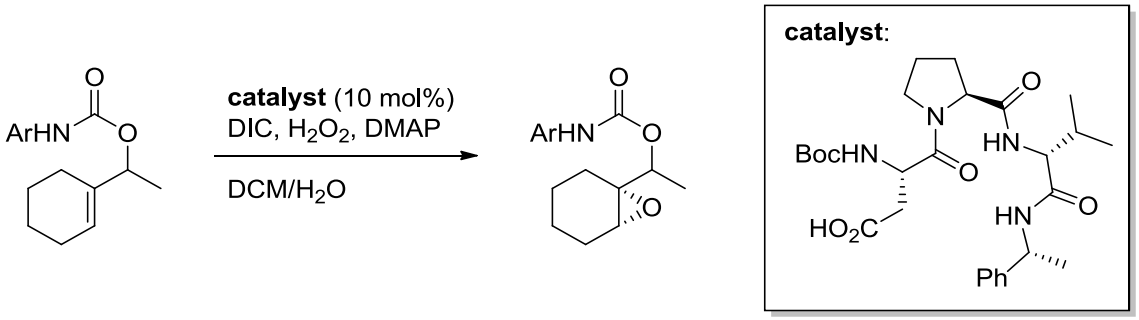
Chapter 5

Mechanistic Investigations on the Organo-Catalyzed Conjugate Addition Reaction

5.1 Introduction

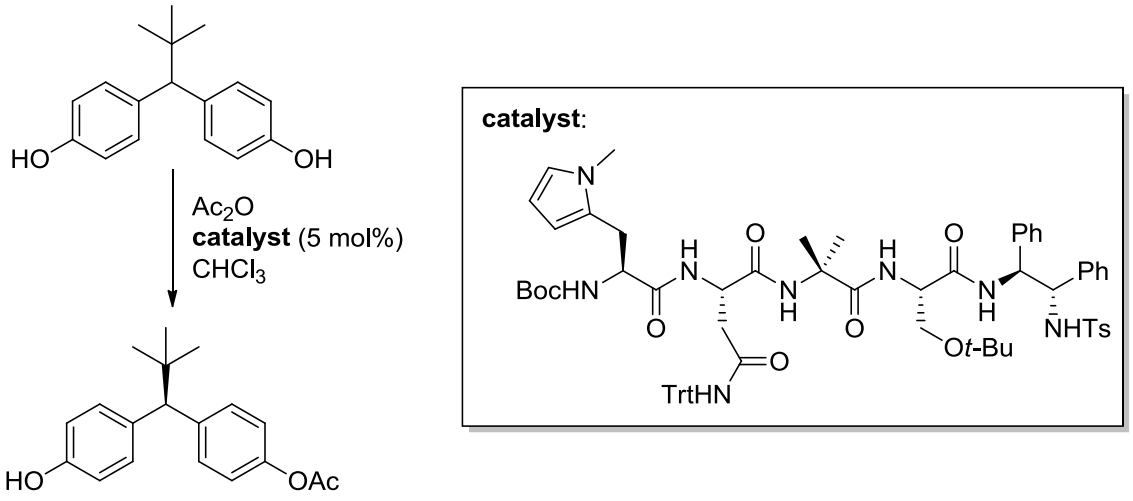
5.1.1 Peptides in Asymmetric Catalysis

Peptides are found in various areas in daily life as for instance in hormones, toxins, drugs, artificial sweeteners and many other examples.[103] As well in the field of asymmetric catalysis peptides have been applied successfully in various transformations.[104] Peptide based catalysts often provide unique features which cannot be achieved with conventional catalyst systems. One example of the applicability of peptides in asymmetric catalysis has been shown by MILLER and co-workers, who reported on the asymmetric epoxidation of alkene carbamates (scheme 57).[105]



Scheme 57. *Asymmetric epoxidation of alkene carbamates.*[105]

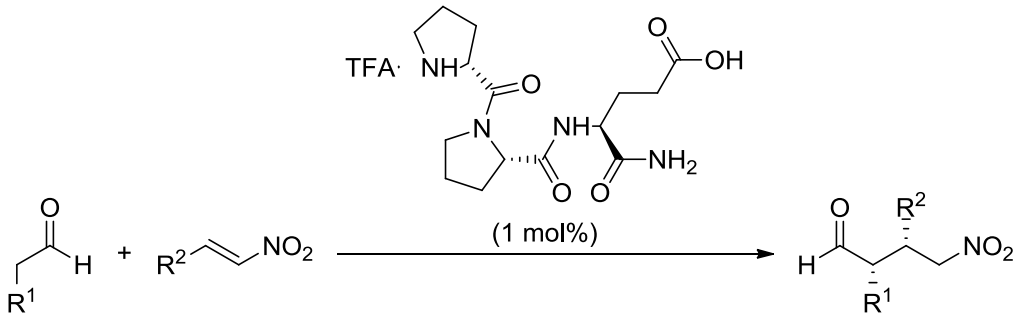
The same group described the use of a peptide-catalyst for the desymmetrization of meso-diols (scheme 58).[106] As well in C-C bond forming reaction such peptide catalysts attracted interest as for example in aldol reactions.[107]



Scheme 58. *Desymmetrization of bis-phenols.*[106]

5.1.2 Tripeptide Catalyzed Conjugate Addition Reaction of Aldehydes to Nitroolefins

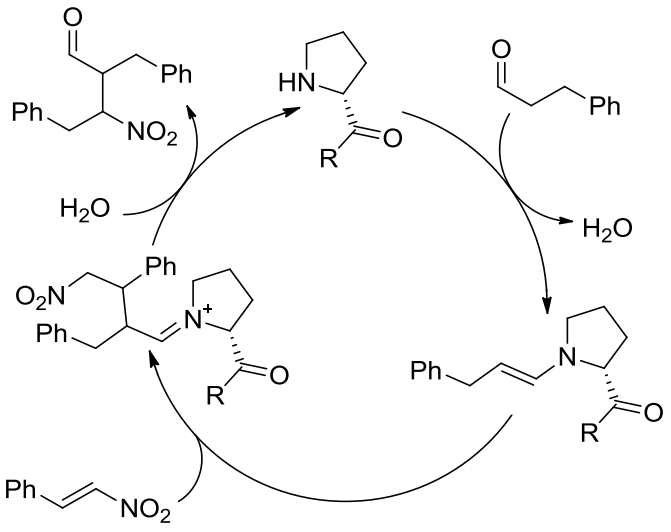
In 2010 WIESNER and WENNEMERS described the tripeptide-catalyzed conjugate addition of aldehydes to nitroolefins (scheme 59).[108]



Scheme 59. *Tripeptide-catalyzed conjugate addition of aldehydes to nitroolefins.*[108]

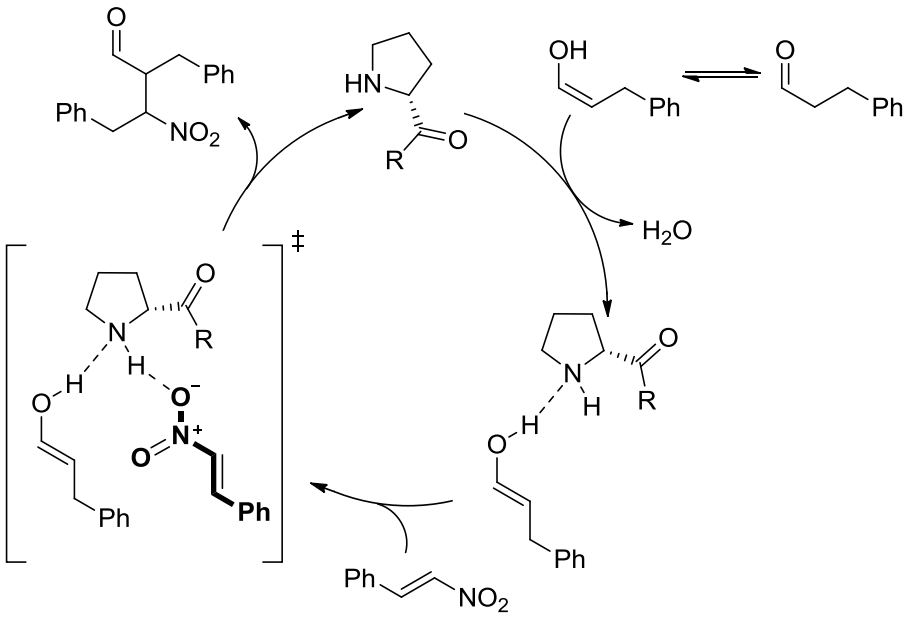
In this report they could show that for all substrates tested an enantiomeric excess of at least 90% was obtained. Furthermore this catalyst proved to be highly active as the reaction was conducted using only 1 mol% catalyst loading still reaching high yields. This is a remarkable low catalyst loading in the field of organo-catalysis which could be improved even more towards 0.1 mol% after kinetic studies and optimization of reaction conditions.[109]

In analogy to organo-catalyzed aldol reactions,[110] the proposed mechanism proceeds via formation of an enamine species by reaction between the organocatalyst and the aldehyde (scheme 60). This is then followed by attack of the enamine onto the nitroolefin which should be the enantiodiscriminating step. Hydrolysis of the resulting iminium finally leads to the regeneration of the catalyst and release of the addition product.[109]



Scheme 60. *Proposed catalytic cycle assuming an enamine-catalysis pathway.*[109]

However, this mechanistical pathway is not fully accepted yet. KRAUSE and ALEXAKIS for example proposed a mechanistical pathway via enol formation (scheme 61).[111] Hydrogen bonding between this enol and the catalyst and additional hydrogen bonding to the nitroolefin would then lead to an asymmetric transition state and subsequent attack of the enol onto the nitroolefin would liberate the product.

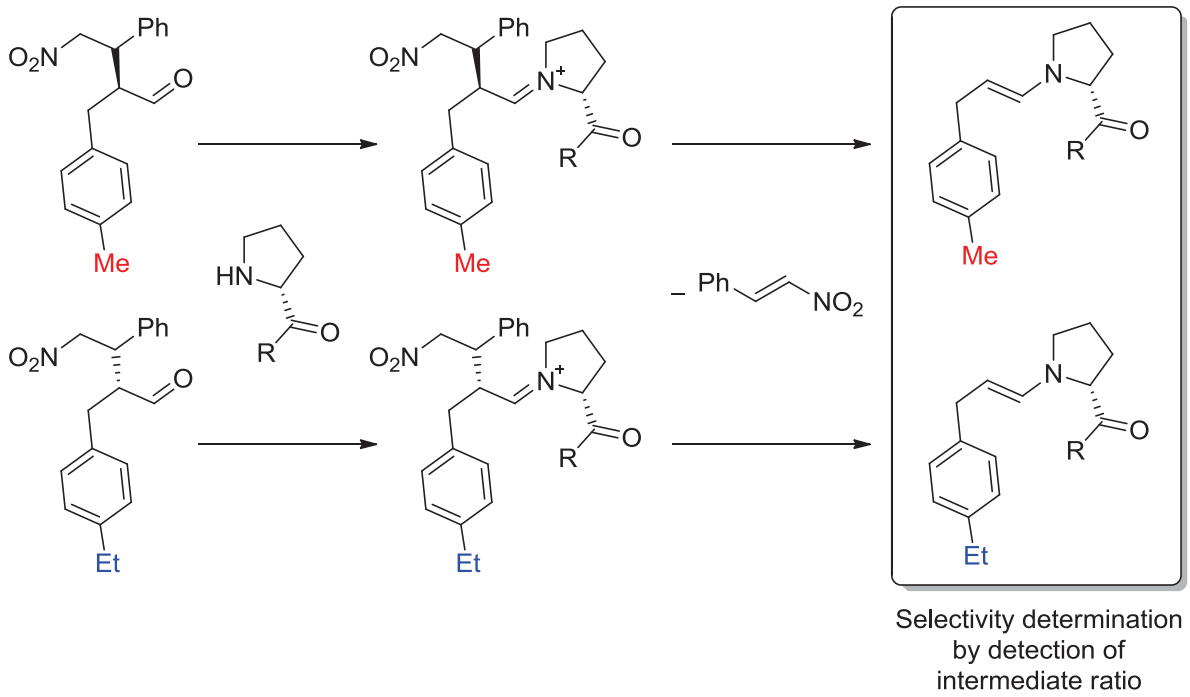


Scheme 61. *Proposed catalytic cycle assuming an enol pathway.*[111]

By conducting labeling experiments KRAUSE and ALEXAKIS found some evidence for this assumption, though it has to be mentioned that these studies were carried out in aqueous media, what of course has a strong influence on the enamine formation tendency and its stability.

5.1.3 Objectives of This Work

The aim of this project was to elucidate the actual mechanistical pathway in the organo-catalyzed conjugate addition of aldehydes to nitroolefins using the highly active and selective tripeptide-catalyst previously reported. In collaboration with JÖRG DUSCHMALÉ and HELMA WENNEMERS it was aimed to perform ESI-MS studies in order to prove the existence of the enamine- and iminium-intermediates proposed for the enamine pathway. Furthermore, selectivity determination by ESI-MS screening of the back reaction was supposed to be carried out (scheme 62) based on the concept previously published by FLEISCHER and PFALTZ.[23]



Scheme 62. *Aimed selectivity determination by ESI-MS back reaction screening.*

By this methodology the intrinsic selectivity of the attack of the enamine onto the nitroolefin can be determined as the enamine species is supposed to be detected by ESI-MS. If this selectivity equals the selectivity of the preparative reaction, this would be very strong evidence that the attack of the enamine species is the enantiodiscriminating step in the catalytic cycle. As this is only true for the proposed mechanism which is proceeding via enamine-catalysis this study should account to the elucidation of the reaction mechanism in this transformation.

5.2 Mechanism Studies

5.2.1 Investigating the Forward Reaction

First, the forward reaction of the organo-catalyzed conjugate addition of aldehydes to nitroolefins was examined by ESI-MS. For this purpose aldehyde **88a** was reacted with the tripeptidic catalyst **89a** in a mixture of *i*-PrOH/$CHCl_3$ (9:1) and analyzed by ESI-MS. This corresponds to the reaction conditions previously reported by WENNEMERS.[108] When this experiment was carried out the corresponding mass signals of the protonated catalyst **89a** and the protonated enamine species **90a** were observed (figure 22, left). Additional signals, which were found, could be assigned to a dimeric species of the catalyst and in a small amount the sodium adduct of the catalyst was observed as well. When the nitroolefin **91** was added an additional signal corresponding to the desired iminium species **92a** was found (figure 22, right). All other previously detected signals were still present in the spectrum.

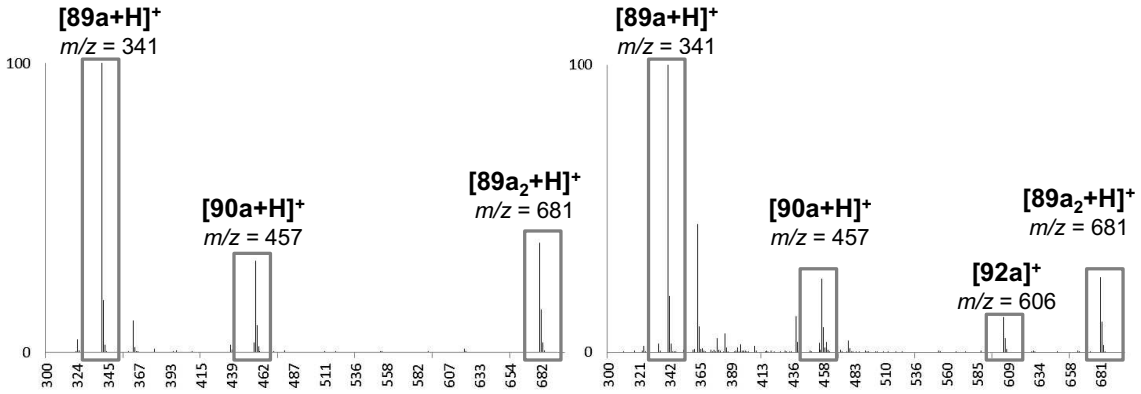
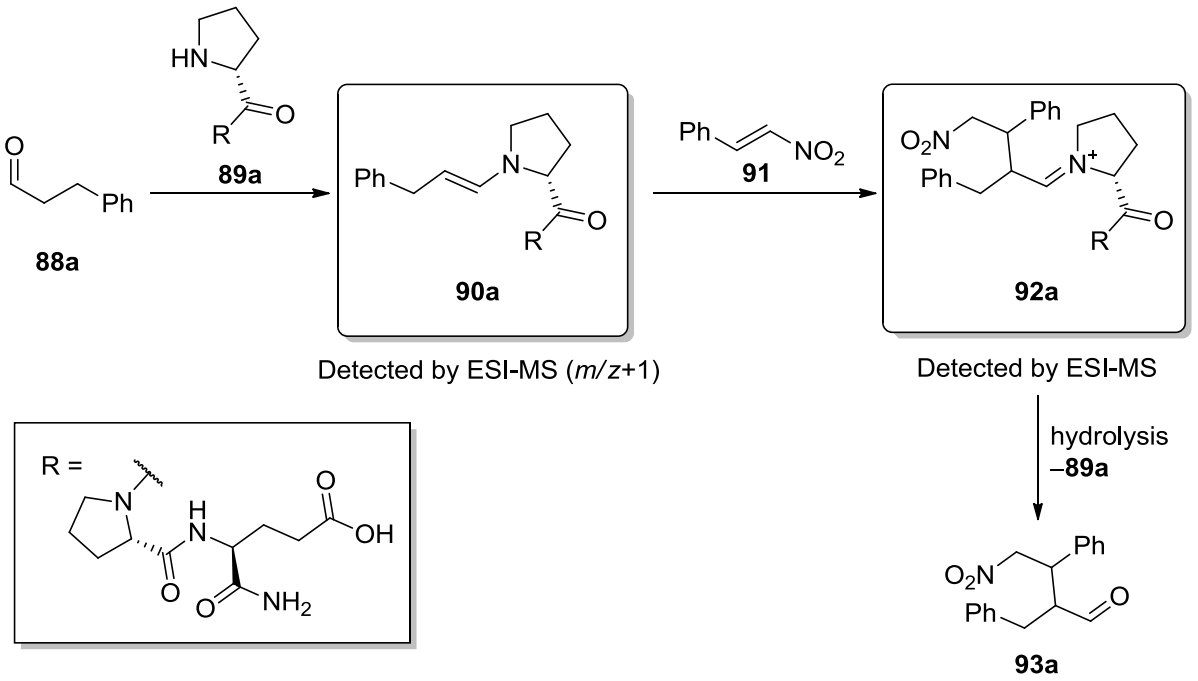


Figure 22. *ESI-MS spectra of the studies on the forward reaction (left: after reaction between aldehyde **88a** and catalyst **89a**; right: after addition of nitroolefin **91**).*

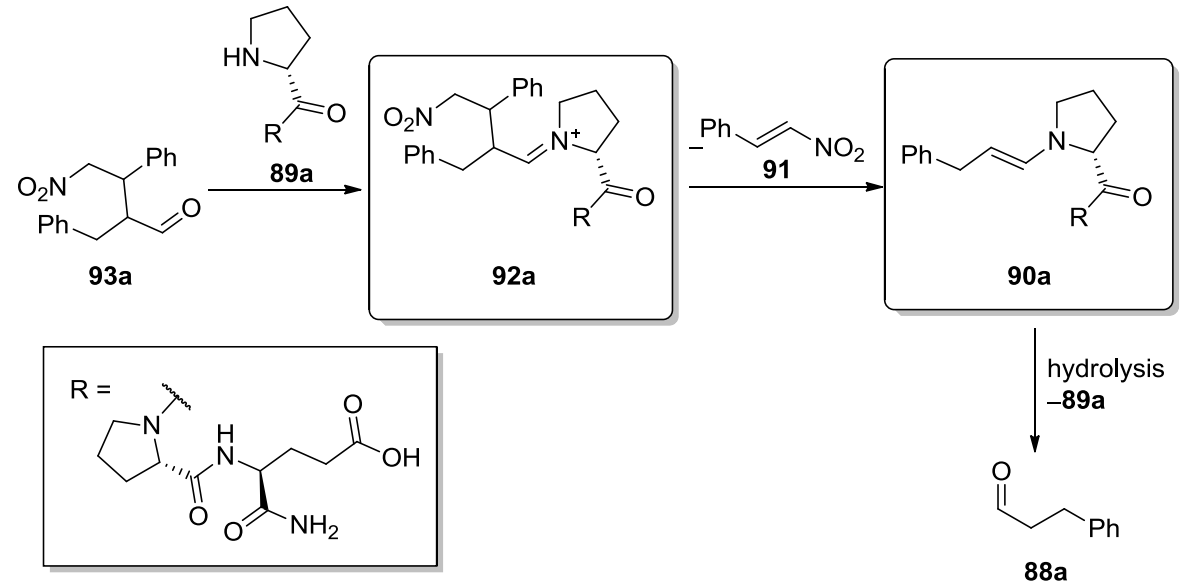
These findings support the assumption, that an enamine-catalysis pathway is taking place. Scheme 63 shows again this route.



Scheme 63. *Proposed pathway of the formation of* ***93a*** *according to the observed intermediates.*

5.2.2 Investigating the Back Reaction

Having observed all desired reaction intermediates in the forward reaction the attention was focused on studying the back reaction (scheme 64).



Scheme 64. *ESI-MS studies on the back reaction.*

For this purpose the catalysis product **93a** was mixed with the tripeptidic catalyst **89a** under the same reaction conditions as before. When this was done, again both desired intermediates **92a** and **90a** were observed although the enamine species was detected with only very low intensity (figure 23).

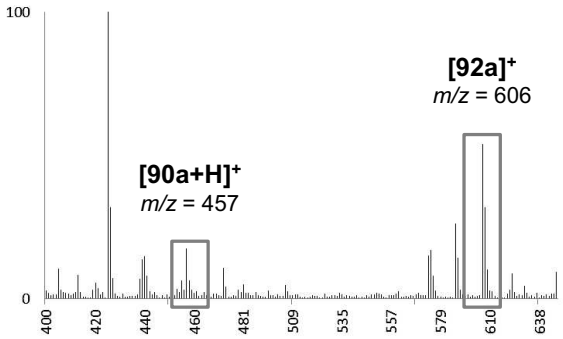
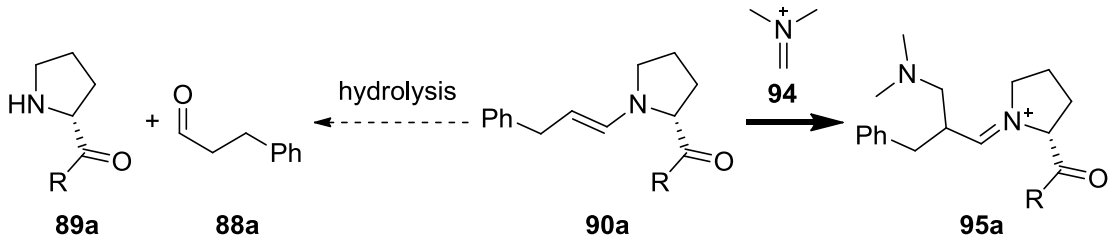


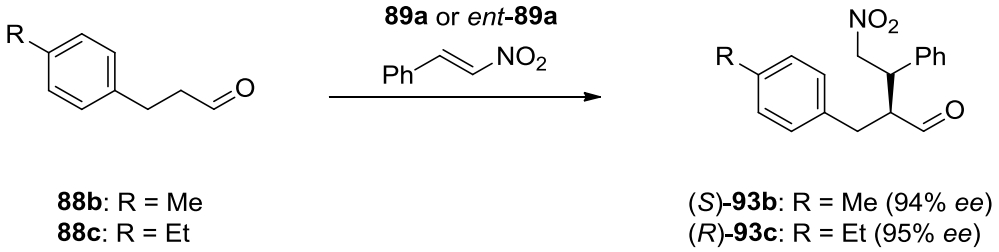
Figure 23. *ESI-MS spectra of the studies on the back reaction.*

The difficulty in this approach lies in the detection of the enamine species. One problem in here is the fact that this is an uncharged species and in order to detect it by ESI-MS it has to be protonated. However the reaction conditions are not very acidic and thus such protonation might take place to a low extend. Furthermore this species lies in equilibrium with the iminium species **92a** and as well with the free catalyst **89a**. Especially the latter has been proven to be far on the side of the free catalyst.[109] Hence, if only low amounts of enamine species **90a** are formed in the back reaction, it is already hard to detect the desired signal and gets even more complicated as the enamine tends to hydrolyze to give the free catalyst and the aldehyde. One idea to overcome this difficulty was to trap the enamine intermediate with a highly reactive electrophile (as for example the Eschemoser´s salt **94**). This would lead to the formation of a positively charges iminium species **95a** which can be more easily detected by ESI-MS. Furthermore it would act as a sink, trapping all enamine formed and by this taking it out of the equilibriums (scheme 65). Unfortunately this attempt was not successful and the desired signal corresponding to **95a** could not be detected.



Scheme 65. *Attempted trapping of the enamine species to facilitate intermediate visualization by ESI-MS.*

Nevertheless it was decided to determine the selectivity of the enamine attack onto the nitroolefin by ESI-MS using mass labeled quasi-enantiomeric substrates.[23] For this purpose such substrates were synthesized following the previously published protocol (scheme 66).[108]



Scheme 66. *Synthesis of mass-labeled quasi-enantiomeric substrates.*

The desired substrates were formed with the same selectivity as the unsubstituted product **93a** (95% *ee*).[108] This indicates that the *para*-position of the phenyl ring on the aldehyde seems to be a suitable position for the installation of mass labels, showing no significant influence on the outcome of the reaction.

When the back reaction screening was carried out under the previously used reaction conditions using an equimolar mixture of these quasi-enantiomers the mass spectrum shown in figure 24 was obtained.

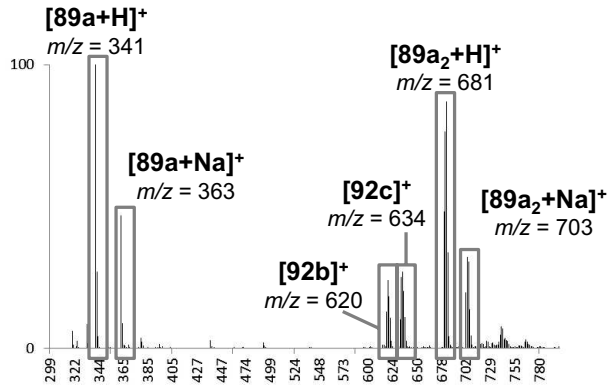


Figure 24. *ESI-MS back-reaction screening using mass-labeled substrates.*

Again basically all of the detected signals could be assigned to the corresponding reaction intermediates. Most of the signals observed were related to the tripeptidic catalyst. The iminium species **92b** and **92c** were observed as well. However, again the detection of the enamine intermediates **90** was difficult and this time the corresponding mass signals could not be found. It seemed likely, that under the reported reaction conditions the enamine intermediates are not formed in sufficient quantities in order to observe them by ESI-MS and

thus an optimization of the screening protocol was desirable. One approach to achieve this aim would be the use of charge tags on the catalyst in order to facilitate the detection of the otherwise uncharged enamine intermediate in analogy to previously reported ESI-MS studies.[112] Thus, the corresponding derivative of the tripeptidic catalyst was synthesized bearing an imidazolium function connected via an amide-bond in the 4-position of the second proline-moiety (figure 25).

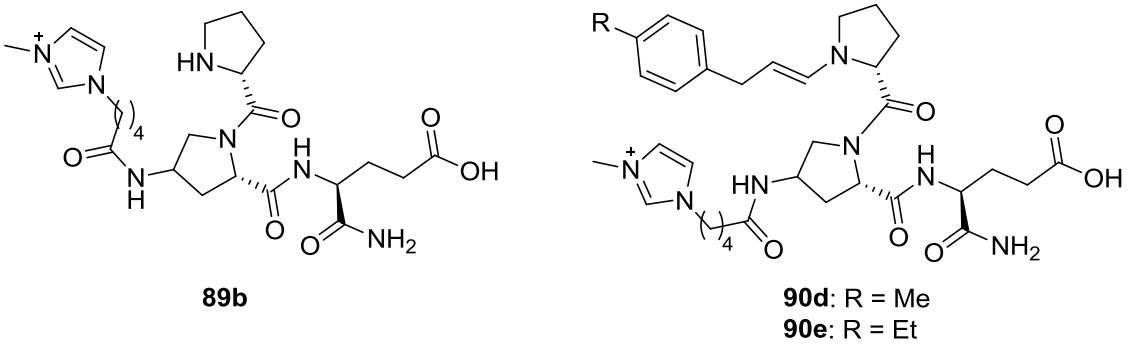
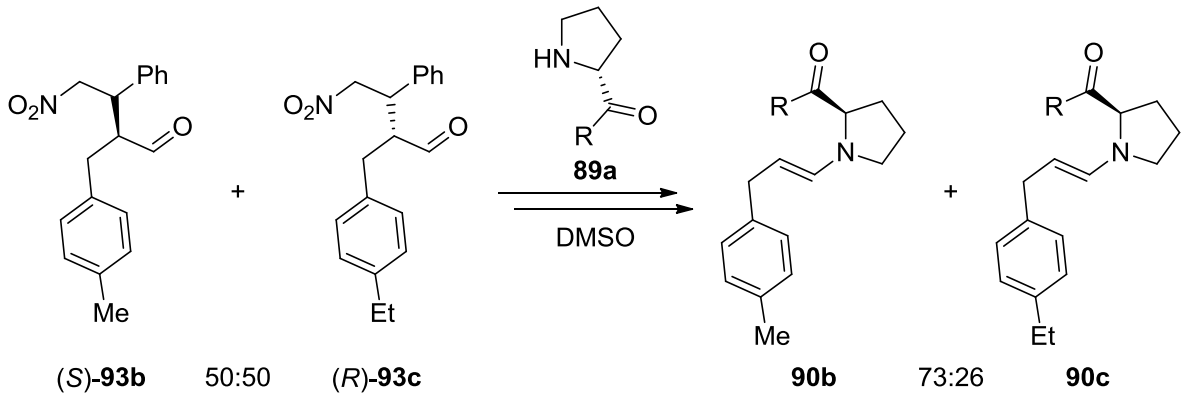


Figure 25. *Charge-tagged tripeptidic catalyst* ***89b*** *and the corresponding enamine species* ***90d*** *and* ***90e****.*

When this catalyst was tested in the preparative catalysis reaction, catalyst **89b** showed a slightly decreased selectivity compared to the uncharged catalyst-species **89a**, yielding the conjugate addition product with 90% *ee*. The reason for the lowered selectivity is most likely found in the changed ring-conformation of the proline moiety due to the additional amide function in the 4-position. This catalyst derivative was then subjected to the ESI-MS back-reaction screening. Due to solubility issues of the catalyst, the screening had to be carried out in $CHCl_3$/*i*-PrOH = 1:1. When such a screening was performed unfortunately no desired enamine signals could be detected. Only the signal corresponding to the free catalyst was observed. Furthermore, the signals corresponding to the iminium-species, which had always been observed previously, were not found either. This suggests that the additional substituent on the tripeptidic catalyst shifts the equilibrium between free catalyst and the iminium species almost completely on the side of the unbound catalyst. Thus the back-reaction did not proceed and therefore no enamine intermediate could be detected.

Another approach to achieve detection of the reaction intermediates was inspired by the finding in NMR studies of the reaction mixture. This experiment showed that the nature of the solvent has a significant influence on the stability of the enamine formed. When ^{1}H-NMR experiments were carried out in $CDCl_3$/d_4-MeOH the α-proton of the aldehyde did exchange with the solvent but no enamine signal was observed. When on the other hand the same

experiment was conducted in d_6-DMSO the enamine could be detected by ^{1}H-NMR. Thus it was decided to perform the ESI-MS screening as well in DMSO (scheme 67). The resulting mass spectrum is shown in figure 26.



Scheme 67. *ESI-MS screening in DMSO.*

Indeed this time the desired enamine intermediates **90b** and **90c** could be detected by ESI-MS although still only in low intensity (signal-to-noise ratio of 3:1 for the minor signal). The ratio in which they were formed was found to be at 73:26 which corresponds to a theoretical *ee* induced by the catalyst of 47%. For comparison the preparative reaction was carried out in DMSO which resulted in the formation of the catalysis product with 46% *ee*, matching the value found by the ESI-MS screening.

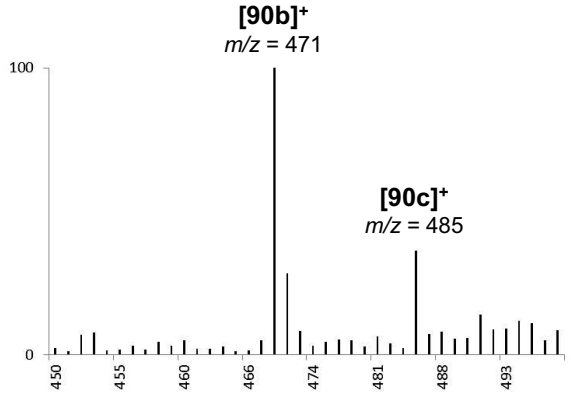


Figure 26. *Resulting mass spectrum for the ESI-MS back reaction screening in DMSO.*

5.3 Summary and Outlook

In summary, in collaboration with JÖRG DUSCHMALÉ and HELMA WENNEMERS, ESI-MS studies were carried to elucidate the reaction mechanism in the organo-catalyzed conjugate addition of aldehydes to nitroolefins. By examination of the forward reaction all intermediates proposed for the enamine-catalysis pathway have been observed. As well when the back reaction was studied the same intermediates have been found although the enamine intermediate could only be detected in low intensity.

The selectivity of the enamine attack onto the nitroolefin was studied by an ESI-MS screening of the back reaction using mass-labeled product enantiomers. Under the optimized reaction conditions which were reported to be the best for this reaction this was not possible due to low enamine concentration in the reaction mixture. However, when the screening was carried out in DMSO small quantities of the mass-labeled enamine intermediates were detected and the selectivity of the catalyst could be determined. Comparison with the preparative reaction under these conditions matched the outcome of the ESI-MS screening. This is a very solid hint that the organo-catalyzed conjugate addition of aldehydes to nitroolefins proceeds via enamine formation.

Further evidence supporting this assumption was previously reported by WENNEMERS and co-workers.[109] They found that the presence of water in the reaction media slows down the product formation, which most likely is true due to the influence of water on the enamine formation.

Future work on this project might be dedicated to the optimization of the screening conditions in order to obtain better signal intensities. Unfortunately it was found in this work that the use of a charge-tagged catalyst did not enhance the detection of the reaction intermediates. However, having found an optimized screening protocol, additional catalysts and as well other reaction conditions might be evaluated to further verify the results found during this work.

Chapter 6

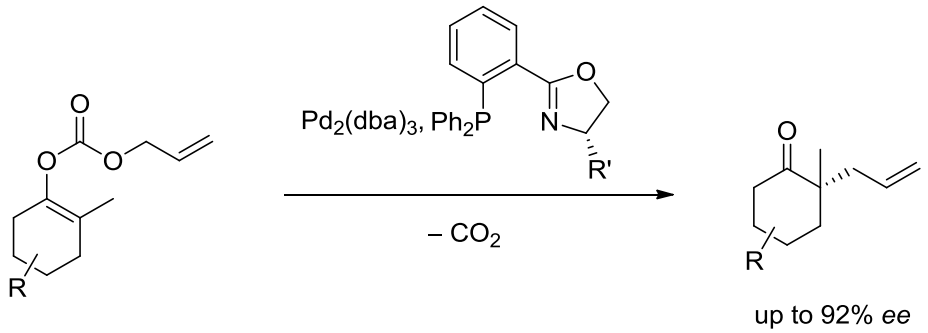
α-Allylation of Carbonyl Compounds by Palladium-Enamine Tandem Catalysis

6.1 Introduction

Among various C-C bond forming reactions the asymmetric allylic alkylation reaction has proved to be a very versatile and powerful method for the creation of chiral compounds by reaction of various allyl sources with different nucleophiles in the presence of a transition-metal catalyst.[25b] Upon use of ketone enolates as nucleophiles this reaction allows for the formation of α-allylated carbonyl compounds.[113] Such molecules are highly valuable and widely used in organic synthesis[114] especially as the allyl moiety allows for facile further functionalization by various methods as for example asymmetric di-hydroxylation,[115] epoxidation[116] or cross-metathesis.[117]

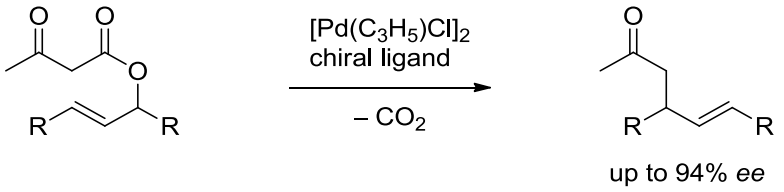
6.1.1 α-Allylation of via Preformation Activated Carbonyl Compounds

The synthesis of such α-allylated carbonyl compounds has previously achieved mainly by decarboxylative intramolecular α-allylation.[118] In 2004 STOLTZ and co-workers for example reported on the enantioselective Tsuji-Trost allylation using different cyclic enol carbonates (scheme 68).[118a]



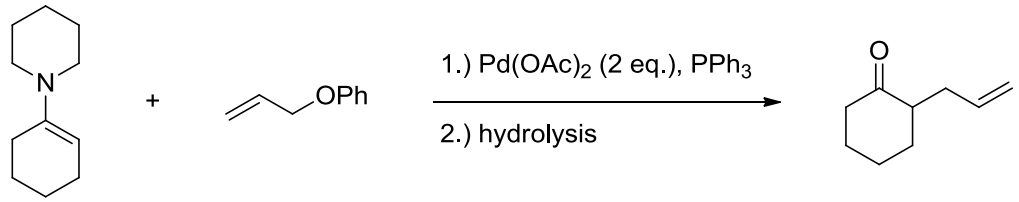
Scheme 68. *Asymmetric Tsuji-Trost allylation for the formation of chiral α-allyl ketones.*[118a]

Later TROST and co-workers have shown that the reaction is as well applicable to acyclic enol carbonates[118d] and that α-hydroxy, α-allyl aldehydes and ketones can be synthesized with high enantioselectivities.[118c] In 2004 BURGER and TUNGE have shown that decarboxylative α-allylation does proceed as well starting from allyl β-keto esters (scheme 69).[118b]



Scheme 69. *a-allylation by use of allyl β-keto esters.*[118b]

Another approach towards α-allylated carbonyl compounds was accomplished using a preformed enamine species as the nucleophile for the subsequent palladium-catalyzed allylic alkylation reaction as shown already in 1973 by ONOUE, MORITANI and MURAHASHI (scheme 70).[119] Asymmetric versions of this methodology have later been demonstrated by HIROI and co-workers.[120] In 2007 HARTWIG reported on the iridium-catalyzed equivalent of this transformation.[121]

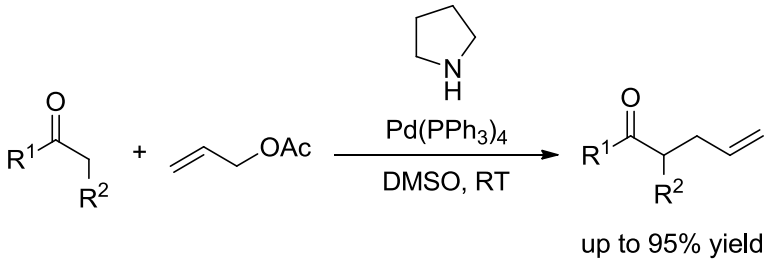


Scheme 70. *Use of an enamine as nucleophile in the allylic alkylation for the formation of α-allyl ketones.*[119]

The drawback of these examples is the requirement of the preformation of the allylic carbonates, β-keto esters or of the enamine species. Thus, very recently several reports on the direct conversion of carbonyl compounds to their α-allylated analogs have been published.

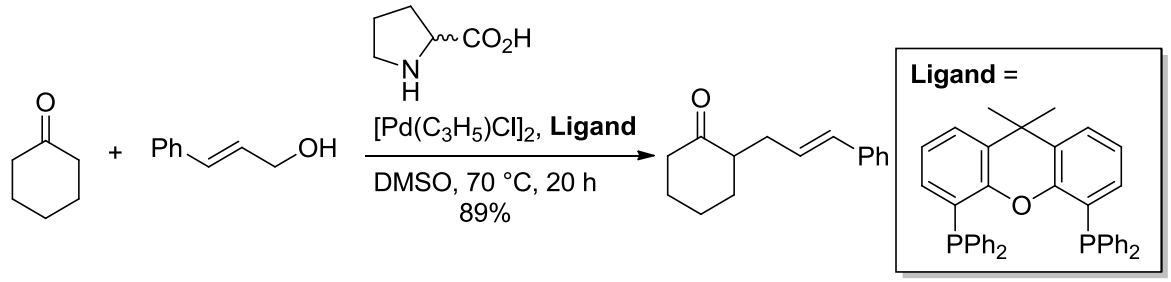
6.1.2 α-Allylation of via Tandem Catalysis

Based on the previously described findings of the ability of enamines to act as the nucleophile in allylic alkylation reactions, reports on the α-allylation of carbonyl compounds proceeding via *in-situ* formation of the enamine and subsequent allylic alkylation have emerged since 2006.[122] The first description of such a protocol has been published by IBRAHEM and CORDOVA (scheme 71).[122a] This report represents the first example of a new concept of combined transition metal catalysis and amino-catalysis.[72e,123]



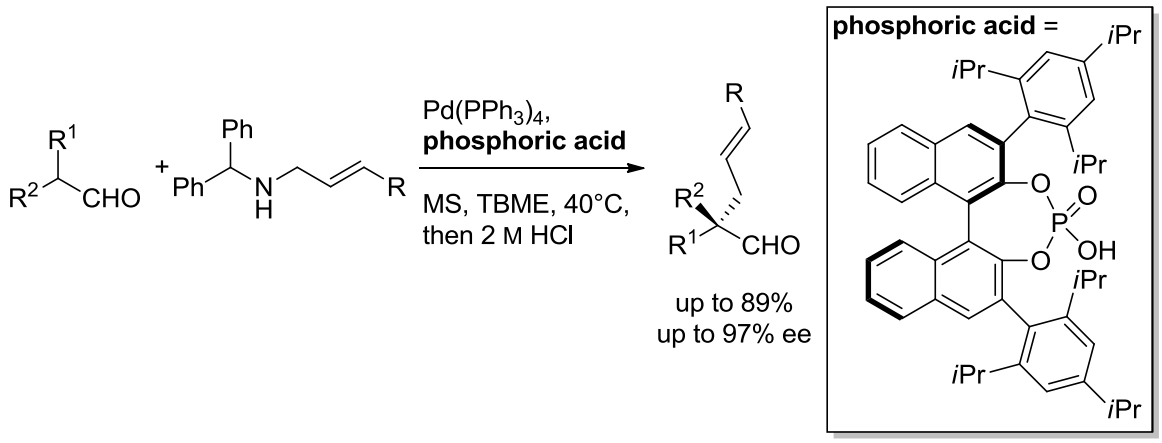
Scheme 71. *First example of a palladium- organo- tandem catalyzed α-allylation.*[122a]

They showed that upon reaction between a ketone or an aldehyde and allylic acetate in the presence of both a palladium- and a secondary amine-catalyst α-allylation can be obtained with high yields. However, no enantioselective versions have been reported. A comparable protocol was reported by BREIT and co-workers (scheme 72).[122d]



Scheme 72. *Palladium- organo- tandem catalyzed α-allylation using allylic alcohols.*[122d]

They have performed the same reaction using allylic alcohols instead of acetates. This circumvents the synthesis of the allylic acetate from the corresponding alcohol and leads to water formation as a side product instead of acetic acid. Attempts to perform this reaction asymmetrically have not been successful. COZZI and co-workers could show that upon use of an indium catalyst instead of palladium, medium selectivities could be obtained in the α-allylation of aldehydes.[122e] A highly selective version was reported by MUKHERJEE and LIST using a chiral phosphoric acid as additive (scheme 73).[122c] Here as well only the α-allylation of aldehydes was described.



Scheme 73. *First highly selective approach.*[122c]

SAICIC and co-workers have described an intramolecular tandem-catalysis approach.[122b] However only few studies on enantioselective versions of this reaction were included and the obtained selectivities were not generally satisfying.

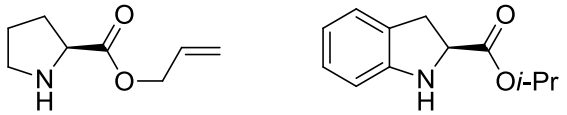
Another strategy to achieve the α-allylation of carbonyl compounds has been reported by BRAUN and MEIER.[124] They have realized this aim via lithium enolate formation and subsequent allylic alkylation upon use of chiral additives. However this methodology suffers from low selectivities. A more successful concept was developed by MACMILLAN and co-workers. Applying their new concept of SOMO activation in organo-catalysis they could achieve highly selective α-allylation of aldehydes without the need of an additional transition metal.[125]

6.1.3 Objectives of This Work

The aim of this project was the development of a selective version of the palladium-enamine tandem-catalyzed α-allylation of carbonyl compounds. As shown above there is only one selective variant known in literature where an intermolecular approach using a palladium catalyst could be accomplished, as reported by LIST and co-workers.[122c] This, however, only seems to be applicable for the transformation of aldehydes. Based on the findings of IBRAHEM and CORDOVA[122a] the aim was to test different pyrrolidine-based organo-catalysts and various palladium-catalysts in the reaction between carbonyl compounds, both ketones and aldehydes, and allylic acetates.

6.2 Synthesis

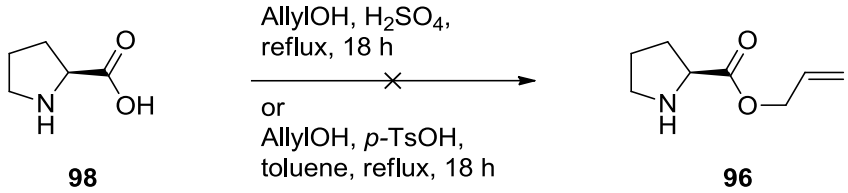
Along with various organo-catalysts available from commercial sources and some which were kindly provided by IVANA FLEISCHER, two new organo-catalysts were supposed to be tested and thus had to be synthesized (figure 27).



96 **97a**

Figure 27. *Organo-catalysts to be synthesized.*

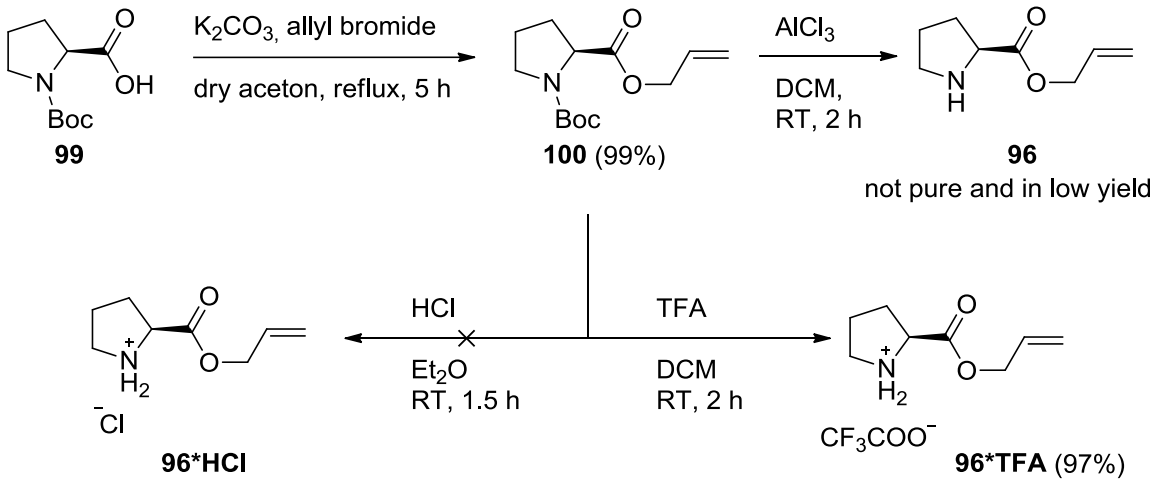
Synthesis of (*S*)-allyl pyrrolidine-2-carboxylate (**96**) was first tried to be accomplished following a previously reported protocol.[120c] Therefore L-proline (**98**) was reacted with neat allyl alcohol under acidic conditions for 18 h (scheme 74). Unfortunately only traces of desired product were formed. As well the reaction in refluxing toluene upon use of a Dean-Stark condenser did not lead to an improved result.



98 **96**

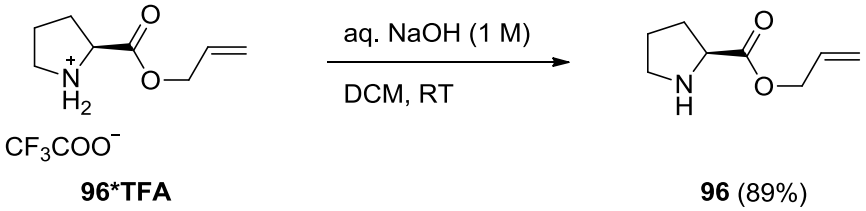
Scheme 74. *Attempted synthesis of* ***96****.*

As the condensation under acidic conditions did not proceed successfully, base promoted esterification was tested (scheme 75).



Scheme 75. *Synthesis of the TFA salt of* ***96****.*

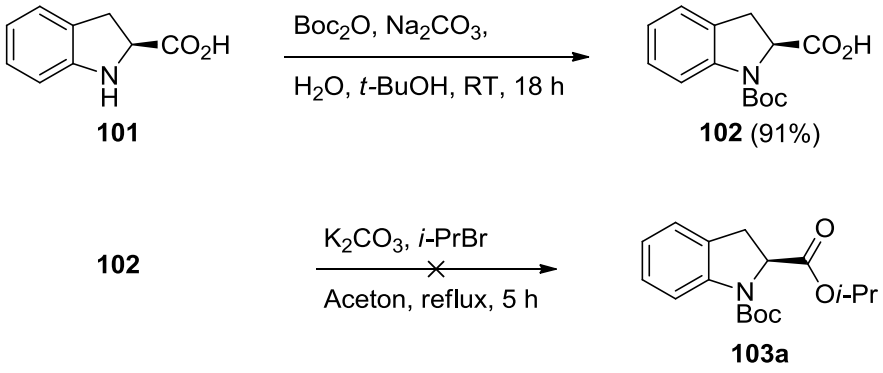
This route proved to be successful and upon treatment of **99** with allyl bromide in the presence of K_2CO_3[126] the desired *N*-Boc protected allyl ester **100** was obtained in virtually quantitative yield. Boc deprotection was then firstly tested using a Lewis-acid[127] in order to avoid cleavage of the ester bond. However, this did not lead to satisfying formation of the desired compound. **96** was only formed in low yield and could not be purified by column chromatography. Thus, deprotection by use of HCl in Et_2O was tested. Unfortunately again the desired hydrochloride salt could not be obtained. When changing the conditions towards use of TFA in DCM the corresponding TFA salt of **96** was obtained in almost perfect yield.



Scheme 76. *TFA removal to obtain* ***96****.*

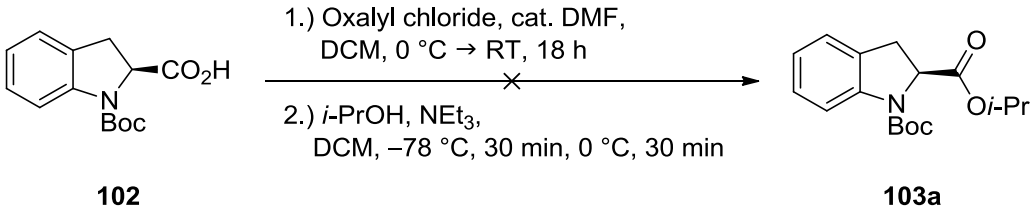
Finally TFA removal was achieved by basic washing of the salt with aqueous NaOH and extraction with DCM (scheme 76). By this the desired organo-catalyst **96** was obtained in two steps from commercially available *N*-Boc L-proline (**99**).

Synthesis of organo-catalyst **97** was attempted following the same route as described for **96**. For this purpose (*S*)-indoline-2-carboxylic acid (**101**) was first *N*-Boc protected. Subsequent esterification under basic conditions unfortunately failed and the desired ester **103a** could not be obtained (scheme 77).



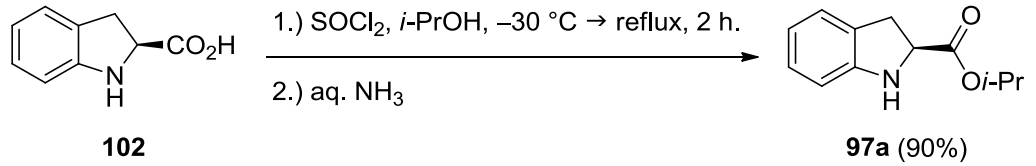
Scheme 77. *N-Boc protection of (S)-indoline-2-carboxylic acid (****101****) and attempted synthesis of* ***103a*** *under basic reaction conditions.*

Thus, ester formation was also tested upon *in-situ* formation of the corresponding acid chloride and subsequent treatment with *iso*-propanol (scheme 78). Again the desired compound was not obtained. Analysis of the reaction-products indicated Boc-deprotection resulting in undesired side reactions. This deprotection most likely occurred due to the formation of an equivalent of HCl during the reaction.



Scheme 78. *Attempted synthesis of* ***103a*** *via in-situ formation of the acid chloride.*

Finally the synthesis of **97a** was achieved by direct esterification of **102**.[128] By this the desired organo-catalyst was obtained in a single step from a commercial available precursor in 90% yield (scheme 79).

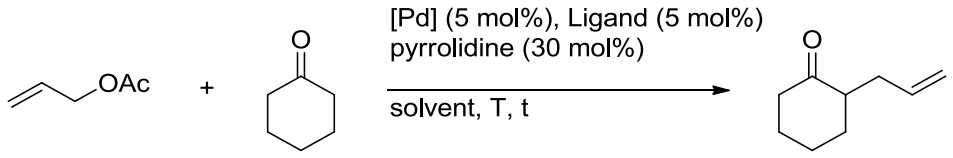


Scheme 79. *Synthesis of* ***97a****.*

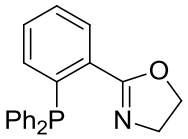
6.3 α-Allylation of Ketones

For initial experiments the conditions reported by IBRAHEM and CORDOVA for the α-allylation of cyclohexanone (**104**) were applied.[122a] Both DMSO and THF were tested as solvents using different palladium-catalysts (table 19).

Table 19. *Initial attempts to realize the α-allylation of ketones.*



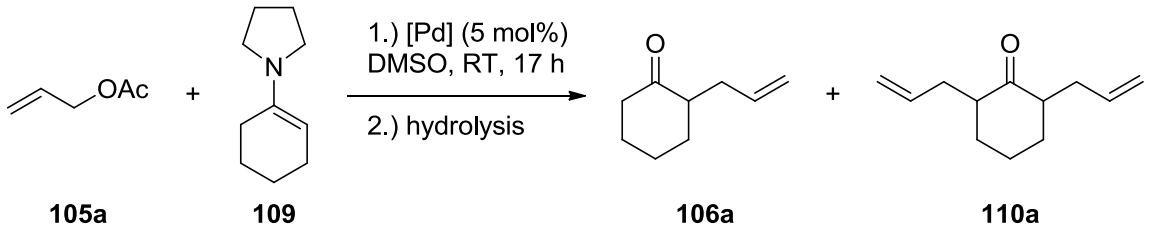
105a **104** **106a**

Entry	[Pd]	Ligand	Solvent	T [°C]	t [h]	Yield[a] [%]
1	$Pd(PPh_3)_4$	-	DMSO	RT	17	<3
2	$Pd(PPh_3)_4$	-	THF	RT	18	0
3	$[Pd(C_3H_5)Cl]_2$	-	DMSO	RT	18	<3
4	$[Pd(C_3H_5)Cl]_2$	 **108**	DMSO	RT	20	<3
5	$[Pd(C_3H_5)Cl]_2$	**108**	DMSO	70	14	<3[b]

[a]: Determined by ^{1}H-NMR analysis; [b]: Pd(0) precipitated from reaction mixture.

Under the conditions tested only traces of product were formed. Moreover in THF no conversion was observed at all (entry 2). As well using achiral PHOX ligand **108** proved to be unsuccessful even at elevated temperature.

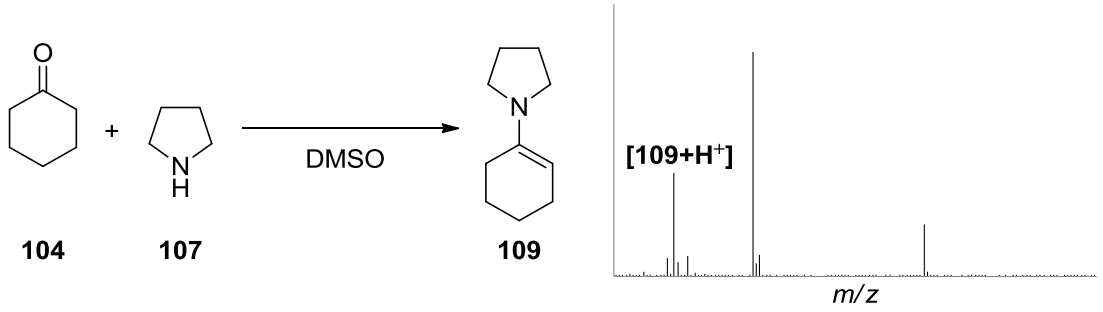
As no product was formed in the tandem-process the individual steps were examined. To evaluate the allylic alkylation step, enamine **109** was reacted with allyl acetate (**105a**) in the presence of a palladium catalyst (scheme 80).



Scheme 80. *Testing the allylic alkylation reaction between enamine **109** and allyl acetate.*

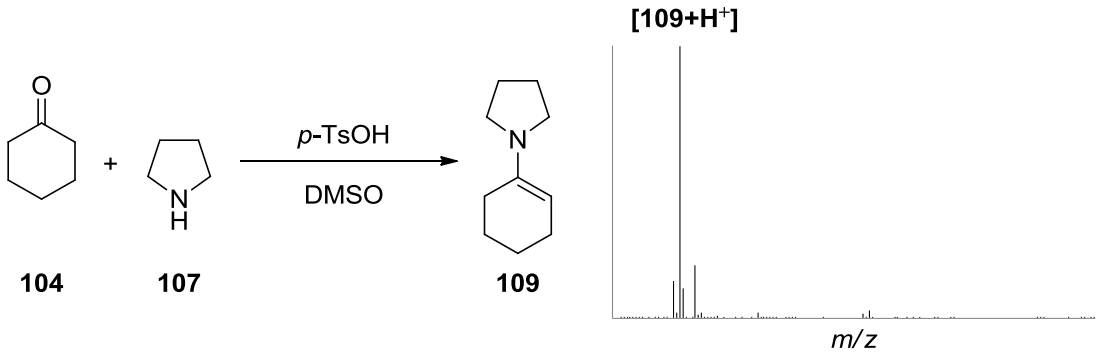
After hydrolysis, α-allylated ketone was isolated. It was found that both mono- and di-allylation did occur, an observation which was already previously reported.[119,120c] ^{1}H-NMR analysis of those products showed, that di-allylation took place in α and α' position rather than on the same α-carbon. Upon use of $Pd(PPh_3)_4$ as transition-metal catalyst the allylation product was obtained in 62% yield in a mono- to di-allylation ratio of **106a**/**110a** = 3.3:1. Use of $Pd(PPh_3)_2Cl_2$ gave the product in 57% yield (**106a**/**110a** = 6.5:1).

Next, the formation of the desired enamine species **109** was tested. For this purpose, ketone **104** was reacted with pyrrolidine (**107**) in DMSO and an aliquot of this mixture, diluted in MeOH, was subjected to ESI-MS analysis (scheme 81).



Scheme 81. *ESI-MS analysis of the reaction between **104** and **107** under previously used reaction conditions.*

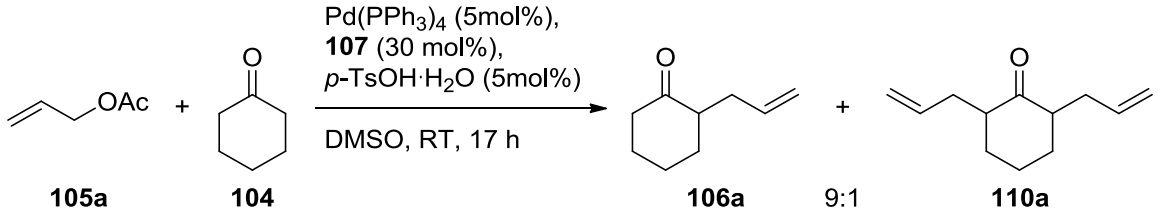
The desired signal corresponding to the protonated enamine species was observed. However, the detected signal was of very low intensity. Thus, the influence of addition of an acid to facilitate the enamine formation was investigated. Again the reaction mixture was analyzed by ESI-MS and this time the enamine-species was the dominant signal in the spectrum (scheme 82).



Scheme 82. *ESI-MS analysis of the reaction between **104** and **107** in the presence of an acid.*

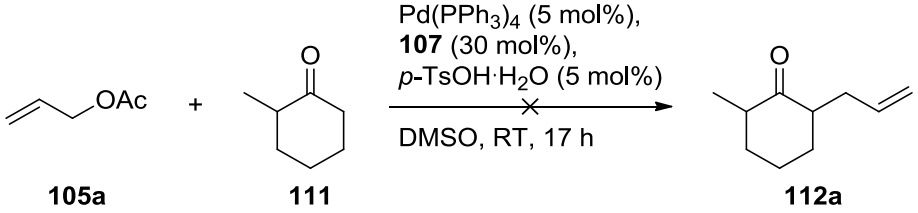
Although this observation might as well result from the facilitated protonation of the already formed enamine species by which it becomes more easily detected by ESI-MS, it could as well be a hint that an additional acid in the reaction mixture is required for sufficient enamine formation.

When, encouraged by the above shown finding, the tandem-catalysis was carried out under these optimized conditions, indeed quantitative α-allylation was observed (scheme 83). Again mono- and di-allylation was found in a ratio of **106a**/**110a** = 9:1.



Scheme 83. *Successful α-allylation under acidic reaction conditions.*

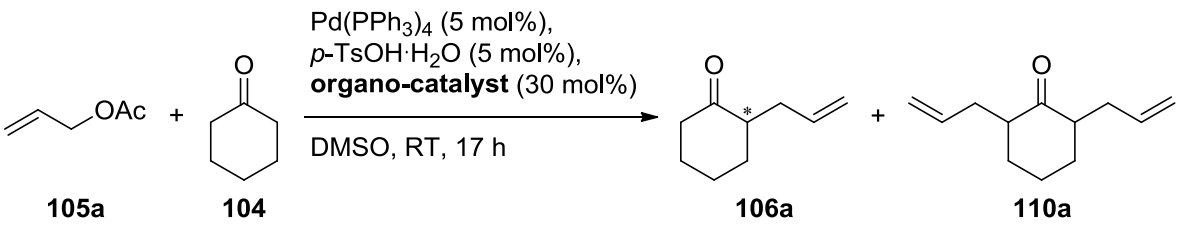
However, when these conditions were applied to the α-allylation of 2-methyl cyclohexanone (**111**) no conversion was found (scheme 84) although enamine formation could be observed by ESI-MS.



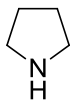
Scheme 84. *Attempted α-allylation of 2-methyl cyclohexanone (**104**).*

Having found suitable conditions for the transformation of cyclohexanone (**104**) into the α-allyl derivative, different chiral organo-catalysts have been screened in order to achieve an asymmetric version of this methodology (table 20).

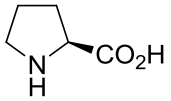
Table 20. *Organo-catalyst screening in the α-allylation of cyclohexanone.*



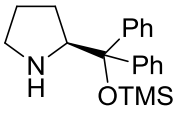
organo-catalyst:



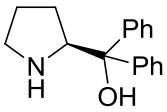
107
>99% yield[a]
106a/**110a** = 9:1



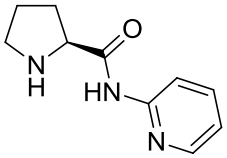
98
33% yield[a]
without *p*-TsOH
106a/**110a** = 57:1
0% *ee* (**106a**)



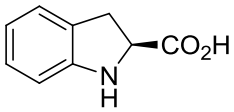
113
0% yield



114
0% yield



115
0% yield



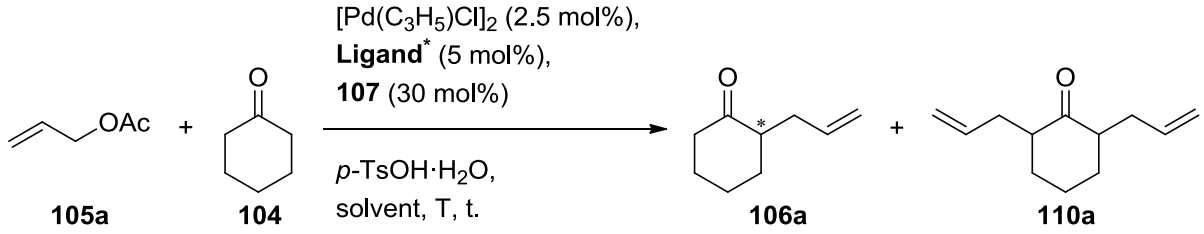
102
0% yield

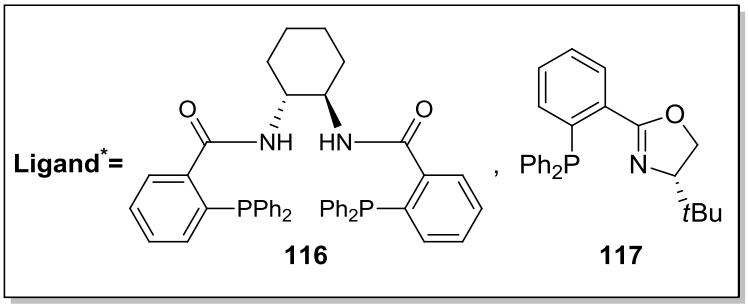
*[a]: Combined yield of **106a** and **110a**.*

Among the tested organo-catalysts only L-proline (**98**) was active in this reaction, yielding the α-allylation product in 33%. Notably, due to the carboxylic acid functionality of proline, additional use of an acid was not required. While di-allylation occurred in significant amount using pyrrolidine as the organo-catalyst, L-proline led to more selective formation of the mono-allylated product (**106a**/**110a** = 57:1). Unfortunately the transformation was found to be unselective and the product was obtained as a racemate. Thus, two different chiral palladium-ligands were tested as well. Both, the Trost-ligand **116** and the PHOX-ligand **117**, which have been previously used as palladium-ligands for the asymmetric allylic alkylation and deliver high enantioselectivities, were tested.[25b,26a] Pyrrolidine was used as organo-catalyst for this

screening as it had shown the highest activity in the previous organo-catalyst screening (table 21).

Table 21. *Palladium-ligand screening in the α-allylation of cyclohexanone.*





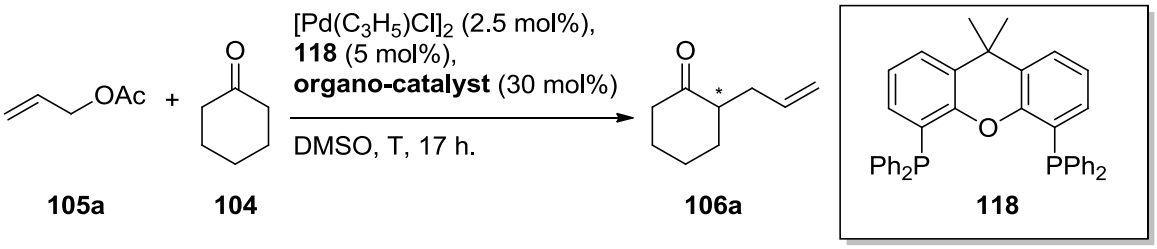
Entry	Solvent	T [°C]	t [h]	Ligand*	Yield[a] [%]	106a/110a	*ee* (106a)[b] [%] (Config.)
1	DMSO	25	17	**116**	23	20:1	3 (*S*)
2	THF	60	17	**116**	<3[c]	n.d.	n.d.
3	DMSO	25	17	**117**	15	>30:1	4 (*S*)
4	THF	60	17	**117**	<3[c]	n.d.	n.d.

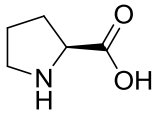
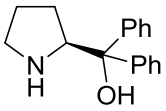
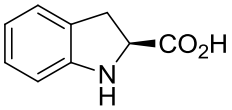
*[a]: Combined yield of **106a** and **110a**; [b]: Determined by HPLC analysis on chiral stationary phase; [c]: Pd(0) precipitated from reaction mixture.*

Again very low yields were obtained in this transformation. An increase of reaction-temperature could not overcome this issue. In fact the reaction in THF at 60 °C always led to precipitation of Pd(0) from the reaction mixture and only traces of the product could be obtained. For both ligands the reaction in DMSO at room temperature yielded preferentially the mono-allylation product in an almost racemic fashion.

BREIT and co-workers have shown that phosphine ligands are required, which provide a large bite-angle in order to be active in the α-allylation of ketones.[122d] Thus, Xantphos (**118**) was tested in this work as well (table 22).

Table 22. *Use of Xantphos (**118**) as palladium-ligand.*



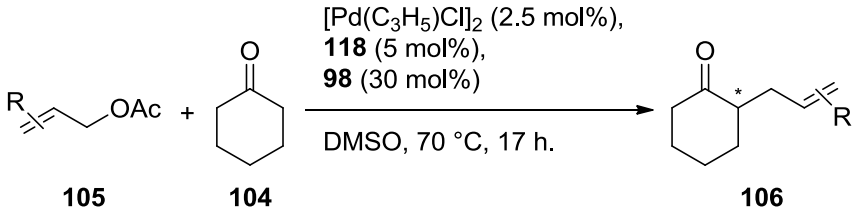
Entry	Organo-catalyst	T [°C]	Yield[a] [%]	*ee*[b] [%]
1	 **98**	25	22[c]	23
2		70	95[c]	10
3[d]	 **114**	70	0	-
4	 **102**	70	0	-

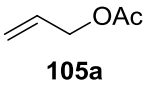
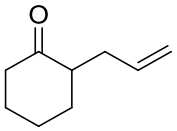
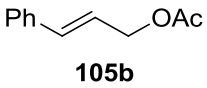
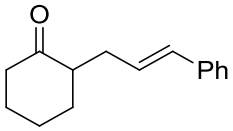
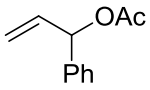
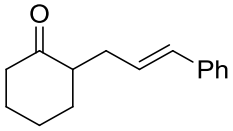
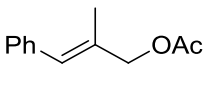
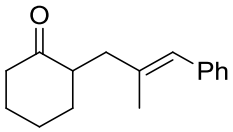
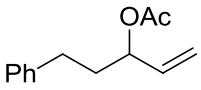
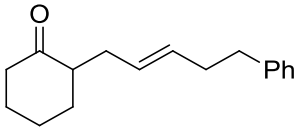
[a]: Isolated yield; [b]: determined by HPLC analysis on a chiral stationary phase; [c]: no di-allylation product formation was observed; [d]: additional p-TsOH was used.

When a combination of Xantphos (**118**) as palladium-ligand and L-proline as organo-catalyst was applied in this reaction the desired allylation product **106a** was obtained in low yield. However, under these conditions no di-allylation was observed at all. Furthermore, an enantiomeric excess of 23% of the mono-allylation product was found (entry 1). In order to increase the yield, the reaction was carried out at elevated temperature, and indeed the desired product could be isolated in 95% yield. Unfortunately the *ee* dropped down to 10% (entry 2). When other organo-catalysts, providing an increased sterical demand, were tested the reaction did not proceed anymore and no product was formed (entries 3 and 4).

As Xantphos (**118**) and L-proline (**98**) in DMSO at elevated temperature has shown to be the most promising combination in terms of activity, the influence of the allyl-source under these conditions was evaluated (table 23).

Table 23. *Influence of the allyl-source.*



Entry	105	106	Yield[a] [%]	(*E*)/(*Z*)[b]	*ee*[c] [%] (Config.)
1	 **105a**	 **106a**	95	-	10 (*S*)
2	 **105b**	 **106b**	87	>99:1	7 (*S*)
3	 **105c**	 **106b**	82	>99:1	6 (*S*)
4	 **105d**	 **106c**	69	10:1	15 (–)[d]
5	 **105e**	 **106d**	60	3:1	22 (–)

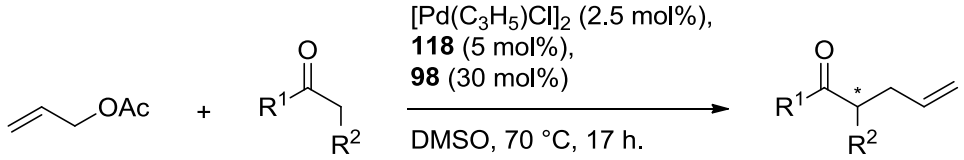
[a]: Isolated yield; [b]: determined by GC analysis; [c]: determined by HPLC analysis on a chiral stationary phase; [d]: ee of the (Z)-product was found to be at 18% (determined by GC analysis on a chiral stationary phase).

When 3-phenyl-allyl acetate (**105b**) was applied to the reaction, the mono-allylation product **106b** was obtained in good yield. The selectivity remained in the same region as seen before. When the regioisomeric 1-phenyl-allyl acetate (**105c**) was applied, the results did not change significantly. In both cases the same regioisomer **106b** was obtained as product. Allyl species **105d** gave the desired allylation product **106c** in medium yield with an *E*/*Z*-ratio of 10:1. The enantiomeric excess of the (*E*)-product was found to be at 15%, which is slightly higher than the results obtained before. The (*Z*)-product was formed with 18% *ee*. When the alkyl

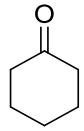
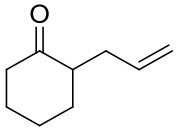
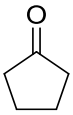
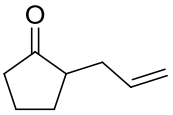
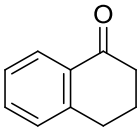
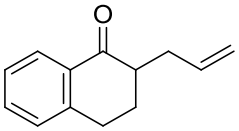
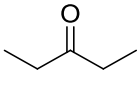
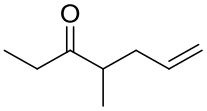
substituted allyl species **105e** was tested, **106d** was formed in 60% yield with an E/Z ratio of 3:1. The (*E*)-product showed 22% enantiomeric excess.

Next different ketones were applied in the reaction (table 24). A change of the carbonyl species from cyclohexanone (**104**) to cyclopentanone (**119**) resulted in lower yield and in racemic product. When α-tetralone (**121**) was used, the desired product was obtained in less than 3% yield. Acyclic 3-pentanone (**123**) did not undergo α-allylation.

Table 24. *α-Allylation of different ketones.*

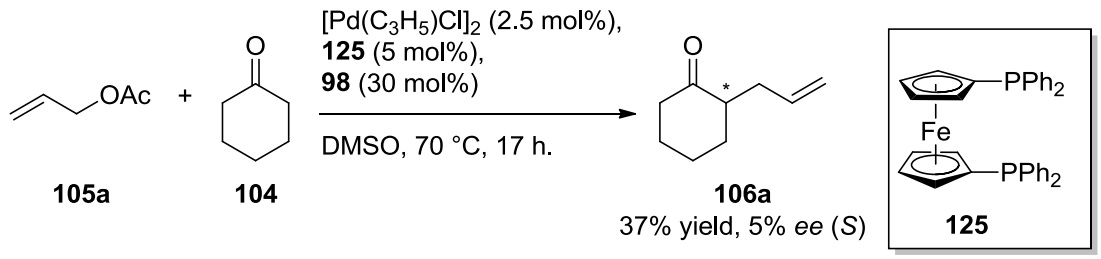


105a **ketone** **product**

Entry	Ketone	Product	Yield[a] [%]	*ee* [%] (Config.)
1	 **104**	 **106a**	95	10 (*S*)[b]
2	 **119**	 **120**	43	*rac.*[c]
3	 **121**	 **122**	<3	n.d.
3	 **123**	 **124**	0	-

[a]: Isolated yield; [b]: determined by HPLC analysis on a chiral stationary phase; [c]: determined by optical rotation.

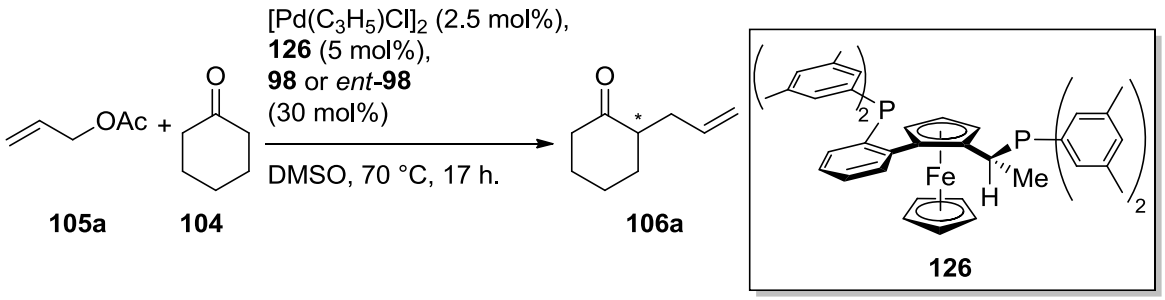
As the system described above has shown to be not very selective, again other palladium-ligands, which provide a large bite-angle, were evaluated in this reaction. First, achiral DPPF (**125**) was tested in combination with L-proline (**98**). Only the mono-allylation product was observed under these conditions. However, a significantly lower yield was obtained and furthermore the selectivity dropped as well (scheme 85).

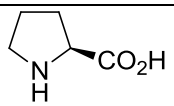
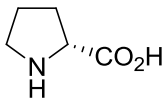


Scheme 85. *Use of DPPF (**125**) as palladium-ligand.*

Next, the combination of a chiral palladium-ligand and a chiral organo-catalyst was evaluated. For this purpose (*R*),(*R*)-Walphos (**126**) was used as the palladium-ligand and L- or D-proline (**98**) as the organo-catalyst (table 25).

Table 25. *Combination of a chiral palladium-ligand and a chiral organo-catalyst.*



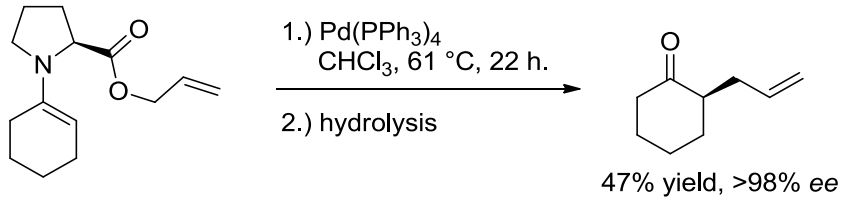
Entry	Organo-catalyst	Yield[a] [%]	*ee*[b] [%] (Config.)
1	 **98**	54	3 (*S*)
2	 *ent*-**98**	33	3 (*R*)

[a]: Isolated yield; [b]: determined by HPLC analysis on a chiral stationary phase.

In both cases again only mono-allylation was observed. Upon use of **98** the desired allylation-product could be isolated in 54% yield. A very low enantiomeric excess of 3% was found (entry 1). When *ent*-**98** was applied in this experiment an even lower yield of 33% was obtained. This time again only 3% *ee* were found but in favor of the other product-enantiomer. As, in terms of selectivity, no match or mismatch case and formation of the opposite enantiomers was observed, the influence of the palladium-ligand on the

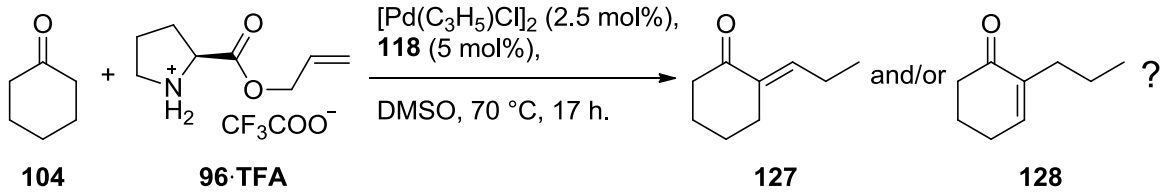
stereochemical outcome of the reaction seems to be negligible, at least under this reaction conditions. Thus, further screening for other chiral palladium-ligands seemed to be not promising.

Therefore a different approach was tested. HIROI and co-workers had previously shown in the reaction between an enamine and a palladium-allyl complex that high selectivities could be obtained upon use of an intramolecular allyl source (scheme 86).[120c]



Scheme 86. *Selective α-allylation by use of an intramolecular allyl source.*[120c]

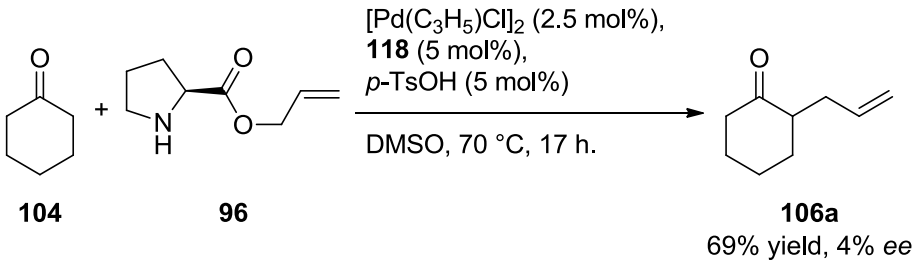
Inspired by this finding, L-proline allyl ester (**96**) was used as the organo-catalyst together with Xantphos (**118**) in the tandem-catalyzed α-allylation of cyclohexanone (**104**). As the allyl ester is no more bearing an acidic function in a first attempt its TFA salt was applied, hoping that the TFA would facilitate the enamine formation. Of course in this approach the organo-catalyst had to be used in stoichiometric amounts as it acts at the same time as the allyl-source. When this reaction was carried out no desired product was formed but an unidentified compound was isolated. GC-MS and NMR analyses gave some evidence for the formation of the isomerization products as depicted in scheme 87.



Scheme 87. *Attempted α-allylation by use of an intramolecular allyl-source.*

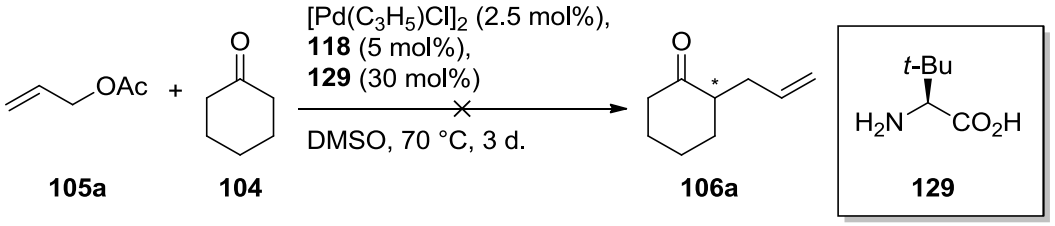
However, these undesired products could be only obtained by isomerization of the desired α-allyl-compound. Therefore optimization of the reaction conditions was carried out. And indeed, when the reaction was performed without TFA but in the presence of *p*-TsOH the desired product **106a** could be isolated in 69% yield (scheme 88). Unfortunately only 4% *ee* were found. Most likely the formation of the palladium-allyl complex proceeds significantly

faster than the formation of the enamine intermediate. Thus the allyl ester does not act as an intramolecular allyl source and no increased selectivity was obtained.



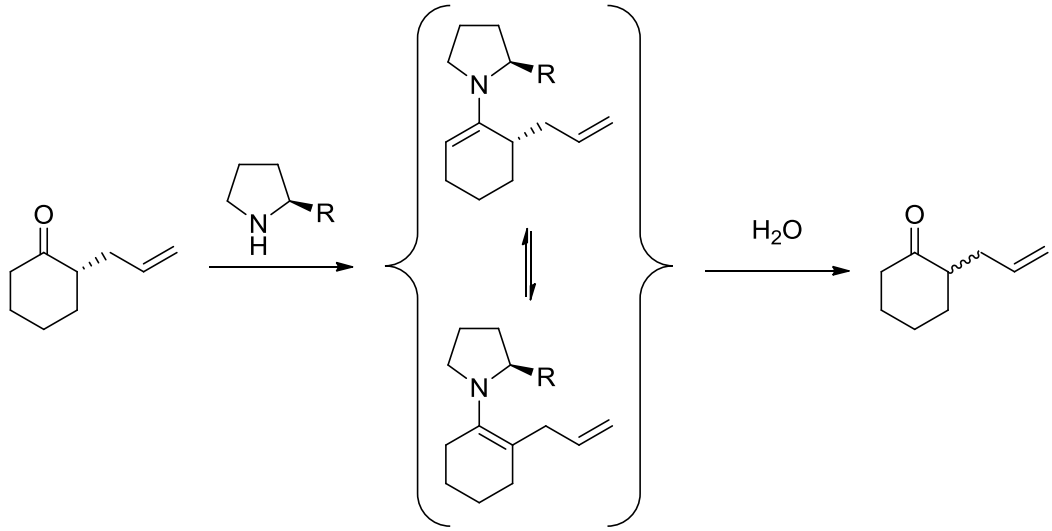
Scheme 88. *α-Allylation by use of an intramolecular allyl-source.*

Next, a primary amine was tested as the organo-catalyst for the reaction. For an initial experiment L-*tert*-leucine (**129**) was chosen (scheme 89). However, no desired product was formed at all even after a reaction time of 3 days and thus the search for suitable primary amine catalysts was no longer pursued.



Scheme 89. *Attempted α-allylation by use of a primary amine organo-catalyst.*

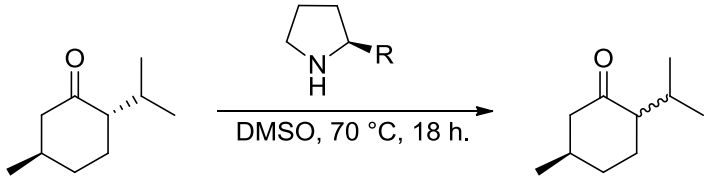
All above described asymmetric attempts resulted in low enantiomeric excesses of the formed allylation products. Besides the most obvious explanation of low selectivity of the used catalysts, another reason for these observations could be found in racemization of the product subsequent to the α-allylation. This might occur via enamine formation upon reaction of the allylation-product with the amine-catalyst (scheme 90).



Scheme 90. *Possible racemization pathway.*

In order to evaluate the racemization tendency of an α-chiral ketone compound under the used reaction conditions, L-menthone (**130**), as it is commercially available in very high enantiomeric purity, was subjected to these conditions and the diastereomeric ratio was analyzed after 18 h using different organo-catalysts (table 26).

Table 26. *Racemization studies under the reaction conditions.*



130 **130**

entry	R	*d.r.* SM[a]	*d.r.* after 18 h[a]
1	H	18 : 1	8 : 1
2	CO_2H	18 : 1	12 : 1

[a]: Determined by GC analysis.

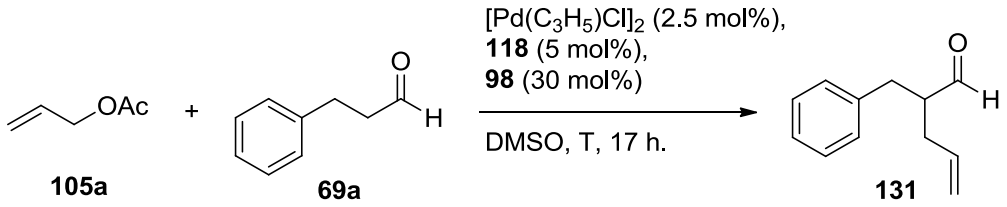
Indeed it was found that the diastereomeric ratio did decrease under the reaction conditions in significant amounts. Such a racemization might strongly contribute to the fact that so far only low enantiomeric excesses could be obtained.

6.4 α-Allylation of Aldehydes

All the results shown above indicate that the system described does not tolerate any significant sterical hindrance between the amine-catalyst and the carbonyl compound. Therefore it was decided to reduce the sterical demand of the carbonyl compound in order to be able to use more sterically demanding and thus more selective organo-catalyst. This aim was supposed to be achieved by use of aldehydes instead of ketone compounds, as they commonly show higher activities in various transformations. Therefore it might be as well possible to create a quaternary stereogenic center which then would avoid racemization of the product by enamine formation.

Before the formation of a quaternary stereogenic center was attempted, initial experiments on the α-allylation of hydro-cinnamaldehyde (**69a**) were carried out using Xantphos (**118**) and L-proline (**98**) as catalyst combination (table 27).

Table 27. *α-Allylation of hydro-cinnamaldehyde (**69a**).*



105a **69a** **131**

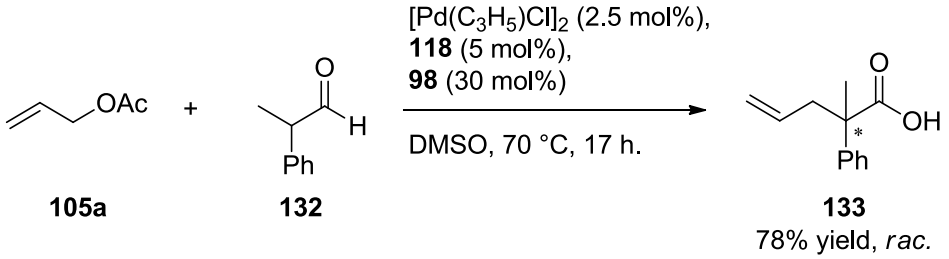
Entry	T [°C]	Yield [%]	*ee*[a] [%]
1	25	15[b]	n.d.
2	70	99[c]	3

[a]: Determined by HPLC analysis of the corresponding alcohol after reduction with $NaBH_4$ on a chiral stationary phase; [b]: determined by ^{1}H-NMR, mainly side-products were formed; [c]: isolated yield, little impurities present.

When the reaction was carried out at room temperature mainly side-products were observed and the desired product was formed in only 15% yield (entry 1). Increasing the reaction temperature could overcome this issue and the product was formed in nearly quantitative yield (entry 2) but in an almost racemic fashion. Again racemization upon enamine formation could be the reason for this.

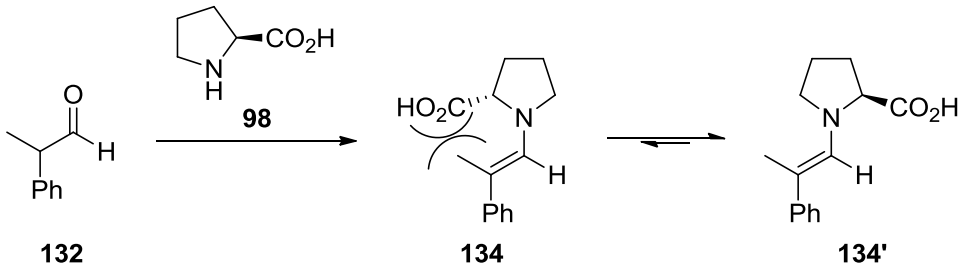
In order to avoid such racemization the focus was concentrated on the α-allylation of α-branched aldehydes to form a quaternary stereogenic center which can no more undergo

racemization. For this purpose 2-phenylpropanal (**132**) was chosen as test substrate. A first attempt using Xantphos (**118**) as the palladium-ligand and L-proline (**98**) as the organocatalyst indeed yielded in the formation of the desired allylation-product **133** however in racemic form (scheme 91).



Scheme 91. *α-Allylation of an α-branched aldehyde.*

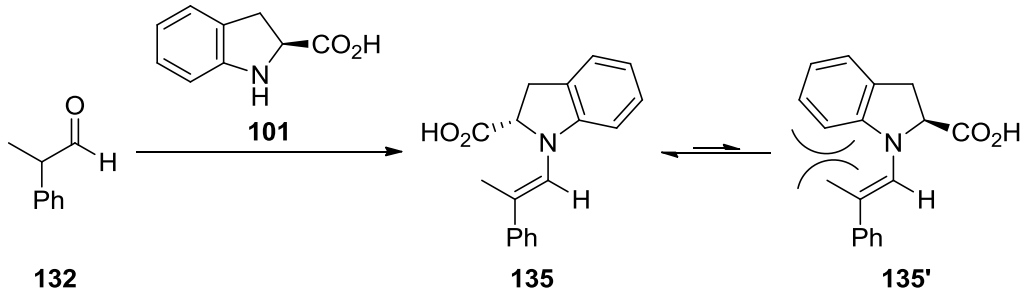
A possible explanation for the lack of selectivity might be found in the configuration of the formed enamine intermediate. Upon reaction of the aldehyde compound **132** with L-proline (**98**) the carboxylic acid functionality could be either pointing towards or away from the α-position to be substituted (scheme 92). Due to sterical repulsion enamine-species **134'** should be favored. If this is the case, the stereogenic center is in large distance to the reactive center and thus might have almost no influence on the stereochemical outcome of the reaction.



Scheme 92. *Possible explanation for the low selectivity of the transformation.*

In order to overcome this issue it was decided to test an organo-catalyst where the stereogenic center is preferentially on the same side as the reaction center. Indoline-2-carboxylic acid (**101**) for example should provide such a feature. Due to the conjugation between the benzene moiety of the catalyst and the enamine residue, these two parts of the intermediate are co-planer and by this the steric repulsion between the benzene ring and the α-methyl substituent should be stronger than the one between the carboxylic acid functionality and the α-methyl (scheme 93). Therefore formation of **135** should be favored over the formation of **135'**. As in

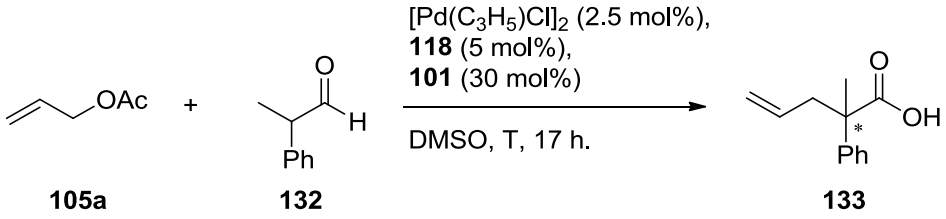
this case the stereogenic center of the organo-catalyst is pointing towards the reaction center, an increased selectivity might be obtained.



Scheme 93. *Controlled formation of the desired enamine-species upon use of organo-catalyst* ***101****.*

Unfortunately, when catalyst **101** was applied in the a-allylation of aldehyde **132** only a very low enantiomeric excess was found (table 28). While at 70 °C 3% *ee* were obtained, surprisingly at lower reaction-temperature racemic product was isolated.

Table 28. *α-Allylation of* ***132*** *using organo-catalyst* ***101****.*

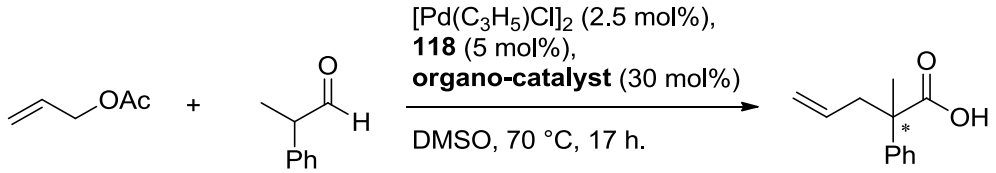


Entry	T [°C]	Yield[a] [%]	*ee*[b] [%] (Config.)
1	70	97	3 (–)
2	25	73	*rac.*

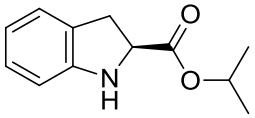
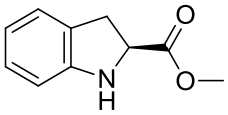
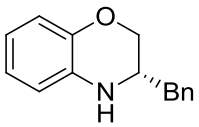
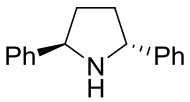
[a]: Isolated yield; [b]: determined by HPLC analysis on a chiral stationary phase.

However, allylation product **133** was isolated in high yields. Therefore it seemed to be possible to increase the sterical demand of the organo-catalyst (table 29). This was done be using the methyl- and *iso*-propyl ester of catalyst **101**. The idea was that a more bulky substituent on the stereogenic center might induce a higher selectivity in the transformation. However, when these catalysts were tested only trace-amounts of the product were found in both cases (entries 1 and 2). The benzoxazine catalyst **63a** was not active in the α-allylation as well (entry 3 and 4).

Table 29. *Organo-catalyst screening.*

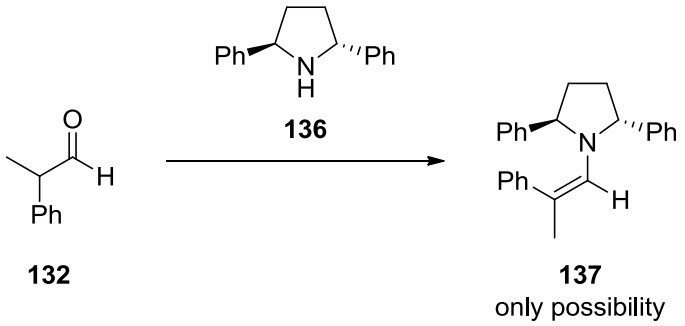


105a **132** **133**

Entry	Organo-Catalyst	T [°C]	Yield[a] [%]
1	 **97a**	70	3
2	 **97b**	70	6
3	 **63a**	25	<3
4		70	3
5	 **136**	25	<3
6		70	<3

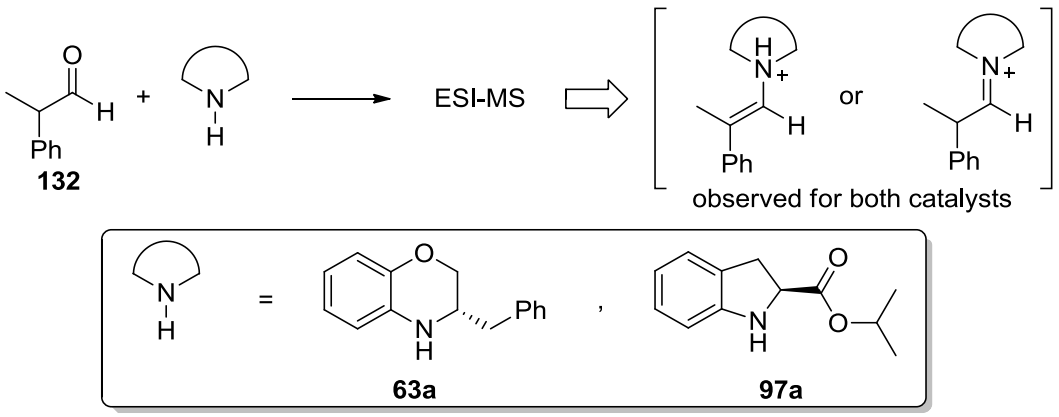
[a]: Determined by ^{1}H-NMR analysis of the crude mixture.

Another approach towards the controlled formation of the desired configuration of the enamine intermediate would be the use of a C_2-symmetrical organo-catalyst as for example (2*R*,5*R*)-2,5-diphenylpyrrolidine (**136**). In here only one enamine-species can be formed as rotation of the catalyst along C-N bond does not change the configuration of the enamine species (scheme 94). Unfortunately, when catalyst **136** was tested in the α-allylation only traces of product were formed at both room temperature and elevated temperature (table 29, entries 5 and 6).



Scheme 94. *Use of a C_2-symmetric organo-catalyst.*

When the ability of the organo-catalysts **63a** and **97a** to form an enamine upon reaction with aldehyde **132** was tested by ESI-MS studies (scheme 95), the desired signals could be detected. Actually in both cases the enamine signal was the dominant signal in the spectrum.

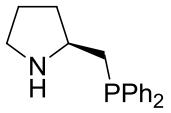


Scheme 95. *Testing for enamine formation.*

The finding that indoline-2-carboxylic acid (**101**) gave the desired product in 97% yield (table 28) while already upon use of its methyl ester **97b** only traces of product were formed, led to the assumption that in the α-allylation of aldehydes a carboxylic acid moiety on the catalyst is required to obtain product formation. As enamine formation seems to be not the problem the acid functionality has to play an important role as well at another point of the process. However, if the acid functionality is required, it is not possible to increase the sterical demand of the catalyst. Thus a different catalyst system had to be developed.

6.5 Development of a Bifunctional Tandem Catalyst

Another approach towards the selective α-allylation of aldehydes could be the use of a bifunctional tandem-catalyst, bearing both the amine-moiety, responsible for the enamine formation, and as well the palladium coordinating residue, as for example shown in catalyst **138** (figure 28). This compound was kindly provided by DENISE RAGEOT.

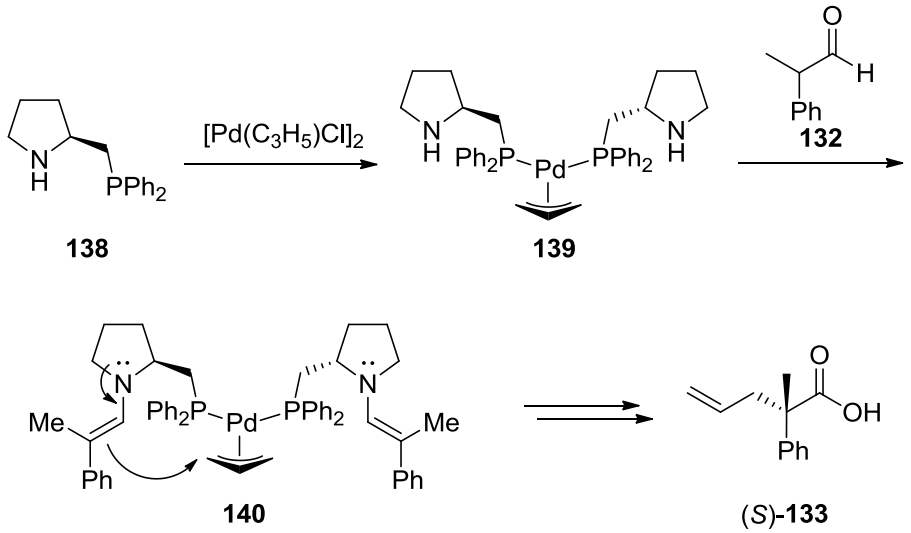


138

Figure 28. *Bifunctional tandem catalyst **138**.*

The general applicability of such a system was previously shown by HIROI and co-workers for a two-step approach[120a,120b] and by SATO and TOMIOKA for an intramolecular approach.[129]

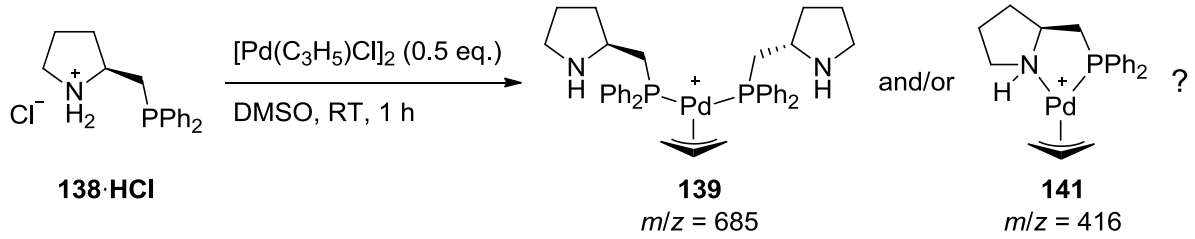
In theory, starting from a palladium-allyl species, two of such molecules should coordinate to a palladium-center and form a complex as shown in scheme 96. Reaction of the free amine on the complex and the aldehyde **132** would then form enamine species **140**. Due to the stereogenic center on the pyrrolidine ring, the allyl-moiety would be oriented in a face-selective fashion relative to the enamine residue. Thus, attack of the enamine onto the allyl should lead to a highly enantioenriched allylation product after hydrolysis (scheme 96). Since complex **139** is C_2-symmetric, reaction between the allyl and both of the possible enamine species would lead to the same product enantiomer.



138 **139** **140** (*S*)-**133**

Scheme 96. *α-Allylation by use of a bifunctional tandem catalyst.*

To evaluate the ability of such a bifunctional catalyst to form the desired complex **139** ESI-MS studies were carried out for initial experiments. In a first attempt the HCl-salt of compound **138** was reacted with a palladium-allyl precursor and the resulting mixture was analyzed by ESI-MS (scheme 97). As the nitrogen-atom in **138** might as well be able to coordinate to the palladium center two complexes are possibly formed. One would be the desired species **139** where two ligands bind in a monodentate fashion, the other one would be complex **141** where one ligand binds in a bidentate manner. Starting from the HCl salt of **139** it was hoped that *P*-coordination is favored over coordination with the protonated amine.



Scheme 97. *Complexation study by ESI-MS.*

When this experiment was carried out using Pd/**138**-ratio of 1:1 the signal corresponding to the desired complex **139** could not be detected but the formation of complex **141** was observed (figure 29, left). The two additional signals at *m*/*z* = 879 and 1054 could not be assigned but upon MS/MS analysis of these peaks fragmentation to the mass *m*/*z* = 416 was observed again. When a Pd/**138**-ratio of 1:2 was applied additional signals were detected (figure 29, right). One signal at *m*/*z* = 682 was detected with a complex isotope pattern. This signal might correspond to the desired complex **139**.

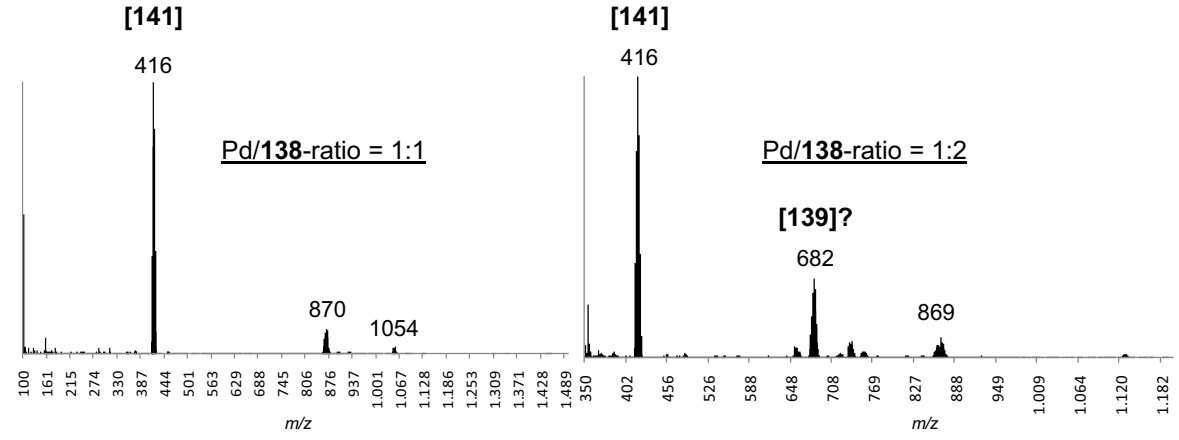


Figure 29. *ESI-MS spectra upon complexation of* ***138·HCl****.*

When the aldehyde **132** was added to the reaction mixture the signal at *m*/z = 679 even gained intensity. However, no desired enamine signal could be detected (figure 30). This time an additional signal at *m*/*z* = 644 was observed which corresponds to the palladium-complex **142** which would be formed after enamine attack onto the allyl moiety. This observation gives some evidence that the reaction might be able to proceed.

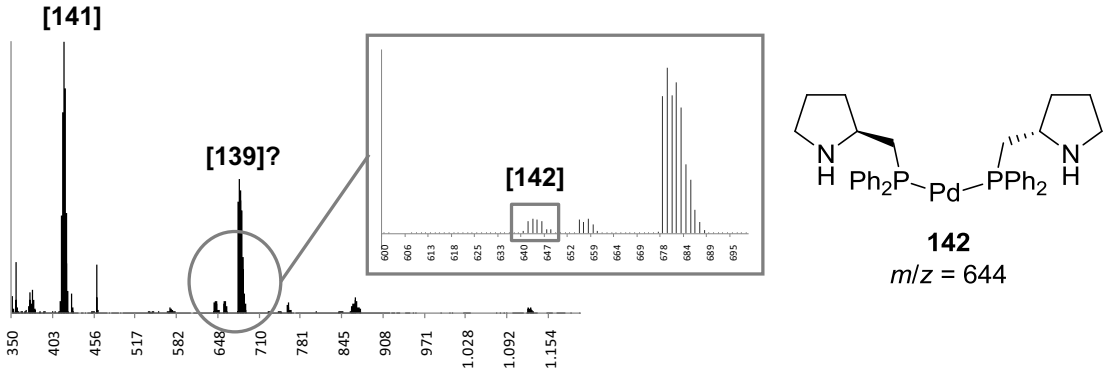


Figure 30. *ESI-MS spectrum after addition of aldehyde* ***132****.*

The same experiment as described above was as well carried out using the HCl free compound **138**. Again complexation mainly led to the formation of complex **141** and the exact mass of complex **139** was not found but a signal in this range (figure 31, left). This time however less undesired signals were found. Upon addition of aldehyde **132** again no enamine signal was observed but the signal corresponding to the allyl free complex **142** (figure 31, right).

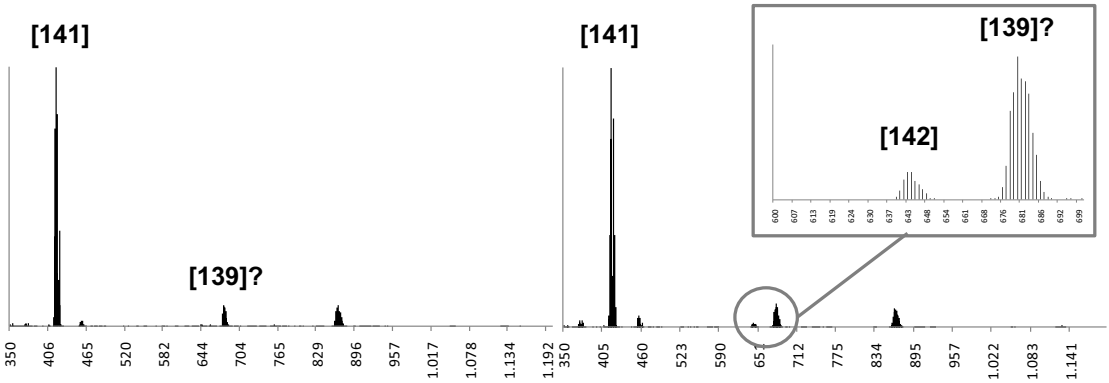


Figure 31. *ESI-MS studies using salt-free tandem-catalyst* ***138*** *(left: complexation; right: after addition of aldehyde* ***132****).*

When *p*-TsOH was added to this mixture, the signal corresponding to **142** dramatically increased in intensity (figure 32, left). Furthermore two new signals have been observed at

m/*z* = 816 and 1005, which could not be clearly assigned to any complex. MS/MS analysis of the signal at *m*/*z* = 1005 showed defragmentation to the complex **141** while analysis of the signal at *m*/*z* = 816 resulted in fragmentation towards complex **142** (figure 32, right). Interestingly this occurred by loss of a fragment with the mass of *m*/*z* = 172, which is close to the mass of the allylation product **133** (*m*/*z* = 174). This observation again gives some evidence for the formation of the desired reaction product.

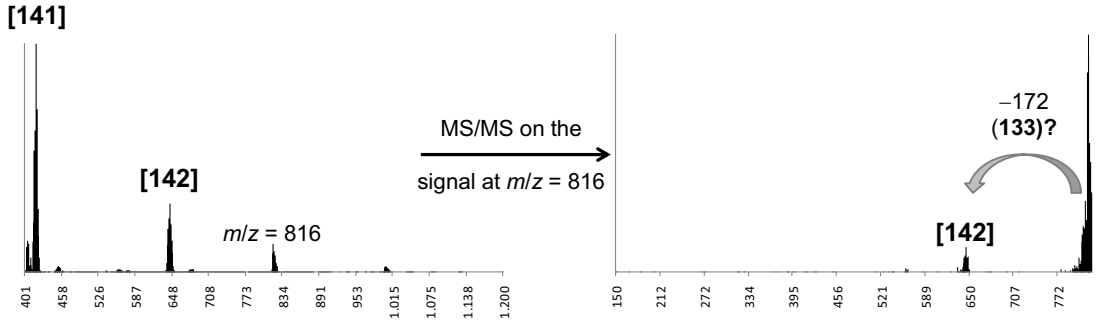
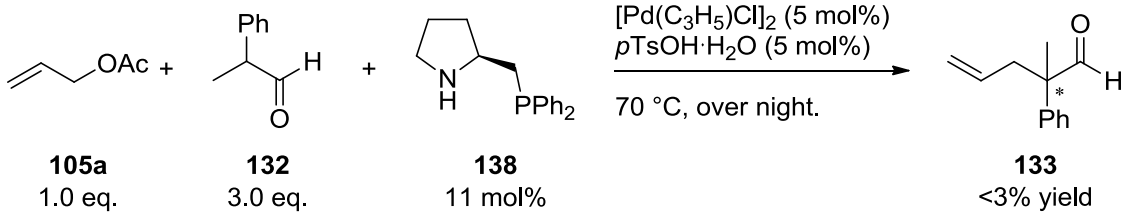


Figure 32. *Left: ESI-MS spectra after addition of p-TsOH; right: MS/MS analysis of the signal at m/z = 816.*

Encouraged by these experiments and the finding of some evidence for the formation of the desired allylation product the reaction was carried out on a preparative scale using 10 mol% catalyst loading. Unfortunately only traces of the allylation product were isolated (scheme 98).



Scheme 98. *Testing the bifunctional tandem-catalyst in the preparative reaction.*

The reason for this most likely is found in the predominant formation of complex **141** where the tandem catalyst coordinates in a bidentate fashion to the palladium center. In this complex the amine functionality is no more able to act as an organo-catalyst and cannot undergo enamine formation. Furthermore it was shown previously that a large bite-angle of the palladium-ligand is required to obtain α-allylation in good yields which is not the case upon use of the tandem-catalyst **138**.

6.6 Summary and Outlook

In summary different palladium-ligands and various organo-catalysts have been evaluated in the tandem-catalyzed α-allylation of carbonyl compounds. A combination of L-proline as organo-catalyst and Xantphos as palladium-ligand has been found to be the best combination for this transformation. Furthermore it was shown that *p*-TsOH as additive was crucial to achieve the desired transformation. Under these conditions selective-mono-allylation of ketones has been achieved and di-allylation could be completely suppressed. Although only very low enantioselectivities have been reached (6-22% *ee*), this is the first asymmetric example of a palladium-organo tandem-catalyzed intermolecular α-allylation of ketones. A possible explanation for the low selectivities was found in the tendency of α-chiral ketones to undergo racemization in the presence of a secondary amine via enamine formation.

In the α-allylation of aldehydes the formation of a quaternary stereogenic center has been achieved, although in a non enantioselective fashion (3% *ee*). In order to achieve higher selectivities the development of a bifunctional tandem-catalyst bearing both the amine-moiety, responsible for the enamine formation, and as well the palladium coordinating residue, was attempted. Coordination- and reactivity-studies by ESI-MS showed some evidence for the possibility to achieve the desired reaction. However, the tandem-catalyst tested in particular did form the allylation-product only in trace amounts.

Future work on this project might be dedicated to the optimization of the structure of such a bifunctional tandem-catalyst. In this work it was shown that coordination of such a catalyst in a bidentate fashion leads to an inactive catalyst-species. Therefore future catalyst-structures might be containing two palladium-coordinating groups besides the secondary amine functionality. These two centers could than coordinate to the palladium in a bidentate fashion. In this way, the free coordination-sites of the metal-center would be occupied and the amine moiety would remain unbound and thus active. As it was shown that the palladium-ligand should provide a large bite-angle, a catalyst structure based on a xanthene core might be promising (figure 33). For example upon use of compounds **143** or **144** an allyl palladium-P,P complex should be formed and the free amine could act as the organo-catalyst. As the phosphine moieties in these two compounds are chiral all different diastereoisomers would have to be tested. In order to avoid such issues, sulfur-containing tandem-catalysts might be evaluated. Compound **145** would be a C_2-symmetrical variant of this class. It has been shown

previously that bis-thio containing xanthene-ligands are active in the palladium-catalyzed allylic alkylation,[130] and thus compound **145** might be a promising tandem-catalyst as well.

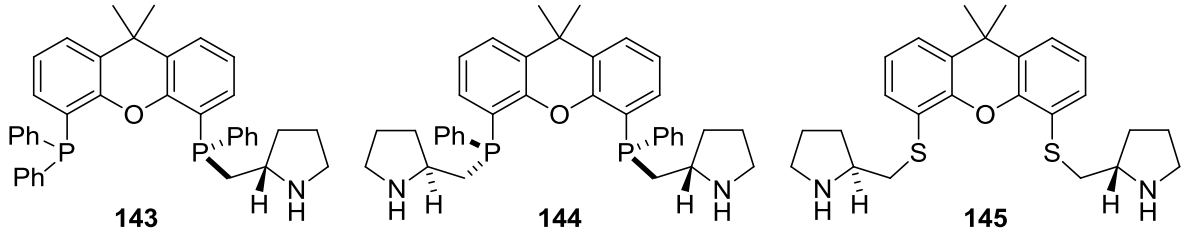
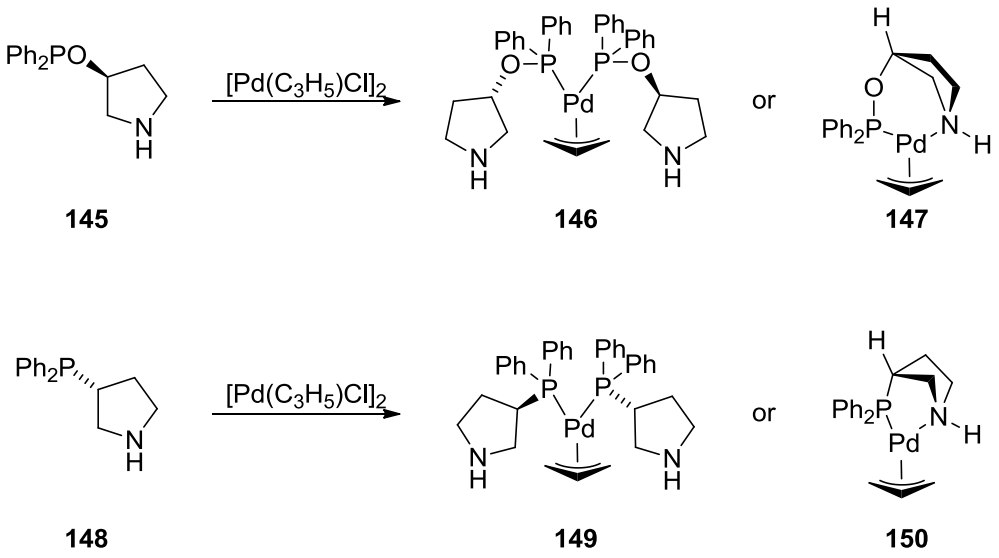


Figure 33. *Bidentate tandem-catalyst structures.*

Another approach to optimize the structure of such a tandem-catalyst would be to avoid amine-coordination by increase of conformational strain. Upon use of for example compound **145** formation of complex **146** should be favored as in complex **147** both the palladium and the oxygen-substituents on the pyrrolidine ring are in unfavorable axial position. The same would be true upon use of tandem-catalyst **148**, making those two structures promising catalyst candidates (scheme 99).



Scheme 99. *Controlled monodentate binding via increased conformational strain.*

Chapter 7

Experimental

7.1 Working Techniques and Reagents

The synthetic procedures were performed in flame-dried glassware under argon using Schlenk techniques or under purified nitrogen in a glovebox (Mbraun Labmaster 130).

Commercially available reagents were purchased from Acros, Aldirch, Alfa-Aesar, Fluka, Strem or TCI and used without further purification. *N*,*N*,*N*,*N*-Tetramethylethylenediamine was distilled from calcium hydride prior to use.

Solvents were collected from a purification column system (PureSolv, Innovative Technology Inc.) or purchased from Aldrich or Fluka in septum-sealed bottles over molecular sieves.

Column chromatographic purifications were performed on Merk silica gel 60 (Darmstadt, particle size 40-63 mm) or Fluka silica gel 60 (Buchs, particle size 40-63 mm) under 0.1-0.5 bar nitrogen pressure. The eluents were of technical grade and distilled prior to use.

7.2 Analytical Methods

NMR-Spectroscopy (NMR): NMR spectra were measured on a Bruker Avance 250 (250 MHz), a Bruker Avance 400 (400 MHz) or a Bruker Avance 500 (500 MHz) spectrometer, equipped with BBO broadband probe heads at room temperature. The chemical shifts (δ) are given in ppm. ^{1}H and ^{13}C spectra are referenced relative to tetramethylsilane (δ = 0 ppm) using the solvent residual peaks ($CDCl_3$ 7.26 ppm, CD_2Cl_2 5.32 ppm, C_6D_6 7.16 ppm) and the signals of the deuterated solvents ($CDCl_3$ 77.16 ppm, CD_2Cl_2 53.5 ppm, C_6D_6 128.1 ppm), respectively as internal standards.[131] ^{31}P spectra are calibrated relative to 85% phosphoric acid (δ = 0 ppm) and ^{19}F spectra relative to $CFCl_3$ (δ = 0 ppm) as external standards. The assignment of ^{1}H and ^{13}C signals was realized with the help of DEPT and, if needed, two-dimensional correlation experiments (COSY, HMQC, HMBC and NOESY). Multiplets are assigned as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), m (multiplet) and s br (broad singlet).

Infrared Spectroscopy (IR): Infrared spectra were collected on a Perkin Elmer 1600 series FTIR spectrometer. The spectra of liquids and oils were measured as thin films between two sodium chloride plates, those of solid samples as potassium bromide discs. The absorption bands are given in wavenumbers ($\tilde{\nu}$ [cm^{-1}]). The peak intensity is described by s (strong), m (medium) and w (weak). The index br stand for broad.

Mass Spectrometry (MS): Mass spectra were measured by Dr. H. Nadig (Department of Chemistry, University of Basel) on a VG70-250 spectrometer (electron-impact ionization (EI)) or on a MAR 312 spectrometer (fast atom bombardment (FAB)). FAB was performed with 3-nitrobenzyl alcohol (NBA) as matrix.

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 200 °C, 75 V capillary voltage, 1500 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.

High Resolution Mass Spectroscopy (HRMS): High resolution mass spectra were measured by the group of Prof. Dr. Schürch (Department of Chemistry and Biochemistry, University of Bern) on a Thermo Fisher Scientific / LTQ Orbitrap XL with Nanoelectrospray Ion Source.

Elemental Analysis: Elemental analyses were measured by Mr. W. Kirsch (Department of Chemistry, University of Basel) on a Leco CHN-900. The data are indicated in mass percent.

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

Optical Rotations ($[a]_D^{20}$): Optical rotations were measured on a Perkin Elmer Polarimeter 341 in a cuvette (l = 1 dm) at 20 °C. The concentration (c) is given in g/100 mL.

Gas Chromatography (GC): Gas chromatograms were collected on Carlo Erba HRGC Mega2 Series 800 (HRGS Mega 2) instruments. Achiral separations were performed on a Restek Rtx-1701 (30 m × 0.25 mm × 0.12 µm), a Macherey-Nagel Optima 5-Amin (30 m × 0.25 mm × 0.5 µm), a Macherey-Nagel Optima 5 PhMeSi (25 m × 0.2 mm × 0.35 µm) or a Macherey-Nagel Optima 5 Me_2Si (15 m × 0.2 mm × 0.35 µm) column. For chiral separations *Chiraldex* γ-cyclodextrin TFA G-TA (30 m × 0.25 mm × 0.12 µm) and *Brechbühler* β-cyclodextrin DEtTButSil (SE54) (25 m × 0.25 mm × 0.25 µm) columns were used.

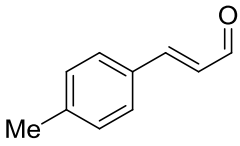
High Performance Liquid Chromatography (HPLC): HPLC analyses were measured on Shimadzu systems with SLC-10A system controller, CTO-10AC column oven, LC10-AD pump system, DGU-14A degasser and SPD-M10A diode array- or UV/VIS detector. As columns with chiral stationary phase Chiracel AD-H, OD-H or AS (4.6 × 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 AD (2 × 25 cm) from Daicel Chemical Industries was used.

Thin Layer Chromatography (TLC): TLC plates were obtained from Macherey-Nagel (Polygram SIL/UV254, 0.2 mm silica with fluorescence indicator). UV light (254 nm), basic permanganate solution or ceric ammonium molybdate solution were used for the visualization of the respective compounds.

7.3 ESI-MS Screening of Racemic Catalyst Mixtures

7.3.1 Substrate Synthesis



(*E*)-3-(*p*-Tolyl)acrylaldehyde (3a)

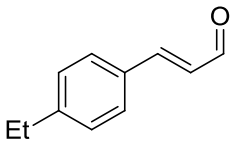
To a solution of 4-iodo-toluene (5.00 g, 22.9 mmol, 1.00 eq.) in DMF (85 mL), acroleine diethyl acetal (**2**) (8.94 g, 68.7 mmol, 3.00 eq.), [*n*-Bu_4N]OAc (13.8 g, 48.8 mmol, 2.00 eq.), K_2CO_3 (4.75 g, 34.4 mmol, 1.50 eq.), KCl (1.71 g, 22.9 mmol, 1.00 eq) and $Pd(OAc)_2$ (154 mg, 687 µmol, 3 mol%) were added and the solution was heated to 90 °C for 3 h. After cooling to room temperature aq. HCl (100 mL, 2 M) was added slowly and the mixture was stirred for 10 min. It was then diluted with Et_2O (350 mL) and washed with ice-water (750 mL). The aqueous phase was extracted with Et_2O (3 × 150 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 5 × 20 cm, hexanes/EtOAc = 10:1) gave the title compound **3a** as a slightly yellow solid (2.93 g, 88%). The analytical data match the literature values.[20]

$C_{10}H_{10}O$ (146.07 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.61 (d, $^3J_{HH}$ = 7.7 Hz, 1H, C*H*O), 7.39 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ar-C*H*), 7.37 (d, $^3J_{HH}$ = 16.2 Hz, 1H, C*H*CHCHO), 7.16 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-C*H*), 6.61 (dd, $^3J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 7.7 Hz, 1H, CHC*H*CHO), 2.32 (s, 3H, CH_3) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 193.9 (s, *C*HO), 153.1 (s, *C*HCHCHO), 142.1 (s, Ar-*C*), 131.4 (s, Ar-*C*), 130.0 (s, Ar-*C*H), 128.7 (s, Ar-*C*H), 127.8 (s, CH*C*HCHO), 21.7 (s, *C*H_3) ppm.

$\boldsymbol{R_f}$ = 0.23 (SiO_2, hexanes/EtOAc = 10:1).



(*E*)-3-(4-Ethylphenyl)acrylaldehyde (3b)

To a solution of 1-ethyl-4-iodo-benzene (8.40 g, 36.3 mmol, 1.00 eq.) in DMF (100 mL), acroleine diethyl acetal (**2**) (14.2 g, 109 mmol, 3.00 eq.), [*n*-Bu_4N]OAc (21.9 g, 72.6 mmol, 2.00 eq.), K_2CO_3 (7.53 g, 54.5 mmol, 1.50 eq.), KCl (2.71 g, 36.3 mmol, 1.00 eq) and $Pd(OAc)_2$ (247 mg, 1.09 mmol, 3 mol%) were added and the solution was heated to 90 °C for 3 h. After cooling to room temperature aq. HCl (100 mL, 2 M) was added slowly and the mixture was stirred for 10 min. It was then diluted with Et_2O (400 mL) and washed with ice-water (800 mL). The aqueous phase was extracted with Et_2O

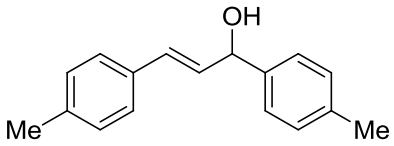
(4 × 200 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 5 × 20 cm, hexanes/EtOAc = 10:1) gave the title compound **3b** as a slightly yellow solid (5.25 g, 90%). The analytical data match the literature values.[20]

$C_{11}H_{12}O$ (160.09 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.59 (d, $^3J_{HH}$ = 7.8 Hz, 1H, C*H*O), 7.40 (d, $^3J_{HH}$ = 8.2 Hz, 2H, Ar-C*H*), 7.36 (d, $^3J_{HH}$ = 16.1 Hz, 1H, C*H*CHCHO), 7.17 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ar-C*H*), 6.59 (dd, $^3J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 7.7 Hz, 1H, CHC*H*CHO), 2.59 (q, $^3J_{HH}$ = 7.6 Hz, 2H, C*H*$_2$CH$_3$), 2.32 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C*H*$_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 193.8 (s, *C*HO), 153.0 (s, *C*HCHCHO), 148.3 (s, Ar-*C*), 131.6 (s, Ar-*C*), 128.7 (s, Ar-*C*H), 128.7 (s, Ar-*C*H), 127.8 (s, CH*C*HCHO), 28.9 (s, *C*H$_2$CH$_3$), 15.3 (s, CH$_2$*C*H$_3$) ppm.

R_f = 0.21 (SiO_2, hexanes/EtOAc = 10:1).



(*E*)-1,3-di-*p*-Tolylprop-2-en-1-ol (5a)

To a solution of 1-bromo-4-methylbenzene (**4a**) (4.26 g, 24.9 mmol, 1.40 eq.) in THF (50 mL), *sec*-BuLi (14.2 mL, 2.5 M in hexane, 35.6 mmol, 2.00 eq.) was added dropwise at −78 °C. The resulting colorless suspension was warmed to −25 °C until all the precipitate was dissolved. After cooling to −78 °C a solution of (*E*)-3-(*p*-tolyl)acrylaldehyde (**3a**) (2.60 g, 17.8 mmol, 1.00 eq.) in THF (8 mL) was added and the reaction mixture was warmed to room temperature overnight. After addition of sat. aq. NH_4Cl-solution (100 mL), the aqueous phase was extracted with Et_2O (3 × 30 mL), the combined organic layers were washed with sat. aq. NH_4Cl-solution (3 × 30 mL) and brine (3 × 30 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 5 × 20 cm, Pent/Et_2O = 5:1) gave the title compound **5a** as a colorless solid (3.78 g, 90%). The analytical data match the literature values.[20]

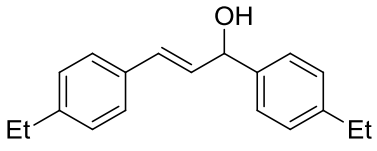
$C_{17}H_{18}O$ (238.14 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, $^3J_{HH}$ = 7.9 Hz, 2H, Ar-C*H*), 7.31 (d, $^3J_{HH}$ = 7.9 Hz, 2H, Ar-C*H*), 7.21 (d, $^3J_{HH}$ = 7.8 Hz, 2H, Ar-C*H*), 7.15 (d, $^3J_{HH}$ = 7.8 Hz, 2H, Ar-C*H*), 6.66 (d, $^3J_{HH}$ = 15.8 Hz, 1H, C*H*CHCHOH), 6.36 (dd, $^3J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 6.6 Hz, 1H,

CHC*H*CHOH), 5.35 (d, $^3J_{HH}$ = 6.5 Hz, 1H, CHCHC*H*OH), 2.40 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.35 (s, 1H, O*H*) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 138.5 (s, Ar-*C*), 137.5 (s, Ar-*C*), 137.3 (s, Ar-*C*), 134.1 (s, Ar-*C*), 131.4 (s, *C*HCHCHOH), 131.1 (CH*C*HCHOH), 129.3 (s, Ar-*C*H), 127.2 (s, Ar-*C*H), 127.2 (s, Ar-*C*H), 126.6 (s, Ar-*C*H), 79.0 (s, CHCH*C*HOH), 21.3 (s, *C*H_3) ppm.

$\boldsymbol{R_f}$ = 0.25 (SiO_2, Pent/Et_2O = 5:1).



(*E*)-1,3-bis(4-Ethylphenyl)prop-2-en-1-ol (5b)

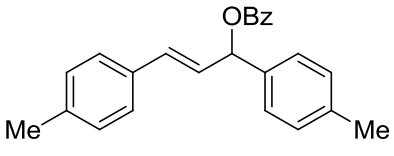
To a solution of 1-iodo-4-ethylbenzene (**4b**) (9.51 g, 41.0 mmol, 1.40 eq.) in THF (80 mL), *sec*-BuLi (23.4 mL, 2.5 M in hexane, 58.6 mmol, 2.00 eq.) was added dropwise at −78 °C. The resulting colorless suspension was warmed to −25 °C until all the precipitate was dissolved. After cooling to −78 °C a solution of (*E*)-3-(4-ethylphenyl)acrylaldehyde (**3b**) (4.69 g, 29.3 mmol, 1.00 eq.) in THF (13 mL) was added and the reaction mixture was warmed to room temperature overnight. After addition of sat. aq. NH_4Cl-solution (150 mL), the aqueous phase was extracted with Et_2O (3 × 80 mL), the combined organic layers were washed with sat. aq. NH_4Cl-solution (3 × 50 mL) and brine (3 × 50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 5 × 20 cm, Pent/Et_2O = 5:1) gave the title compound **5a** as a colorless solid (2.90 g, 37%). The analytical data match the literature values.[20]

$C_{19}H_{22}O$ (266.17 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-C*H*), 7.30 (d, $^3J_{HH}$ = 7.1 Hz, 2H, Ar-C*H*), 7.19 (d, $^3J_{HH}$ = 8.2 Hz, 2H, Ar-C*H*), 7.13 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ar-C*H*), 6.65 (d, $^3J_{HH}$ = 15.8 Hz, 1H, C*H*CHCHOH), 6.34 (dd, $^3J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 6.6 Hz, 1H, CHC*H*CHOH), 5.36-5.32 (m, 1H, CHCHC*H*OH), 2.65-2.61 (m, 4H, CH_2CH$_3$), 2.02 (s, 1H, O*H*), 1.26-1.20 (m, 6H, CH$_2$CH_3) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 144.1 (s, Ar-*C*), 144.0 (s, Ar-*C*), 140.3 (s, Ar-*C*), 134.2 (s, Ar-*C*), 130.8 (s, *C*HCHCHOH), 130.4 (CH*C*HCHOH), 128.2 (s, Ar-*C*H), 128.2 (s, Ar-*C*H), 126.7 (s, Ar-*C*H), 126.5 (s, Ar-*C*H), 75.2 (s, CHCH*C*HOH), 28.7 (s, *C*H$_2$CH$_3$), 28.7 (s, *C*H$_2$CH$_3$), 15.8 (s, CH$_2$*C*H$_3$), 15.7 (s, CH$_2$*C*H$_3$) ppm.

$\boldsymbol{R_f}$ = 0.23 (SiO_2, Pent/Et_2O = 10:1).



(*E*)-1,3-di-*p*-Tolylallyl benzoate (7a)

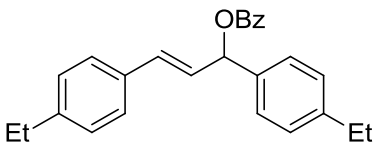
To a solution of (*E*)-1,3-di-*p*-tolylprop-2-en-1-ol (**5a**) (1.90 g, 7.90 mmol, 1.00 eq.) in DCM (32 mL), NEt_3 (1.75 g, 17.3 mmol, 2.2 eq.) and catalytic amounts of DMAP was added. After cooling to −78 °C benzoyl chloride (**6**) (1.46 g, 10.4 mmol, 1.3 eq.) was added dropwise. The reaction mixture was warmed to room temperature overnight and afterwards quenched with sat. aq. NH_4Cl-solution (20 mL). The aqueous phase was extracted with DCM (3 × 30 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 5 × 20 cm, hexanes/EtOAc/NEt_3 = 18:1:1) gave the title compound **7a** as a colorless solid (2.48 g, 91%). The analytical data match the literature values.[20]

$C_{24}H_{22}O_2$ (342.43 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, $^3J_{HH}$ = 7.1 Hz, 2H, Ar-C*H*), 7.57 (t, $^3J_{HH}$ = 7.3 Hz, 1H, Ar-C*H*), 7.48-7.40 (m, 4H, Ar-C*H*), 7.30 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-C*H*), 7.21 (d, $^3J_{HH}$ = 7.8 Hz, 2H, Ar-C*H*), 7.12 (d, $^3J_{HH}$ = 7.9 Hz, 2H, Ar-C*H*), 6.70 (d, $^3J_{HH}$ = 16.3 Hz, 1H, C*H*CHCHOBz), 6.67 (d, $^3J_{HH}$ = 6.9 Hz, 1H, CHCHC*H*OBz), 6.43 (dd, $^3J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 6.7 Hz, 1H, C*H*CHCHOBz), 2.37 (s, 3H, CH_3), 2.34 (s, 3H, CH_3) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 165.7 (s, Ph*C*(O)O), 138.1 (s, Ar-*C*), 138.0 (s, Ar-*C*), 136.6 (s, Ar-*C*), 133.6 (s, Ar-*C*), 133.1 (s, *C*HCHCHOBz), 132.7 (s, CH*C*HCHOBz), 130.6 (s, Ar-*C*), 129.9 (s, Ar-*C*H), 129.5 (s, Ar-*C*H), 129.4 (s, Ar-*C*H), 128.5 (s, Ar-*C*H), 127.2 (s, Ar-*C*H), 126.8 (s, Ar-*C*H), 126.8 (s, Ar-*C*H), 76.9 (CHCH*C*HOBz), 21.4 (s, *C*H_3), 21.3 (s, *C*H_3) ppm.

R_f = 0.56 (SiO_2, hexanes EtOAc = 4:1).



(*E*)-1,3-bis(4-Ethylphenyl)allyl benzoate (7b)

To a solution of (*E*)-1,3-bis(4-ethylphenyl)prop-2-en-1-ol (**5b**) (492 mg, 1.84 mmol, 1.00 eq.) in DCM (8 mL), NEt_3 (383 mg, 3.80 mmol, 2.1 eq.) and catalytic amounts of DMAP was added. After cooling to −78 °C benzoyl chloride (**6**) (338 g, 2.40 mmol, 1.3 eq.) was added dropwise. The reaction mixture was warmed to room temperature overnight and afterwards quenched with sat. aq. NH_4Cl-solution (5 mL). The aqueous phase was extracted with DCM (3 × 15 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure.

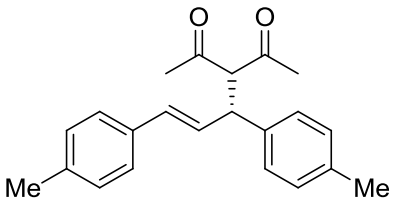
Purification by recrystallization from hexanes/DCM gave the title compound **7b** as a colorless solid (512 mg, 75%). The analytical data match the literature values.[20]

$C_{26}H_{26}O_2$ (370.48 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, $^3J_{HH}$ = 7.3 Hz, 2H, Ar-C*H*), 7.57 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar-C*H*), 7.46-7.40 (t, $^3J_{HH}$ = 8.5 Hz, 4H, Ar-C*H*), 7.34 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-C*H*), 7.24 (d, $^3J_{HH}$ = 7.9 Hz, 2H, Ar-C*H*), 7.16 (d, $^3J_{HH}$ = 7.9 Hz, 2H, Ar-C*H*), 6.73 (d, $^3J_{HH}$ = 15.9 Hz, 1H, C*H*CHCHOBz), 6.69 (d, $^3J_{HH}$ = 6.8 Hz, 1H, CHCHC*H*OBz), 6.45 (dd, $^3J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 6.7 Hz, 1H, C*H*CHCHOBz), 2.68-64 (m, 4H, CH_2CH$_3$), 1.27-1.22 (m, 6H, CH$_2$CH_3) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 165.7 (s, Ph*C*(O)O), 138.1 (s, Ar-*C*), 138.0 (s, Ar-*C*), 136.6 (s, Ar-*C*), 133.6 (s, Ar-*C*), 133.1 (s, *C*HCHCHOBz), 132.7 (s, CH*C*HCHOBz), 130.6 (s, Ar-*C*), 129.9 (s, Ar-*C*H), 129.5 (s, Ar-*C*H), 129.4 (s, Ar-*C*H), 128.5 (s, Ar-*C*H), 127.2 (s, Ar-*C*H), 126.8 (s, Ar-*C*H), 126.8 (s, Ar-*C*H), 76.9 (CHCH*C*HOBz), 21.4 (s, *C*H$_3$), 21.3 (s, *C*H$_3$) ppm.

R_f = 0.53 (SiO_2, hexanes EtOAc = 4:1).



(*R*,*E*)-3-(1,3-di-*p*-Tolylallyl)pentane-2,4-dione (8a)

A solution of $[Pd(C_3H_5)Cl]_2$ (8.00 mg, 21.9 µmol, 2.5 mol%) and (*R*)-*i*-Pr-**PHOX** (19.3 mg, 51.7 µmol, 5.9 mol%) in DCM (2.0 mL) was degassed in a Young tube by three freeze-pump-thaw cycles and afterwards stirred at 50 °C for 2 h. In a second Young tube (*E*)-1,3-di-*p*-tolylallyl benzoate (**7a**) (300 mg, 875 µmol, 1.00 eq.) was dissolved in DCM (3.5 mL). To this solution BSA (535 mg, 2.63 mmol, 3.00 eq.), pentane-2,4-dione (263 mg, 2.63 mmol, 3.00 eq.) and catalytic amounts of KOAc were added. After three freeze-pump-thaw cycles the catalyst solution was added via syringe and the resulting mixture was stirred at 0 °C for 40 h. Then the reaction was diluted with Et_2O (50 mL) and washed with ice-cold sat. aq. NH_4Cl-solution (30 mL). The aqueous phase was extracted with Et_2O (3 × 30 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 2 × 20 cm, hexanes/EtOAc/NEt_3 = 18:1:1) gave the title compound (*R*)-**8a** as a colorless solid (252 mg, 90%, >99% *ee*). The analytical data match the literature values.[20]

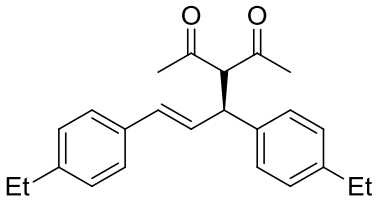
$C_{22}H_{24}O_2$ (320.42 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.17-7.13 (m, 8H, Ar-C*H*), 6.38 (d, $^3J_{HH}$ = 15.8 Hz, 1H, C*H*CHCHacac), 6.12 (dd, $^3J_{HH}$ = 15.7 Hz, $^3J_{HH}$ = 7.3 Hz, 1H, CHC*H*CHacac), 4.30-4.27 (m, 2H, CHCHC*H*acac, C*H*(C(O)CH_3)$_2$), 2.30 (s, 6H, ArCH_3), 2.24 (s, 3H, C(O)CH_3), 1.93 (s, 3H, C(O)CH_3).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 203.2 (s, *C*O), 203.2 (s, *C*O), 137.6 (s, Ar-*C*), 137.3 (s, Ar-*C*), 137.0 (s, Ar-*C*), 134.0 (s, Ar-*C*), 131.4 (s, *C*HCHCHacac), 129.8 (s, Ar-*C*H), 129.3 (s, Ar-*C*H), 128.5 (s, CH*C*HCHacac), 127.9 (s, Ar-*C*H), 126.4 (s, Ar-*C*H), 74.8 (s, CHCHC*CH*acac), 49.0 (s, *C*H(C(O)CH_3)$_2$), 30.1 (s, C(O)*C*H_3), 29.9 (s, C(O)*C*H_3), 21.3 (s, Ar*C*H_3), 21.2 (s, Ar*C*H_3) ppm.

HPLC (Daicel Chiracel AD-H, Hept/*i*-PrOH = 97:3, 0.9 mL/min, 20 °C): t_R = 16.2 min (*R*)-**8a**, 17.5 min (*S*)-**8a**).

$\boldsymbol{R_f}$ = 0.47 (SiO_2, hexanes/EtOAc = 4:1).



(*S*,*E*)-3-(1,3-bis(4-Ethylphenyl)allyl)pentane-2,4-dione (8b)

A solution of [Pd(C_3H_5)Cl]$_2$ (3.70 mg, 10.1 µmol, 2.5 mol%) and (*S*)-*i*-Pr-**PHOX** (8.91 mg, 23.9 µmol, 5.9 mol%) in DCM (1.0 mL) was degassed in a Young tube by three freeze-pump-thaw cycles and afterwards stirred at 50 °C for 2 h. In a second Young tube (*E*)-1,3-bis(4-ethylphenyl)allyl benzoate (**7b**) (150 mg, 405 µmol, 1.00 eq.) was dissolved in DCM (1.6 mL). To this solution BSA (248 mg, 1.22 mmol, 3.00 eq.), pentane-2,4-dione (122 mg, 1.22 mmol, 3.00 eq.) and catalytic amounts of KOAc were added. After three freeze-pump-thaw cycles the catalyst solution was added via syringe and the resulting mixture was stirred at 0 °C for 40 h. Then the reaction was diluted with Et_2O (20 mL) and washed with ice-cold sat. aq. NH_4Cl-solution (15 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 2 × 20 cm, hexanes/EtOAc/NEt_3 = 18:1:1) gave the title compound (*S*)-**8b** as a colorless solid (131 mg, 93%, >99% *ee*). The analytical data match the literature values.[20]

$C_{24}H_{28}O_2$ (348.48 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.16-7.13 (m, 8H, Ar-C*H*), 6.39 (d, $^3J_{HH}$ = 15.8 Hz, 1H, C*H*CHCHacac), 6.13 (dd, $^3J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 7.1 Hz, 1H, CHC*H*CHacac), 4.32-4.28 (m,

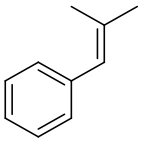
2H, CHCHC*H*acac, C*H*(C(O)CH_3)$_2$), 2.60 (q, $^3J_{HH}$ = 7.5 Hz, 4H, C$H_2$$CH_3$), 2.24 (s, 3H, C(O)C$H_3$), 1.93 (s, 3H, C(O)C$H_3$), 1.22-1.18 (m, 6H, CH_2CH_3) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 203.2 (s, *C*O), 203.1 (s, *C*O), 144.1 (s, Ar-*C*), 143.3 (s, Ar-*C*), 137.5 (s, Ar-*C*), 134.2 (s, Ar-*C*), 131.4 (s, *C*HCHCHacac), 128.7 (s, CH*C*HCHacac), 128.6 (s, Ar-*C*H), 128.1 (s, Ar-*C*H), 127.9 (s, Ar-*C*H), 126.5 (s, Ar-*C*H), 74.8 (s, CHCHC*CH*acac), 49.0 (s, *C*H(C(O)CH_3)$_2$), 30.2 (s, C(O)*C*H_3), 29.9 (s, C(O)*C*H_3), 28.7 (s, *C*$H_2$$CH_3$), 28.5 (s, *C*$H_2$$CH_3$), 15.7 (s, CH_2*C*H_3), 15.5 (s, CH_2*C*H_3) ppm.

HPLC (Daicel Chiracel AD-H, Hept/*i*-PrOH = 97:3, 0.9 mL/min, 20 °C): t_R = 24.9 min (*R*)-**8b**, 29.4 min (*S*)-**8b**).

$\boldsymbol{R_f}$ = 0.48 (SiO_2, hexanes/EtOAc = 4:1).

7.3.2 Ligand Synthesis



(2-Methylprop-1-enyl)benzene (13a)

To a solution of isopropyltriphenylphosphonium iodide (**15**) (5.88 g, 13.6 mmol, 1.80 eq.) in THF (15 mL), *n*-BuLi (9.07 mL, 1.5 M in hexane, 13.6 mmol, 1.80 eq.) was added dropwise at 0 °C. After stirring for 30 min benzaldehyde (**14a**) (767 µl, 802 mg, 7.56 mmol, 1.00 eq.) was added. The mixture was stirred at RT for 5 h and then hydrolyzed with water (20 mL). The THF was removed under reduced pressure and the residue diluted with Et_2O (30 mL). After filtration over celite and phase separation the organic layer was washed with water (3 × 30 mL), then dried over $MgSO_4$ and the solvent was removed under reduced pressure without going below 180 mbar at 40 °C. Purification by column chromatography (SiO_2, 3 × 20 cm, hexanes) gave the title compound **13a** as a colorless liquid (718 mg, 72%).

$C_{10}H_{12}$ (132.20 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, $^3J_{HH}$ = 7.4 Hz, 2H, Ar-CCHC*H*), 7.22 (d, $^3J_{HH}$ = 7.1 Hz, 2H, Ar-CC*H*), 7.17 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar-CCHCHC*H*), 6.27, (s, 1H, C*H*C(CH_3)$_2$), 1.90 (s, 3H, CH_3), 1.86 (s, 3H, CH_3') ppm.

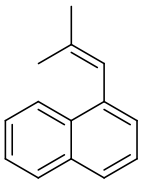
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 138.8 (s, *C*(CH_3)$_2$), 135.6 (s, Ar-*C*), 128.9 (s, Ar-*C*H), 128.2 (s, Ar-*C*H), 125.9 (s, Ar-*C*H), 125.3 (s, *C*HC(CH_3)$_2$), 27.0 (s, *C*H_3), 19.5 (s, *C*H_3') ppm.

IR (NaCl): $\tilde{\nu}$ = 3024s, 2970s, 2922s, 1946w, 1883w, 1805w, 1656m, 1598m, 1492m, 1444s, 1379m, 1180w, 1072w, 1027w, 982w, 914m, 834m, 740s, 698s, 629w cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 132 (73, M^+), 131 (15), 117 (100), 115 (36), 91 (26).

Elemental analysis calc. (%) for $C_{10}H_{12}$: C 90.85, H 9.15; found: C 90.95, H 9.25.

R_f = 0.43 (SiO_2, hexanes).



(2-Methylprop-1-enyl)naphthalene (13b)

To a suspension of isopropyltriphenylphosphonium iodide (**15**) (12.8 g, 29.7 mmol, 1.80 eq.) in THF (40 mL), *n*-BuLi (19.8 mL, 1.5 M in hexane, 29.7 mmol, 1.80 eq.) was added dropwise at 0 °C. After stirring for 30 min 1-naphthaldehyde (**14b**) (2.25 mL, 2.57 g, 16.5 mmol, 1.00 eq.) was added. The mixture was stirred at RT for 4 h and then hydrolyzed with water (30 mL). The THF was removed under reduced pressure and the residue diluted with Et_2O (40 mL). After filtration over celite and phase separation the organic layer was washed with water (3 × 40 mL), then dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was diluted with Et_2O and the obtained white solid was filtered off, whereupon the solvent was again removed under reduced pressure. Purification by column chromatography (SiO_2, 5 × 20 cm, hexanes) gave the title compound **13b** as a colorless oil (2.80 g, 93%).

$C_{14}H_{14}$ (182.26 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99-7.97 (m, 1H, Ar-C*H*), 7.82-7.80 (m, 1H, Ar-C*H*), 7.70 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Ar-C*H*), 7.45-7.43 (m, 2H, Ar-C*H*), 7.40 (d, $^3J_{HH}$ = 8.1 Hz, 1H, Ar-C*H*), 7.28 (d, $^3J_{HH}$ = 7.0 Hz, 1H, Ar-C*H*), 6.65 (s, 1H, C*H*(CH_3)$_2$), 2.00 (d, $^4J_{HH}$ = 1.4 Hz, 3H, CH_3), 1.70 (d, $^3J_{HH}$ = 1.2 Hz, 3H, CH_3') ppm.

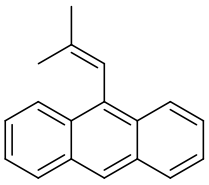
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 137.0 (s, *C*(CH_3)$_2$), 136.1 (s, Ar-*C*), 133.7 (s, Ar-*C*), 132.3 (s, Ar-*C*), 128.4 (s, Ar-*C*H), 126.8 (s, Ar-*C*H), 125.7 (s, Ar-*C*H), 125.5 (s, Ar-*C*H), 125.4 (s, Ar-*C*H), 123.1 (s, *C*HC(CH_3)$_2$), 26.3 (s, *C*H_3), 19.7 (s, *C*H_3') ppm.

IR (NaCl): $\tilde{\nu}$ = 3054s, 2969s, 2913s, 1926w, 1815w, 1657m, 1587m, 1506m, 1444s, 1382m, 1333w, 1266w, 1188m, 1057w, 1012m, 978w, 865w, 828m, 784s, 649w cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 182 (64), 181 (16), 168 (12), 167 (100), 166 (19), 165 (40), 152 (21).

Elemental analysis calc. (%) for $C_{14}H_{14}$: C 92.26, H 7.74; found: C 92.06, H 7.88.

R_f = 0.52 (SiO_2, hexanes).



9-(2-methylprop-1-en-1-yl)anthracene (13c)

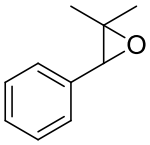
To a suspension of $(CH_3)_2CHP(Ph)_3I$ (**15**) (10.0 g, 23.2 mmol, 1.80 eq.) in THF (40 mL), *n*-BuLi (15.0 mL, 1.5 M in hexanes, 23.2 mmol, 1.80 eq.) was added dropwise at 0 °C. After stirring for 30 min anthracene-9-carbaldehyde (**14c**) (2.65 g, 12.9 mmol, 1.00 eq.) was added. The mixture was stirred at RT for 4 h and then hydrolyzed with water (25 mL). The THF was removed under reduced pressure and the residue diluted with Et_2O (30 mL). After filtration over celite and phase separation the organic layer was washed with water (3 × 30 mL), then dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was diluted with Et_2O and the obtained white solid was filtered off, whereupon the solvent was again removed under reduced pressure. Purification by column chromatography (SiO_2, 5 × 20 cm, hexanes) gave the title compound **13c** as a colorless oil (2.59 g, 86%).

$C_{18}H_{16}$ (232.32 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, Ar-C*H*), 8.14-8.10 (m, 2H, Ar-C*H*), 7.99-7.95 (m, 2H, Ar-C*H*), 7.45-7.40 (m, 4H, Ar-C*H*), 6.75-6.77 (m, 1H, C*H*$(CH_3)_2$), 2.15 (d, $^4J_{HH}$ = 1.4 Hz, 3H, CH_3), 1.39 (d, $^3J_{HH}$ = 1.0 Hz, 3H, CH_3') ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 139.0 (s, *C*$(CH_3)_2$), 133.7 (s, Ar-*C*), 131.6 (s, Ar-*C*), 130.0 (s, Ar-*C*), 128.7 (s, Ar-*C*H), 126.7 (s, Ar-*C*H), 125.8 (s, Ar-*C*H), 125.2 (s, Ar-*C*H), 121.2 (s, *C*HC$(CH_3)_2$), 25.7 (s, *C*H_3), 20.0 (s, *C*H_3') ppm.

R_f = 0.43 (SiO_2, hexanes).



2,2-Dimethyl-3-phenyloxirane (11a)

To a solution of (2-methylprop-1-enyl)benzene (**13a**) (1.50 g, 11.3 mmol, 1.00 eq.) in DCM (50 mL), MCPBA (3.07 g, 70%, 12.43 mmol, 1.10 eq.) were added slowly at 0 °C. The reaction mixture was stirred for 3 d and then diluted with pentane (50 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (3 × 50 mL) and sat. aq. NaCl (1 × 50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, hexanes/Et_2O 5:1) gave the title compound **11a** as a yellow liquid (1.57 g, 94%).

$C_{10}H_{12}O$ (148.20 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37-7.26 (m, 5H, Ar-C*H*), 3.87 (s, 1H, $(CH_3)_2CCH$), 1.49 (s, 3H, CH_3), 1.08 (s, 3H, CH_3') ppm.

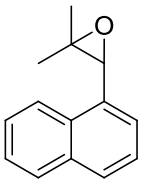
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 136.7 (s, Ar-*C*), 128.1 (s, Ar-*C*H), 127.5 (s, Ar-CCHCH*C*H), 126.5 (s, Ar-*C*H), 64.7 (s, $(CH_3)_2CCH$), 61.2 (s, $C(CH_3)_2$), 24.9 (s, CH_3), 18.1 (s, CH_3') ppm.

IR (NaCl): $\tilde{\nu}$ = 3062m, 3032m, 2963s, 2927s, 1956w, 1889w, 1769w, 1604m, 1496m, 1452s, 1381s, 1322m, 1246s, 1117m, 1032m, 910m, 850m, 799m, 743s, 700s, 624m cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 148 (48), 147 (34), 133 (18), 119 (19), 107 (12), 105 (41), 91 (53), 90 (100), 89 (45), 79 (18), 77 (20).

Elemental analysis calc. (%) for $C_{10}H_{12}O$: C 81.04, H 8.16; found: C 80.82, H 8.32.

R_f = 0.53 (SiO_2, hexanes/Et_2O 5:1).



2,2-Dimethyl-3-(naphthalen-1-yl)oxirane (11b)

To a solution of 1-(2-methylprop-1-enyl)naphthalene (**13b**) (2.80 g, 15.4 mmol, 1.00 eq.) in DCM (50 mL), MCPBA (4.12 g, 70%, 16.9 mmol, 1.10 eq.) was added slowly at 0 °C. The reaction mixture was stirred for 2.5 h and then diluted with pentane (80 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (3 × 70 mL) and sat. aq. NaCl (1 × 70 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 5 × 20 cm, hexanes/Et_2O 5:1) gave the title compound **11b** as a colorless liquid (2.96 g, 97%).

$C_{14}H_{14}O$ (198.26 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.94-7.87 (m, 2H, Ar-C*H*), 7.78 (dd, $^3J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 2.6 Hz, 1H, Ar-C*H*), 7.55-7.44 (m, 4H, Ar-C*H*), 4.30 (s, 1H, $C(CH_3)_2CH$), 1.66 (s, 3H, CH_3), 1.01 (s, 3H, CH_3') ppm.

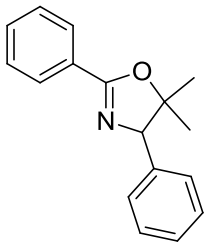
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 133.3 (s, Ar-*C*), 133.0 (s, Ar-*C*), 131.2 (s, Ar-*C*), 128.8 (s, Ar-*C*H), 127.7 (s, Ar-*C*H), 126.3 (s, Ar-*C*H), 125.9 (s, Ar-*C*H), 125.5 (s, Ar-*C*H), 124.2 (s, Ar-*C*H), 123.1 (s, Ar-*C*H), 63.6 (s, $C(CH_3)_2CH$), 61.3 (s, $C(CH_3)_2$), 24.6 (s, CH_3), 18.4 (s, CH_3`) ppm.

IR (NaCl): $\tilde{\nu}$ = 3057m, 2961m, 1569w, 1511w, 1451w, 1381m, 1305w, 1247w, 1161w, 913w, 872w, 788s, 698w cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 198 (37), 183 (27), 169 (11), 155 (17), 141 (19), 140 (100), 139 (53), 127 (11).

Elemental analysis calc. (%) for $C_{14}H_{14}O$: C 84.81, H 7.12; found: C 84.63, H 7.28.

R_f = 0.47 (SiO_2, hexanes/Et_2O 5:1).



5,5-Dimethyl-2,4-diphenyl-4,5-dihydrooxazole (10a)

2,2-dimethyl-3-phenyloxirane (**11a**) (250 mg, 1.69 mmol, 1.00 eq.) was dissolved in benzonitrile (**12**) (3.10 mL, 3.13 g, 30.4 mmol, 18.0 eq.) and the solution was cooled to 0 °C. To this mixture $BF_3 \times OEt_2$ (214 µl, 240 mg, 1.69 mmol, 1.00 eq.) was added over 10 min. The reaction was allowed to warm up to RT and stirred for 3 h. Sat. aq. $NaHCO_3$ (7 mL) was added and the mixture was stirred for further 2 h before being diluted with water (30 mL). The aqueous layer was extracted with DCM (3 × 45 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, hexanes/Et_2O 5:2) gave the title compound **10a** as a colorless oil (169 mg, 40%).

$C_{17}H_{17}NO$ (251.32 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04 (dt, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.4 Hz, 2H, Ar-C*H*), 7.51 (tt, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, Ar-C*H*), 7.44 (t, $^3J_{HH}$ = 7.7 Hz, 2H, Ar-C*H*), 7.40-7.30 (m, 5H, Ar-C*H*), 5.31 (s, 1H, NC*H*), 1.57 (s, 3H, CH_3), 0.85 (s, 3H, CH_3') ppm.

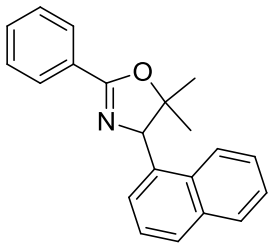
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 161.7 (s, N*C*O), 137.7 (s, Ar-*C*), 131.5 (s, Ar-*C*H), 128.5 (s, Ar-*C*H), 128.5 (s, Ar-*C*H), 128.1 (s, Ar-*C*), 128.1 (s, Ar-*C*H), 125.8 (s, Ar-*C*H), 90.1 (s, N*C*H), 71.0 (s, *C* $(CH_3)_2$), 30.1 (s, *C*H_3), 25.3 (s, *C*H_3') ppm.

IR (NaCl): $\tilde{\nu}$ = 3063m, 3033m, 2972s, 2928m, 2363w, 1651s, 1581w, 1496m, 1453m, 1363m, 1324s, 1289s, 1215m, 1179m, 1064s, 1005m, 971m, 939w, 860w, 780m, 744m, 697s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 251 (1), 146 (11), 145 (100), 104 (39), 77 (10).

Elemental analysis calc. (%) for $C_{17}H_{17}NO$: C 81.24, H 6.82, N 5.57; found: C 80.94, H 6.92, N 5.69.

R_f = 0.31 (SiO_2, hexanes/Et_2O 5:2).



5,5-Dimethyl-4-(naphthalen-1-yl)-2-phenyl-4,5-dihydrooxazole (10b)

2,2-dimethyl-3-(naphthalen-1-yl)oxirane (**11b**) (1.50 g, 7.58 mmol, 1.00 eq.) was dissolved in benzonitrile (13.9 mL, 14.0 g, 136 mmol, 18.0 eq.) and the solution was cooled to 0 °C. To this mixture $BF_3{\times}OEt_2$ (964 µl, 1.08 g, 7.58 mmol, 1.00 eq.) was added over 10 min. The reaction was allowed to warm up to RT and stirred for 3 h. Sat. aq. $NaHCO_3$ (30 mL) was added and the mixture was stirred for further 2 h before being diluted with water (50 mL). The aqueous layer was extracted with DCM (3 × 50 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, hexanes/Et_2O 5:2) gave the title compound **10b** as a colorless oil (690 mg, 27%).

$C_{21}H_{19}NO$ (301.38 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.12 (dt, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.6 Hz, 2H, Ar-C*H*), 7.96 (d, $^3J_{HH}$ = 8.3 Hz, 1H, Ar-C*H*), 7.91 (dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, Ar-C*H*), 7.82 (d, $^3J_{HH}$ = 8.1 Hz, 1H, Ar-C*H*), 7.59-7.45 (m, 7H, Ar-C*H*), 6.23 (s, 1H, NC*H*), 1.76 (s, 3H, CH_3), 0.84 (s, 3H, CH_3') ppm.

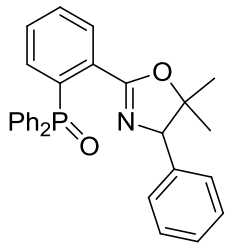
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 161.5 (s, N*C*O), 134.1 (s, Ar-*C*), 133.7 (s, Ar-*C*), 131.6 (s, Ar-*C*H), 131.0 (s, Ar-*C*), 129.2 (s, Ar-*C*H), 128.6 (s, Ar-*C*H), 128.5 (s, Ar-*C*H), 128.3 (s, Ar-*C*H), 128.0 (s, Ar-*C*), 126.5 (s, Ar-*C*H), 125.8 (s, Ar-*C*H), 125.5 (s, Ar-*C*H), 123.4 (s, Ar-*C*H), 122.9 (s, Ar-*C*H), 86.6 (s, N*C*H), 71.4 (s, *C*$(CH_3)_2$), 30.6 (s, *C*H_3), 25.1 (s, *C*H_3') ppm.

IR (NaCl): $\tilde{\nu}$ = 3060m, 3029m, 2969s, 2932m, 2361w, 1651s, 1577w, 1502m, 1453m, 1424w, 1361m, 1319s, 1290s, 1262m, 1215m, 1211w, 1181m, 1062s, 1010m, 1001w, 972m, 943w, 927m, 856w, 777m, 742m, 731w, 695s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 301 (4), 146 (10), 145 (100), 104 (26).

Elemental analysis calc. (%) for $C_{21}H_{19}NO$: C 83.69, H 6.35, N 4.65; found: C 83.45, H 6.34, N 4.91.

R_f = 0.17 (SiO_2, hexanes/Et_2O 5:2).



2-(2-(Diphenylphosphoryl)phenyl)-5,5-dimethyl-4-phenyl-4,5-dihydrooxazole (20a)

A suspension of 5,5-dimethyl-2,4-diphenyl-4,5-dihydrooxazole (**10a**) (300 mg, 1.19 mmol, 1.00 eq.) and TMEDA (200 µl, 152 mg, 1.31 mmol, 1.10 eq.) in THF (6 mL) was cooled to −78 °C. To this, *sec*-BuLi (1.01 mL, 1.3 M in cyclohexane, 1.31 mmol, 1.10 eq.) was added dropwise over 20 min. The mixture was stirred at −78 °C for 60 min and then at 0 °C for 15 min. A solution of Ph_2PCl (271 µl, 342 mg, 1.55 mmol, 1.30 eq.) in THF (2 mL) was added and the reaction mixture was allowed to warm up to RT overnight. H_2O_2 (5 mL, 5 vol% in H_2O) was added, the mixture was stirred for 20 min and then diluted with EtOAc (20 mL). After phase separation the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with sat. aq. Na_2CO_3 (1 × 10 mL) and sat. aq. NaCl (1 × 10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, DCM/MeOH 20:1) gave the title compound **20a** as a yellow solid (346 mg, 64%).

$C_{29}H_{26}NO_2P$ (451.50 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.05 (dd, $^3J_{HH}$ = 7.6 Hz, J = 3.6 Hz, 1H, Ar-C*H*), 7.72-7.66 (m, 2H, Ar-C*H*), 7.64-7.59 (m, 3H, Ar-C*H*), 7.51-7.48 (m, 3H, Ar-C*H*), 7.44-7.40 (m, 3H, Ar-C*H*), 7.37-7.32 (m, 2H, Ar-C*H*), 7.23 (d, J_{HH} = 1.1 Hz, 1H, Ar-C*H*), 7.22 (d, $^4J_{HH}$ = 2.4 Hz, 2H Ar-C*H*), 7.04 (dd, $^3J_{HH}$ = 5.7 Hz, $^4J_{HH}$ = 3.5 Hz, 2H, Ar-C*H*), 4.70 (s, 1H, NC*H*), 1.32 (s, 3H, CH_3), 0.64 (s, 3H, CH_3') ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 162.0 (d, $^3J_{CP}$ = 3.3 Hz, N*C*O), 136.5 (s, CHPh-*C*), 134.9 (d, $^3J_{CP}$ = 10.7 Hz, C(P)C*C*H), 134.0 (d, $^1J_{CP}$ = 108.0 Hz, PPh-*C*), 133.5 (d, $^1J_{CP}$ = 107.0 Hz, PPh'-*C*), 132.8 (d, $^2J_{CP}$ = 16.6 Hz, PC*C*), 132.3 (d, $^1J_{CP}$ = 109.5 Hz, P*C*C), 132.1 (d, $^2J_{CP}$ = 9.8 Hz, PPh-C*C*H), 132.0 (d, $^4J_{CP}$ = 2.5 Hz, C(P)CHCH*C*H), 131.6 (d, $^4J_{CP}$ = 2.8 Hz, PPh-CCHCH*C*H), 131.5 (d, $^2J_{CP}$ = 9.8 Hz, PPh'-C*C*H), 131.4 (d, $^2J_{CP}$ = 8.8 Hz, CC(P)*C*H), 131.3 (d, $^4J_{CP}$ = 2.7 Hz, PPh'-CCHCH*C*H), 130.4 (d, $^3J_{CP}$ = 12.0 Hz, CC(P)CH*C*H), 128.5 (d, $^3J_{CP}$ = 4.5 Hz, PPh-CCH*C*H), 128.4 (d, $^3J_{CP}$ = 4.7 Hz, PPh'-CCH*C*H), 128.0 (s, CHPh-C*C*H), 127.6 (s, CHPh-CCHCH*C*H), 125.5 (s, CHPh-CCH*C*H), 90.7 (s, N*C*H), 70.6 (s, *C*(CH_3)$_2$), 28.4 (s, *C*H_3), 24.3 (s, *C*H_3') ppm.

^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ = 31.2 (s) ppm.

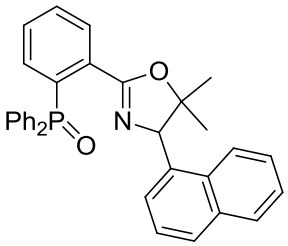
IR (NaCl): $\tilde{\nu}$ = 3420m, 3056m, 2967m, 2926m, 1734m, 1653s, 1568m, 1437s, 1363m, 1320m, 1257w, 1198s, 1118s, 1062m, 998m, 967m, 929w, 860w, 776w, 743s, 721s, 696s, 543s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 451 (2), 436 (10), 346 (24), 345 (100), 344 (83), 330 (10), 320 (19), 319 (19), 316 (21), 305 (13), 304 (18), 289 (27), 287 (29), 226 (11), 183 (15), 172 (11).

HPLC (Daicel Chiracel AD-H, Hept/*i*-PrOH = 75:25, 1.0 mL/min, 40 °C): t_R = 14.9 min, 17.7 min.

Semipreparative HPLC (Daicel Chiracel AD, hexane/*i*-PrOH = 80:20, 6 mL/min, 40 °C, 200 µL, 150 mg/mL): t_R = 22 min, 25 min.

R_f = 0.33 (SiO_2, DCM/MeOH 20:1).



2-(2-(Diphenylphosphoryl)phenyl)-5,5-dimethyl-4-(naphthalen-1-yl)-4,5-dihydrooxazole (20b)

A suspension of 5,5-dimethyl-4-(naphthalen-1-yl)-2-phenyl-4,5-dihydrooxazole (**10b**) (1.17 g, 3.81 mmol, 1.00 eq.) and TMEDA (630 µl, 493 mg, 4.25 mmol, 1.10 eq.) in THF (20 mL) was cooled to −78 °C. To this, *sec*-BuLi (3.30 mL, 1.3 M in cyclohexane, 4.25 mmol, 1.10 eq.) was added dropwise over 20 min. The mixture was stirred at −78 °C for 60 min and then at 0 °C for 20 min. A solution of Ph_2PCl (0.88 mL, 1.11 mg, 5.03 mmol, 1.30 eq.) in THF (6 mL) was added and the reaction mixture was allowed to warm to RT overnight. H_2O_2 (20 mL, 5 vol% in H_2O) was added, the mixture was stirred for 20 min and then diluted with EtOAc (80 mL). After phase separation the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with sat. aq. Na_2CO_3 (1 × 40 mL) and sat. aq. NaCl (1 × 40 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, DCM/MeOH 20:1) gave the title compound **20b** as a yellow solid (1.04 g, 54%).

$C_{33}H_{28}NO_2P$ (501.19 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.11 (ddd, *J* = 7.5 Hz, *J* = 3.7 Hz, *J* = 0.9 Hz, 1H, Ar-C*H*), 7.87-7.84 (m, 1H, Ar-C*H*), 7.75-7.29 (m, 19H, Ar-C*H*), 5.56 (s, 1H, NC*H*), 1.45 (s, 3H, CH_3), 0.60 (s, 3H, CH_3') ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 161.7 (d, $^{3}J_{CP}$ = 2.0 Hz, N*C*O), 135.0 (d, $^{3}J_{CP}$ = 10.5 Hz, C(P)C*C*H), 134.0 (d, $^{1}J_{CP}$ = 108.2 Hz, PPh-*C*), 133.5 (s, NCH*C*), 133.4 (d, $^{1}J_{CP}$ = 106.4 Hz, PPh'-*C*), 132.7 (s, Naph-*C*), 132.7 (s, Naph-*C*), 132.5 (d, $^{2}J_{CP}$ = 22.6 Hz, PC*C*), 132.1 (s, PPh-C*C*H), 132.0 (s, PPh'-C*C*H), 131.6 (s, PCCHCH*C*H), 131.6 (d, $^{4}J_{CP}$ = 3.0 Hz, PPh-CCHCH*C*H), 131.4 (d, $^{2}J_{CP}$ = 8.1 Hz, CC(P)*C*H), 131.3 (d, $^{4}J_{CP}$ = 2.9 Hz, PPh'-CCHCH*C*H), 131.2 (d, $^{1}J_{CP}$ = 112.5 Hz, P*C*C), 130.6 (d, $^{3}J_{CP}$ = 9.6 Hz, CC(P)CH*C*H), 129.0 (s, Naph-*C*H), 128.5 (d, $^{3}J_{CP}$ = 3.2 Hz, PPh-CCH*C*H), 128.4 (d, $^{3}J_{CP}$ = 3.4 Hz, PPh'-CCH*C*H), 128.0 (s, Naph-*C*H), 126.0 (s, Naph-*C*H), 125.5 (s, Naph-*C*H), 125.3 (s, Naph-*C*H), 123.9 (s, Naph-*C*H), 123.1 (s, Naph-*C*H), 87.4 (s, NCH), 71.3 (s, *C*(CH_3)$_2$), 29.0 (s, *C*H_3), 24.8 (s, *C*H_3') ppm.

^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ = 31.2 (s) ppm.

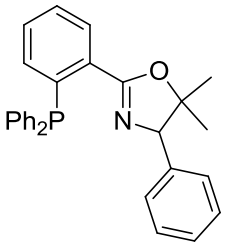
IR (NaCl): $\tilde{\nu}$ = 3420m, 3055m, 2969s, 2924s, 2851m, 1653s, 1560m, 1465m, 1437s, 1363m, 1340m, 1310s, 1257m, 1238w, 1197s, 1118s, 1105s, 1062m, 1047s, 977w, 956m, 930w, 865w, 797s, 780s, 745m, 731s, 721s, 695s, 660w, 645w, 577w, 545s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 501 (15), 487 (14), 486 (40), 346 (23), 345(100), 344 (99), 330 (13), 316 (28), 305 (25), 304 (25), 289 (32), 287 (35), 226 (12), 185 (12), 183 (18), 182 (13), 173 (14).

HPLC (Daicel Chiracel AD-H, Hept/*i*-PrOH = 80:20, 1.0 mL/min, 40 °C): t_R = 6.9 min, 10.7 min.

Semipreparative HPLC (Daicel Chiracel AD, hexane/*i*-PrOH = 80:20, 6 mL/min, 40 °C, 200 µL, 150 mg/mL): t_R = 25 min, 45 min.

R_f = 0.34 (SiO_2, DCM/MeOH 20:1).



2-(2-(Diphenylphosphino)phenyl)-5,5-dimethyl-4-phenyl-4,5-dihydrooxazole (9a)

2-(2-(Diphenylphosphoryl)phenyl)-5,5-dimethyl-4-phenyl-4,5-dihydro-oxazole (**9a**) (300 mg, 644 µmol, 1.00 eq.) was dissolved in phenylsilane (1 mL) and heated at 120 °C for 3 d. After cooling to RT MeOH (2 mL) was added and the mixture was stirred at 50 °C for 3 h. All volatiles were removed under high vacuum and the residue was purified by column chromatography (SiO_2, 3 × 20 cm, hexanes/EtOAc 10:1) to give the title compound **9a** as a white foam (200 mg, 69%).

$C_{29}H_{26}NOP$ (435.50 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.97 (ddd, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 3.9 Hz, J_{PH} = 1.3 Hz, 1H, Ar-C*H*), 7.40-7.27 (m, 15H, Ar-C*H*), 7.13-7.11 (m, 2H, Ar-C*H*), 6.88-6.85 (m, 1H, Ar-C*H*), 4.91 (s, 1H, NC*H*), 1.24 (s, 3H, CH_3), 0.55 (s, 3H, CH_3') ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 161.5 (d, $^{3}J_{CP}$ = 2.7 Hz, N*C*O), 138.9 (d, $^{2}J_{CP}$ = 25.7 Hz, NC*C*), 138.1 (d, $^{1}J_{CP}$ = 11.3 Hz, PPh-*C*), 138.0 (d, $^{1}J_{CP}$ = 11.3 Hz, PPh'-*C*), 137.2 (s, CHPh-*C*), 134.3 (d, $^{2}J_{CP}$ = 22.8 Hz, PPh-C*CH*), 134.1 (d, $^{2}J_{CP}$ = 22.6 Hz, PPh'-C*CH*), 133.6 (d, J_{CP} = 2.1 Hz, Ar-*C*H), 131.9 (d, $^{1}J_{CP}$ = 18.4 Hz, *C*(P)C), 130.5 (s, Ar-*C*H), 130.0 (d, J_{CP} = 2.8 Hz, Ar-*C*H), 128.6 (s, PPh-CCH*C*H), 128.6 (s, PPh'-CCH*C*H), 128.4 (d, J_{CP} = 7.4 Hz, Ar-*C*H), 128.1 (s, Ar-*C*H), 128.0 (s, Ar-*C*H), 127.6 (s, CHPh-CCHCH*C*H), 125.6 (s, CHPh-CCH*C*H), 89.9 (s, N*C*H), 70.9 (s, *C*(CH_3)$_2$), 29.2 (s, *C*H_3), 24.6 (s, *C*H_3') ppm.

^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ = –4.7 (s) ppm.

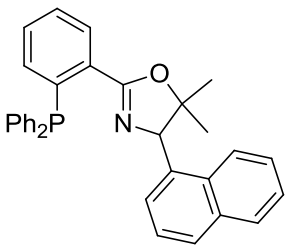
IR (NaCl): $\tilde{\nu}$ = 3049m, 3026m, 2980s, 2965s, 2923m, 2889m, 1950w, 1885w, 1734m, 1641s, 1603m, 1584m, 1559m, 1469m, 1476m, 1461m, 1452m, 1432s, 1379m, 1360m, 1321s, 1311s, 1296s, 1286s, 1251m, 1213m, 1183m, 1161m, 1124m, 1092s, 1069w, 1052s, 1032s, 1001s, 966s, 929m, 915m, 886w, 862m, 804w, 779m, 743s, 717w, 694s, 637w, 620w, 612w, 542w, 524m, 517s, 503s, 485s, 451w, 426m, 413m cm^{-1}.

MS (FAB, NBA): *m/z* (%) = 452 (13), 437 (12), 436 (36), 435 (3), 305 (27), 304 (100), 289 (11).

Elemental analysis calc. (%) for $C_{29}H_{26}NOP$: C 79.98, H 6.02, N 3.22; found: C 79.77, H 6.13, N 3.51.

m.p.: 122-127 °C.

R_f = 0.13 (SiO_2, hexanes/EtOAc 10:1).



2-(2-(Diphenylphosphino)phenyl)-5,5-dimethyl-4-(naphthalen-1-yl)-4,5-dihydrooxazole (9b)

2-(2-(Diphenylphosphoryl)phenyl)-5,5-dimethyl-4-(naphthalen-1-yl)-4,5-dihydrooxazole (**20b**) (300 mg, 590 µmol, 1.00 eq.) was dissolved in phenylsilane (1 mL) and heated at 120 °C for 3 d. After cooling to RT MeOH (2.5 mL) was added and the mixture was stirred at 50 °C for 3 h. The volatiles were removed under high vacuum and the residue was purified by column

chromatography (SiO_2, 3 × 20 cm, hexanes/EtOAc 10:1) to give the title compound **9b** as a white solid (135 mg, 47%).

$C_{33}H_{28}NOP$ (485.56 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.07 (m, 1H, Ar-C*H*), 7.88-7.86 (m, 1H, Ar-C*H*), 7.81-7.45 (m, 2H, Ar-C*H*), 7.50-7.48 (m, 2H, Ar-C*H*), 7.41-7.33 (m, 14H, Ar-C*H*), 6.91-6.88 (m, 1H, Ar-C*H*), 5.83 (s, 1H, NC*H*), 1.38 (s, 3H, CH_3), 0.55 (s, 3H, CH_3') ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 161.2 (d, $^3J_{CP}$ = 3.2 Hz, N*C*O), 139.1 (d, $^2J_{CP}$ = 26.1 Hz, PC*C*), 138.1 (d, $^1J_{CP}$ = 11.4 Hz, PPh-*C*), 138.1 (d, $^1J_{CP}$ = 12.1 Hz, PPh'-*C*), 134.3 (d, J_{CP} = 21.0 Hz, Ar-*C*H), 134.1 (d, J_{CP} = 21.0 Hz, Ar-*C*H), 133.7 (d, J_{CP} = 2.2 Hz, Ar-*C*H), 133.5 (s, Naph-*C*), 133.4 (s, Naph-*C*), 131.7 (d, $^1J_{CP}$ = 17.9 Hz, P*C*C), 130.7 (s, Naph-*C*), 130.5 (s, Ar-*C*H), 130.0 (s, Ar-*C*H), 129.0 (s, Ar-*C*H), 128.6 (s, Ar-*C*H), 128.5 (d, $^3J_{CP}$ = 7.5 Hz, Ar-*C*H), 128.5 (d, J_{CP} = 7.3 Hz, Ar-*C*H), 128.0 (s, Ar-*C*H), 127.9 (s, Ar-*C*H), 126.0 (s, Ar-*C*H), 125.4 (s, Ar-*C*H), 125.3 (s, Ar-*C*H), 123.5 (s, Ar-*C*H), 122.8 (s, Ar-*C*H), 86.3 (s, N*C*O), 71.7 (s, *C*(CH_3)$_2$), 29.7 (s, *C*H_3), 24.7 (s, *C*H_3') ppm.

^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ = –4.6 (s) ppm.

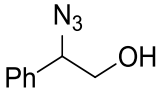
IR (NaCl): $\tilde{\nu}$ = 3050m, 2970m, 2927m, 1844w, 1772w, 1734m, 1700m, 1653s, 1560m, 1451m, 1433s, 1363m, 1330w, 1308s, 1257w, 1213m, 1131w, 1086s, 1047s, 989w, 958m, 930w, 862w, 795s, 777s, 741s, 696s, 668m, 645w, 503m cm^{-1}.

MS (FAB, NBA): *m/z* (%) = 502 (16), 487 (16), 486 (43), 485 (4), 305 (38), 304 (100), 289 (16), 183 (13), 182 (11), 181 (15), 167 (13), 165 (11).

Elemental analysis calc. (%) for $C_{33}H_{28}NOP$: C 81.63, H 5.81, N 2.88; found: C 83.45, H 6.34, N 4.91.

m.p.: 72-75 °C.

R_f = 0.16 (SiO_2, hexanes/EtOAc 10:1).



2-Azido-2-phenylethanol (31a)

To a solution of NaN_3 (2.76 g, 42.5 mmol, 5.00 eq.) in a mixture of H_2O (14 mL) and AcOH (7.8 mL), styrene oxide (**25a**) (1.02 mL, 8.50 mmol, 1.00 eq.) was added at 30 °C and the mixture was stirred at 30 °C for 20 min. After extraction with Et_2O (2 × 40 mL) the aqueous phase was saturated with NaCl and again extracted with Et_2O (1 × 40 mL). The combined organic layers were washed with aqueous NaOH (10%), dried

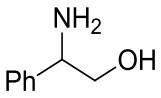
over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, hexanes/Et_2O = 1:1) gave the title compound **31a** as a colorless oil (910 mg, 65%). The analytical data match the literature values.[132]

$C_8H_9N_3O$ (163.18 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43-7.32 (m, 5H, Ar-C*H*), 4.70-4.66 (m, 1H, Alk-C*H*), 3.77-3.74 (m, 2H, Alk-C*H*, O*H*), 2.00-1.96 (m, 1H, Alk-C*H*) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 136.4 (s, Ar-*C*), 129.1 (s, Ar-*C*H), 128.9 (s, Ar-*C*H), 127.3 (s, Ar-*C*H), 68.0 (s, Ph*C*HCH$_2$), 66.7 (s, PhCH*C*H$_2$) ppm.

R_f = 0.41 (SiO_2, hexanes/Et_2O 1:1).



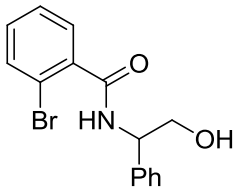
2-Amino-2-phenylethanol (30a)

A mixture of 2-Azido-2-phenylethanol (**31a**) (1.71 g, 10.5 mmol, 1.00 eq.), PPh_3 (5.50 g, 21.0 mmol, 2.00 eq.) and H_2O (2 mL) in THF (37 mL) was stirred at 50 °C for 11 h. After concentration under high vacuum aq. HCl (2 M, 15 mL) was added and the precipitate was filtered off. The filtrate was washed with EtOAc and the aqueous phase was basified by addition of aqueous NaOH (10%). The water phase was extracted with EtOAc (1 × 100 mL, 2 × 50 mL) and the combined organic layers were dried over $MgSO_4$. The crude was purified by filtration over SiO_2 eluting with EtOAc/MeOH (4:1) until all impurities were removed and then eluting with EtOAc/MeOH (1:1). The title compound **30a** was obtained as a slightly yellow solid (906 mg, 63%). The analytical data match the literature values.[133]

$C_8H_{11}NO$ (137.18 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.31-7.22 (m, 5H, Ar-C*H*), 4.14-4.06 (m, 4H, NH_2, O*H*, Alk-C*H*), 3.71 (dd, J_{HH} = 11.2 Hz, J_{HH} = 4.0 Hz, 1H, Alk-C*H*), 3.61 (dd, J_{HH} = 11.1 Hz, J_{HH} = 8.9 Hz, 1H, Alk-C*H*) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 140.8 (s, Ar-*C*), 128.9 (s, Ar-*C*H), 128.0 (s, Ar-*C*H), 127.0 (s, Ar-*C*H), 67.0 (s, Ph*C*HCH$_2$), 57.5 (s, Ph*C*HCH$_2$) ppm.



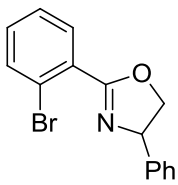
2-Bromo-*N*-(2-hydroxy-1-phenylethyl)benzamide (29a)

To a vigorously stirred solution of 2-amino-2-phenylethanol (**30a**) (500 mg, 3.65 mmol, 1.00 eq.) and Na_2CO_3 (1.17 g, 11.0 mmol, 3.00 eq.) in DCM (12 mL) and H_2O (9 mL), 2-bromobenzoyl chloride (0.55 mL, 920 mg, 4.20 mg, 1.15 eq.) was added dropwise over the course of two minutes and the mixture was stirred at room temperature for 22 h. After extraction with DCM (2 × 10 mL, 2 × 5 mL) a solution of KOH (2 N in MeOH, 2 mL) was added to the combined organic layers and the mixture was stirred at room temperature for 30 min. Afterwards aq. HCl (1 N) was added until a pH of 7 was reached (~1.5 mL). After addition of water (3 mL) and extraction with DCM (4 × 15 mL) the combined organic layers were washed with brine (1 × 20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was diluted with hot acetone (1 mL) and hexane was added. Upon storage at −25 °C the title compound precipitated as a colorless solid (947 mg, 81%). The analytical data match the literature values.[134]

$C_{15}H_{14}BrNO_2$ (163.18 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.61-7.57 (m, 2H, Ar-C*H*), 7.45-7.28 (m, 7H, Ar-C*H*), 6.77 (s br, 1H, N*H*), 5.29 (dd, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 4.7 Hz, 1H, NHC*H*CH_2OH), 4.01 (d, $^3J_{HH}$ = 4.7 Hz, 2H, NHCHC*H*$_2$OH), 2.43 (s br, 1H, O*H*) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 168.0 (s, *C*(O)NH), 138.7 (s, Ar-*C*), 137.6 (s, Ar-*C*), 133.7 (s, Ar-*C*H), 131.7 (s, Ar-*C*H), 130.1 (s, Ar-*C*H), 129.2 (s, Ar-*C*H), 128.3 (s, Ar-*C*H), 127.9 (s, Ar-*C*H), 127.1 (s, Ar-*C*H), 119.5 (s, Ar-*C*Br), 66.7 (s, NHCH*C*H_2OH), 56.8 (NH*C*HCH$_2$OH) ppm.



2-(2-Bromophenyl)-4-phenyl-4,5-dihydrooxazole (28a)

In a flame dried three-necked flask 2-bromo-*N*-(2-hydroxy-1-phenylethyl)benzamide (**29a**) (850 mg, 2.66 mmol, 1.00 eq.) was dissolved in DCM (14 mL) and NEt_3 (886 µL, 644 mg, 6.38 mmol, 2.40 eq.) was added. The solution was cooled to 4 °C and MsCl (238 µL, 352 mg, 3.06 mmol, 1.15 eq.) was added dropwise. The mixture was heated to 50 °C for 7 h. After cooling to room temperature sat. aq. $NaHCO_3$ (5 mL) was added and the mixture was stirred overnight. After phase separation the aqueous layer was extracted with DCM (2 × 5 mL) and the combined organic layers were washed with brine (1 × 6 mL), dried over $MgSO_4$ and the solvent was removed under reduced

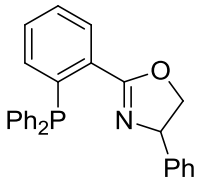
pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, hexanes/EtOAc = 3:1) gave the title compound **28a** as a colorless solid (720 mg, 90%). The analytical data match the literature values.[135]

$C_{15}H_{12}BrNO$ (163.18 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, $^3J_{HH}$ = 7.5 Hz, 1H, Ar-C*H*), 7.68 (d, $^3J_{HH}$ = 7.8 Hz, 1H, Ar-C*H*), 7.45-7.28 (m, 7H, Ar-C*H*), 5.48-5.43 (m, 1H, Alk-C*H*) 4.86-4.81 (m, 1H, Alk-C*H*), 4.32-4.28 (m, 1H, Alk-C*H*) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 164.4 (s, N*C*O), 142.2 (s, Ar-*C*), 134.0 (s, Ar-*C*H), 132.0 (s, Ar-*C*H), 131.7 (s, Ar-*C*H), 129.8 (s, Ar-*C*), 128.9 (s, Ar-*C*H), 127.8 (s, Ar-*C*H), 127.3 (s, Ar-*C*H), 126.9 (s, Ar-*C*H), 122.9 (s, Ar-*C*), 75.2 (s, NCH*C*H$_2$O), 70.6 (s, C*C*HCH$_2$) ppm.

$\boldsymbol{R_f}$ = 0.25 (SiO_2, hexanes/EtOAc 3:1).



2-(2-(Diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole (27a)

In a flame dried two-necked flask 2-(2-bromophenyl)-4-phenyl-4,5-dihydrooxazole (**28a**) (200 mg, 662 µmol, 1.00 eq.) was dissolved in Et_2O (9 mL) and cooled to −78 °C. To this solution *n*-BuLi (455 µL, 1.6 M in hexane, 728 µmol, 1.20 eq.) was added dropwise and the mixture was stirred for 30 min at −78 °C. Afterwards a solution of Ph_2PCl (175 mg, 794 µmol, 1.20 eq.) in Et_2O (1 mL) was added dropwise and the reaction mixture was stirred for 3 h at −78 °C and for further 18 h at room temperature. The solvent was removed under reduced pressure and the residue purified by column chromatography (SiO_2, 3 × 20 cm, hexanes/EtOAc 5:1) to give the title compound as a colorless solid (158 mg, 59%). The analytical data match the literature values.[33]

$C_{27}H_{22}NOP$ (107.44 g mol^{-1})

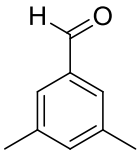
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 (ddd, J_{HH} = 7.5 Hz, J_{HH} = 3.5 Hz, J_{HH} = 1.3 Hz, 1H, Ar-C*H*), 7.39-7.29 (m, 12H, Ar-C*H*), 7.21-7.19 (m, 3H, Ar-C*H*), 6.94-6.90 (m, 3H, Ar-C*H*), 5.23 (t, $^3J_{HH}$ = 9.6 Hz, 1H, NCHC*H*H), 4.56 (dd, $^3J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 8.3 Hz, 1H, NC*H*CHH), 3.88 (t, $^3J_{HH}$ = 8.5 Hz, 1H, NCHCH*H*) ppm.

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ = 164.8 (d, $^3J_{CP}$ = 2.6 Hz, N*C*O), 142.2 (s, NCH*C*), 139.3 (d, $^2J_{CP}$ = 25.7 Hz, PC*C*), 138.2 (d, $^1J_{CP}$ = 12.4 Hz, PPh-*C*), 138.0 (d, $^1J_{CP}$ = 10.0 Hz,

PPh'-*C*), 134.5 (d, $^2J_{CP}$ = 21.1 Hz, PPh-C*C*H), 134.0 (d, $^2J_{CP}$ = 20.6 Hz, PPh'-C*C*H), 134.0 (d, J_{CP} = 1.4 Hz, Ar-*C*H), 131.6 (d, $^2J_{CP}$ =19.0 Hz, P*C*C), 130.9 (s, Ar-*C*H), 130.5 (d, J_{CP} = 3.0 Hz, Ar-*C*H), 128.9 (s, Ar-*C*H), 128.7(s, Ar-*C*H), 128.7 (s, Ar-*C*H), 128.6 (d, J_{CP} = 9.7 Hz, Ar-*C*H), 128.5 (s, $^2J_{CP}$ =19.0 Hz), 128.2 (s, Ar-*C*H), 127.3 (Ar-*C*H), 126.8 (s, Ar-*C*H), 74.6 (s, NCH*C*H$_2$), 70.2 (s, N*C*H), 21.4 (s, *C*H$_3$) ppm.

^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ = –4.8 (s) ppm.

$\boldsymbol{R_f}$ = 0.21 (SiO_2, hexanes/EtOAc = 5:1).



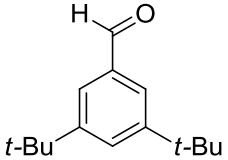
3,5-Dimethylbenzaldehyde (14d)

To a solution of 1-bromo-3,5-dimethylbenzene (**34a**) (2.03 mL, 2.76 g, 14.9 mmol, 1.00 eq.) in THF (50 mL), *n*-BuLi (11.2 mL, 1.6 M in hexane, 17.9 mmol, 1.20 eq.) was added at −78 °C over a period of 20 min and the reaction mixture was stirred for further 20 min until DMF (1.62 mL, 1.53 g, 20.9 mmol, 1.40 eq.) was added. After 1 h, water (20 mL) was added, the layers were separated and the aqueous layer was extracted with Et_2O (1 × 40 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by Kugelrohr-distillation (90 °C, 0.1 mbar) gave the title compound **14d** as a colorless oil (1.90 g, 95%). The analytical data match the literature values.[136]

$C_9H_{10}O$ (134.18 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.95 (s, 1H, C*H*O), 7.49 (s, 2H, C*H*C(CHO)C*H*), 7.27 (s, 1H, C(CH$_3$)C*H*C(CH$_3$)), 2.40 (s, 6H, C*H*$_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 193.0 (s, *C*HO), 138.9 (s, *C*CH$_3$), 136.7 (s, *C*CHO), 136.4 (s, C(CH$_3$)*C*HC(CH$_3$)), 127.2 (s, *C*HC(CHO)*C*H), 21.2 (s, *C*H$_3$) ppm.



3,5-Di-*tert*-butylbenzaldehyde (14e)

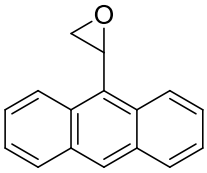
To a solution of 1-bromo-3,5-di-*tert*-butylbenzene (**34b**) (5.00 g, 18.6 mmol, 1.00 eq.) in THF (60 mL), *n*-BuLi (13.9 mL, 1.6 M in hexane, 22.3 mmol, 1.20 eq.) was added at −78 °C over the period of 20 min and the reaction mixture was stirred for further 20 min until DMF (2.01 mL, 1.90 g, 26.0 mmol, 1.40 eq.) was added. After 1 h, water (25 mL) was added, the layers were separated and the aqueous layer was extracted with Et_2O (1 × 40 mL). The combined organic layers were dried over $MgSO_4$ and

the solvent was removed under reduced pressure. Drying under high vacuum gave the title compound **14e** as a colorless solid (4.02 g, 99%). The product was pure according to NMR without further purification and the analytical data matched the literature values.[137]

$C_{15}H_{22}O$ (218.33 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.01 (s, 1H, C*H*O), 7.74-7.71 (m, 3H, Ar-C*H*), 1.37 (s, 18H, CH_3) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 193.3 (s, *C*HO), 152.0 (s, C*C*CH*C*C), 136.3 (s, *C*CHO), 129.0 (s, CC*C*HCC), 124.3 (*C*HCCHO), 35.1 (s, *C*$(CH_3)_3$), 31.5 (s, *C*H_3) ppm.

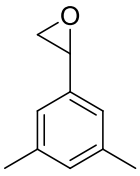


2-(Anthracen-9-yl)oxirane (25b)

A mixture of 9-anthraledhyde (**14c**) (3.00 g, 14.6 mmol, 1.00 eq.), trimethylsulfonium iodide (3.57 g, 17.5 mmol, 1.20 eq.), KOH (1.64 g, 29.2 mmol, 2.00 eq.) and water (66 µl, 66 mg, 3.65 mmol, 0.25 eq.) in MeCN (30 mL) was stirred at 60 °C for 4 h. After cooling to RT the suspension was diluted with DCM, filtered over celite and the solvent was removed under reduced pressure to give the crude product (3.30 g). ^{1}H-NMR analysis indicated 84% purity with additional 16% of the aldehyde. The crude product was used in the next step without further purification.

$C_{16}H_{12}O$ (220.27 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar-C*H*), 8.45 (s, 1H, Ar-C*H*), 8.02 (d, $^3J_{HH}$ = 8.3 Hz, 2H, Ar-C*H*), 7.57-7.53 (m, 2H, Ar-C*H*), 7.51-7.47 (m, 2H, Ar-C*H*), 4.72 (t, $^3J_{HH}$ = 3.3 Hz, 1H, OC*H*H), 3.59 (dd, $^3J_{HH}$ = 5.6 Hz, $^2J_{HH}$ = 4.1 Hz, 1H, OC*H*), 3.06 (dd, $^3J_{HH}$ = 5.6 Hz, $^2J_{HH}$ = 2.9 Hz, 1H, OCH*H*) ppm.

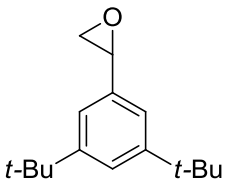


2-(3,5-Dimethylphenyl)oxirane (25c)

A suspension of 3,5-dimethylbenzaldehyde (**14d**) (1.50 g, 11.2 mmol, 1.00 eq.), trimethylsulfonium iodide (2.80 g, 13.4 mmol, 1.20 eq.), KOH (1.26 g, 22.4 mmol, 2.00 eq.) and water (50 µl, 50 mg, 2.80 mmol, 0.25 eq.) in MeCN (20 mL) was stirred at 60 °C for 4 h. After cooling to RT the suspension was diluted with DCM, filtered over celite and the solvent was removed under reduced pressure to give the crude product (1.18 g). ^{1}H-NMR analysis indicated 80% purity with additional 20% of the aldehyde. The crude product was used in the next step without further purification.

$C_{10}H_{12}O$ (148.20 g mol^{-1})

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.94 (s, 1H, C(CH_3)C*H*C(CH_3)), 6.90 (s, 2H, OCHCC*H*), 3.79 (dd, $^3J_{HH}$ = 4.0 Hz, $^2J_{HH}$ = 2.7 Hz, 1H, OC*H*H), 3.12 (dd, $^3J_{HH}$ = 5.5 Hz, $^3J_{HH}$ = 4.1 Hz, 1H, OC*H*), 2.79 (dd, $^3J_{HH}$ = 5.5 Hz, $^2J_{HH}$ = 2.6 Hz, 1H, OCH*H*), 2.31 (s, 6H, CH_3) ppm.

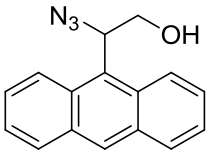


2-(3,5-Di-*tert*-butylphenyl)oxirane (25d)

A suspension of 3,5-di-*tert*-butylbenzaldehyde (**14e**) (3.00 g, 13.8 mmol, 1.00 eq.), trimethylsulfonium iodide (3.47 g, 16.6 mmol, 1.20 eq.), KOH (1.55 g, 27.6 mmol, 2.00 eq.) and water (62 µl, 62.1 mg, 3.45 mmol, 0.25 eq.) in MeCN (30 mL) was stirred at 60 °C for 4 h. After cooling to RT the suspension was diluted with DCM, filtered over celite and the solvent was removed under reduced pressure to give the crude product (3.18 g). ^{1}H-NMR analysis indicated 92% purity with additional 8% of the aldehyde. The crude product was used in the next step without further purification.

$C_{16}H_{24}O$ (232.36 g mol^{-1})

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.40 (t, $^4J_{HH}$ = 1.8 Hz, 1H, CCC*H*CC), 7.14 (d, $^4J_{HH}$ = 1.8 Hz, 2H, OCHCC*H*), 3.89 (dd, $^3J_{HH}$ = 4.0 Hz, $^2J_{HH}$ = 2.6 Hz, 1H, OC*H*HCH), 3.15 (dd, $^3J_{HH}$ = 5.5 Hz, $^3J_{HH}$ = 4.1 Hz, 1H, OCH_2C*H*), 2.84 (dd, $^3J_{HH}$ = 5.5 Hz, $^2J_{HH}$ = 2.6 Hz, 1H, OCH*H*CH), 1.34 (s, 18H, CH_3) ppm.



2-Azido-2-(anthracen-9-yl)ethanol (31b)

A solution of 2-(anthracen-9-yl)oxirane (**25b**) (3.21 g, 84%, 12.2 mmol, 1.00 eq.), sodium azide (3.97 g, 61.0 mmol, 5.00 eq.), water (20 mL), acetic acid (12 mL) and acetone (20 mL) was heated to 50 °C and stirred for 4 h. After cooling to RT acetone was removed under reduced pressure and the aqueous layer was extracted with Et_2O (2 × 40 mL), saturated with NaCl and again extracted with Et_2O (1 × 40 mL). The combined organic layers were washed with aq. NaOH (5%) (1 × 50 mL) dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 5 × 20 cm, hexanes/Et_2O 3:2) gave the title compound **31b** as a yellow solid (2.66 g, 83%).

$C_{16}H_{13}N_3O$ (263.29 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.54 (s br, 1H, Ar-C*H*), 8.50 (s, 1H, Ar-C*H*), 8.05 (d, J_{HH} = 8.3 Hz, 2H, Ar-C*H*), 7.59-7.55 (m, 2H, Ar-C*H*), 7.52-7.48 (m, 2H, Ar-C*H*), 6.33 (dd, J_{HH} = 9.4 Hz, J_{HH} = 4.8 Hz, 1H, Ar-C*H*), 4.46-4.40 (m, 1H, C*H*HOH), 3.96-3.90 (m, 1H, CH*H*OH), 2.26-2.24 (m, 1H, NC*H*) ppm.

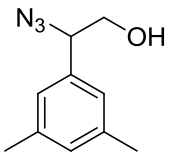
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 131.7 (s, Ar-*C*), 130.2 (s, Ar-*C*), 129.7 (s, Ar-C*H*), 126.8 (s, C*C*HC), 126.5 (s, Ar-*C*), 125.2 (s, Ar-*C*H), 65.1 (s, *C*H_2OH), 64.2 (s, N*C*H) ppm.

IR (NaCl): $\tilde{\nu}$ = 3337m br, 3049m, 2929w, 2845w, 2113s, 1623m, 1522m, 1445m, 1246s, 1159m, 1142w, 1049s, 995m, 954w, 921w, 882s, 839m, 785m, 741m, 732s, 640m, 601m, 546m, 462w, 418m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 263 (22), 205 (22), 204 (100), 203 (27), 179 (12), 178 (22), 177 (33), 176 (27).

Elemental analysis calc. (%) for $C_{16}H_{13}N_3O$: C 72.99, H 4.98, N 15.96; found: C 72.81, H 5.15, N 15.67.

R_f = 0.18 (SiO_2, hexanes/Et_2O 3:2).



2-Azido-2-(3,5-dimethylphenyl)ethanol (31c)

A solution of 2-(3,5-dimethylphenyl)oxirane (**25c**) (2.38 g, 80%, 13.5 mmol, 1.00 eq.), sodium azide (4.39 g, 67.5 mmol, 5.00 eq.), water (20 mL), acetic acid (12 mL) and acetone (20 mL) was heated to 50 °C and stirred for 5 h. After cooling to RT acetone was removed under reduced pressure and the aqueous layer was extracted with Et_2O (2 × 40 mL), saturated with NaCl and again extracted with Et_2O (1 × 40 mL). The combined organic layers were washed with aq. NaOH (5%) (1 × 50 mL) dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, hexanes/Et_2O 3:2) gave the title compound **31c** as a light yellow oil (1.38 g, 53%).

$C_{10}H_{13}N_3O$ (191.23 g mol^{-1})

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.99 (s, 1H, $(CH_3)CCHC(CH_3)$), 6.93 (s, 2H, $CH(N_3)CCH$), 4.60 (t, $^3J_{HH}$ = 6.5 Hz, 1H, N_3CH), 3.73 (t, $^3J_{HH}$ = 6.5 Hz, 2H, CH_2OH), 2.33 (s, 6H, CH_3) ppm.

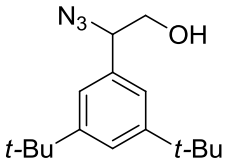
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 138.8 (s, $CH_3CCHCCH_3$), 136.2 (s, NCHC), 130.6 (s, $CH_3CCHCCH_3$), 125.1 (NCHCCH), 68.1 (s, NCH), 66.6 (s, CH_2OH), 21.5 (s, CH_3) ppm.

IR (NaCl): $\tilde{\nu}$ = 3365m br, 3016w, 2920m, 2872w, 2104s, 1609m, 1465m, 1379w, 1332m, 1253m, 1160w, 1041s, 954w, 849m, 702m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 191 (4), 160 (38), 133 (29), 132 (88), 106 (12), 105 (100), 103 (19), 91 (17), 79 (28), 77 (24).

Elemental analysis calc. (%) for $C_{10}H_{13}N_3O$: C 62.81, H 6.85, N 21.97; found: C 62.76, H 7.00, N 21.69.

R_f = 0.29 (SiO_2, hexanes/Et_2O 3:2).



2-Azido-2-(3,5-di-*tert*-butyl phenyl)ethanol (31d)

A solution of 2-(3,5-di-*tert*-butylphenyl)oxirane (**25d**) (1.63 g, 92%, 6.47 mmol, 1.00 eq.), sodium azide (2.10 g, 32.3 mmol, 5.00 eq.), water (10 mL), acetic acid (6 mL) and acetone (10 mL) was heated to 50 °C and stirred for 5 h. After cooling to RT acetone was removed under reduced pressure and the aqueous layer was extracted with Et_2O (2 × 20 mL), saturated with NaCl and again extracted with Et_2O (1 × 20 mL). The combined organic layers were washed with aq. NaOH (5%) (1 × 25 mL) dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, hexanes/EtOAc 3:1) yielded a slightly orange oil which solidified upon storage in the fridge overnight to give the title compound **31d** as a slightly orange solid (653 mg, 37%).

$C_{16}H_{25}N_3O$ (275.39 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.41 (t, $^3J_{HH}$ = 1.8 Hz, 1H, CCC*H*CC), 7.14 (d, $^3J_{HH}$ = 1.5 Hz, 2H, NCHCC*H*), 4.67 (t, $^3J_{HH}$ = 6.5 Hz, 1H, NC*H*), 3.76 (t, $^3J_{HH}$ = 6.5 Hz, 2H, CH_2OH), 2.03 (t, $^3J_{HH}$ = 6.5 Hz, 1H, CH_2OH), 1.33 (s, 18H, CH_3) ppm.

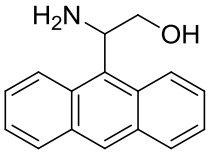
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 151.6 (s, *C*C(CH_3)$_3$), 135.5 (s, NCH*C*), 123.0 (s, CC*C*HCC), 121.3 (NCHC*C*H), 68.8 (s, N*C*H), 66.9 (s, *C*H_2OH), 35.1 (s, *C*(CH_3)$_3$), 31.6 (s, *C*H_3) ppm.

IR (NaCl): $\tilde{\nu}$ = 3316m br, 2964s, 2904m, 2867m, 2095s, 1740w, 1599m, 1476m, 1461m, 1394w, 1363s, 1330w, 1248s, 1201w, 1060m, 925w, 897w, 873m, 823w, 714m, 697w cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 275 (2), 244 (14), 217 (21), 216 (100), 202 (21), 189 (21), 147 (10), 133 (29), 57 (44), 41 (10).

Elemental analysis calc. (%) for $C_{16}H_{25}N_3O$: C 69.78, H 9.15, N 15.26; found: C 70.01, H 9.00, N 14.97.

R_f = 0.30 (SiO_2, hexanes/EtOAc 3:1, visualized with $KMnO_4$).



2-Amino-2-(anthracen-9-yl)ethanol (30b)

A solution of 2-azido-2-(anthracen-9-yl)ethanol (**31b**) (2.20 g, 8.37 mmol, 1.00 eq.) in EtOH (28 mL) was degassed by three freeze-pump-thaw cycles. Pd/C (888 mg, 5%, 419 µmol, 5 mol%) was added and H_2 was bubbled through this suspension for 20 min. Afterwards a balloon filled with H_2 was attached to the flask and the reaction mixture was stirred for 18 h at RT. After filtration over celite the solvent was removed under reduced pressure to give the title compound **30b** as an orange solid (1.58 g, 80%). The crude product was used in the next step without further purification.

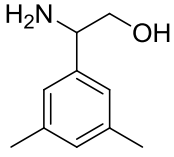
$C_{16}H_{15}NO$ (237.30 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, J_{HH} = 7.3 Hz, 2H, Ar-C*H*), 8.41 (s, 1H, Ar-C*H*), 8.02 (d, J_{HH} = 7.9 Hz, 2H, Ar-C*H*), 7.53-7.44 (m, 4H, Ar-C*H*), 5.60 (dd, $^3J_{HH}$ = 9.7 Hz, $^2J_{HH}$ = 5.3 Hz, 1H, C*H*HOH), 4.37 (t, $^3J_{HH}$ = 10.1 Hz, 1H, NC*H*), 3.92 (dd, $^3J_{HH}$ = 10.8 Hz, $^2J_{HH}$ = 5.3 Hz, 1H, CH*H*OH), 2.40 (s, 3H, NH_2 O*H*) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 133.7 (s, Ar-*C*), 131.9 (s, Ar-*C*), 129.8 (s, Ar-*C*), 129.7 (s, Ar-*C*H), 128.2 (s, Ar-*C*H), 125.9 (s, C*C*HC), 125.0 (s, Ar-*C*H), 66.2 (s, *C*H_2OH), 53.0 (s, N*C*H) ppm.

IR (KBr): $\tilde{\nu}$ = 3338s, 3300m, 3218m br, 3044s, 2879s, 2814s, 2713s, 1623s, 1521m, 1472m, 1445m, 1419w, 1341w, 1281w, 1155m, 1084m, 1049s, 1017m, 971m, 885s, 841m, 828m, 788m, 732s, 713m, 631m, 603m, 564w, 555m, 477w, 420w cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 237 (5), 207 (19), 206 (100), 204 (14), 179 (22), 178 (25).



2-Amino-2-(3,5-dimethylphenyl)ethanol (30c)

A solution of 2-azido-2-(3,5-dimethylphenyl)ethanol (**31c**) (1.35 g, 7.07 mmol, 1.00 eq.) in EtOH (24 mL) was degassed by three freeze-pump-thaw cycles. Pd/C (375 mg, 10%, 354 µmol, 5 mol%) was added and H_2 was bubbled through this suspension for 20 min. Afterwards a balloon filled with H_2 was attached to the flask and

the reaction mixture was stirred for 4 h at RT. After filtration over celite the solvent was removed under reduced pressure to give the title compound **30c** as a slightly yellow solid (1.12 g, 96%). The crude product was used in the next step without further purification.

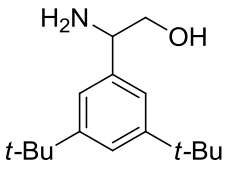
$C_{10}H_{15}NO$ (232.36 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.93 (s, 3H, Ar-C*H*), 3.96 (dd, $^3J_{HH}$ = 8.3 Hz, $^2J_{HH}$ = 4.3 Hz, 1H, C*H*HOH), 3.71 (dd, $^3J_{HH}$ = 10.8 Hz, $^2J_{HH}$ = 4.4 Hz, 1H, CH*H*OH), 3.54 (dd, $^3J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 8.4 Hz, 1H, NC*H*), 2.36 (s br, 3H, NH_2 O*H*), 2.32 (s, 6H, CH_3) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 142.7 (s, NCH*C*), 138.3 (s, *C*CH_3), 129.2 (s, CH_3C*C*HCCH_3), 124.4 (s, NCHC*C*H), 68.1 (s, *C*H_2OH), 57.4 (s, N*C*H), 21.4 (s, *C*H_3) ppm.

IR (NaCl): $\tilde{\nu}$ = 3330s, 3280s, 3181s br, 3008s, 2916s, 2859s, 2731m, 1718m, 1653m, 1606s, 1507w, 1448s, 1378m, 1358s, 1272w, 1166m, 1116m, 1065s, 981s, 943w, 896m, 882m, 845s, 786m, 709s, 675s, 575w, 548w, 535s, 507m, 466m, 433w cm^{-1}.

MS (FAB, NBA): *m/z* (%) = 167 (11), 166 (100), 164 (11), 150 (12), 149 (98), 148 (40), 147 (14), 145 (10), 134 (83), 133 (27), 132 (25), 131 (26), 119 (78), 117 (14), 115 (13), 105 (21), 91 (32), 89 (10), 81 (11), 79 (14), 77 (21), 69 (13), 57 (19), 55 (21), 43 (18), 41 (22), 39 (15).



2-Amino-2-(3,5-di-*tert*-phenyl)ethanol (30d)

A solution of 2-azido-2-(3,5-di-*tert*-butylphenyl)ethanol (**31d**) (500 mg, 1.82 mmol, 1.00 eq.) in EtOH (6 mL) was degassed by three freeze-pump-thaw cycles. Pd/C (96.5 mg, 10%, 91.0 µmol, 5 mol%) was added and H_2 was bubbled through this suspension for 20 min. Afterwards a balloon filled with H_2 was attached to the flask and the reaction mixture was stirred for 4 h at RT. After filtration over celite the solvent was removed under reduced pressure to give the title compound **30d** as an off-white solid (453 g, quant.). The crude product was used in the next step without further purification.

$C_{16}H_{27}NO$ (249.39 g mol^{-1})

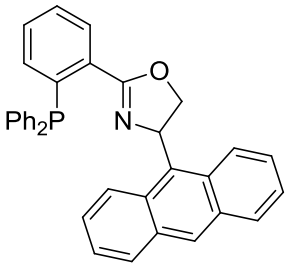
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 (t, $^4J_{HH}$ = 1.8 Hz, 1H, CCC*H*CC), 7.16 (d, $^4J_{HH}$ = 1.8 Hz, 2H, NCHCC*H*), 4.04 (dd, $^3J_{HH}$ = 8.6 Hz, $^2J_{HH}$ = 4.4 Hz, 1H, C*H*HOH), 3.75 (dd, $^3J_{HH}$ = 10.7 Hz, $^2J_{HH}$ = 4.2 Hz, 1H, CH*H*OH), 3.57 (dd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, NC*H*), 2.06 (s br, 3H, NH_2 O*H*), 1.33 (s, 18H, CH_3) ppm.

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ = 151.2 (s, *C*C(CH_3)$_3$), 142.1 (s, NCH*C*), 121.8 (s, CC*C*HCC), 120.7 (s, NCHC*C*H), 68.4 (s, *C*H_2OH), 58.1 (s, N*C*H), 35.1 (s, *C*(CH_3)$_3$), 31.6 (s, *C*H_3) ppm.

IR (NaCl): $\tilde{\nu}$ = 3352 m, 3286m, 3130m br, 3089m, 2962s, 2909m, 2867m, 2812m, 1603s, 1477m, 1465m, 1387w, 1364s, 1332w, 1270w, 1250m, 1197m, 1079s, 1040s, 964m, 925m, 899w, 878s, 860w, 814w, 719s, 668m, 548w cm^{-1}.

MS (FAB, NBA): *m/z* (%) = 251 (17), 250 (100), 218 (18), 177 (20), 57 (67).

Elemental analysis calc. (%) for $C_{16}H_{27}NO$: C 77.06, H 10.91, N 5.62; found: C 76.82, H 10.77, N 5.41.



4-(Anthracen-9-yl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (27b)

A solution of 2-amino-2-(anthracen-9-yl)ethanol (**30b**) (562 mg, 2.37 mmol, 1.20 eq.), 2-(diphenylphosphino)benzonitrile (565 mg, 1.97 mmol, 1.00 eq.) and $ZnCl_2$ (309 mg, 2.27 mmol, 1.15 eq.) in chlorobenzene (17 mL) was heated to reflux for 6 d. After cooling to RT the suspension was diluted with EtOAc and filtered over celite. After removal of the solvent, the residue was diluted with chloroform and upon addition of TBME the dichloro-zinc complex **33b** of the desired ligand precipitated as an orange solid which was filtered off (591 mg, 47%). 300 mg of this solid (466 µmol, 1.00 eq.) were dissolved in chloroform (5 mL) and 2,2'-bipyridine (72.7 mg, 466 µmol, 1.00 eq.) was added. The solution was stirred for 1.5 h at RT and then filtered over a plug of SiO_2. Removal of the solvent under reduced pressure gave the title compound **27b** as a brown solid (127 mg, 54%, 25% over 2 steps).

$C_{35}H_{26}NOP$ (507.56 g mol^{-1})

^1H-NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1H, Ar-C*H*), 8.24-8.21 (m, 2H, Ar-C*H*), 8.07-8.04 (m, 1H, Ar-C*H*), 8.01-7.99 (m, 2H, Ar-C*H*), 7.45-7.32 (m, 13H, Ar-C*H*), 7.26-7.23 (m, 3H, Ar-C*H*), 7.01 (ddd, J_{HH} = 7.3 Hz, J_{HH} = 4.3 Hz, J_{HH} = 0.9 Hz, 1H, Ar-C*H*), 6.50 (t, $^3J_{HH}$ = 11.0 Hz, 1H, NC*H*), 4.66 (dd, $^3J_{HH}$ = 11.4 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, NCHC*H*H), 4.52 (dd, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, NCHCH*H*) ppm.

$^{13}C\{^1H\}$-NMR (126 MHz, $CDCl_3$): δ = 165.0 (d, $^3J_{CP}$ = 1.7 Hz, N*C*O), 139.5 (d, J_{CP} = 25.4 Hz, Ar-*C*), 138.3 (d, J_{CP} = 11.9 Hz, Ar-*C*), 137.6 (d, J_{CP} = 10.3 Hz, Ar-*C*), 134.3 (d,

$^{2}J_{CP}$ = 21.0 Hz, PPh-C*C*H), 134.2 (d, $^{2}J_{CP}$ = 20.9 Hz, PPh'-C*C*H), 132.3 (s, Ar-*C*), 132.1 (s, Ar-*C*), 131.8 (s, Naph-*C*), 130.9 (s, Ar-*C*H), 130.6 (s, Naph-*C*), 130.4 (s, Ar-*C*H), 130.4 (s, Ar-*C*H), 129.6 (s, Ar-*C*H), 128.9 (s, Ar-*C*H), 128.7 (s, Ar-*C*H), 128.7 (s, Ar-*C*H), 128.5 (s, Ar-*C*H), 128.5 (s, Ar-*C*H), 128.4 (s, Ar-*C*H), 126.1 (s, Ar-*C*H), 124.8 (s, Ar-*C*H), 124.1 (s, Ar-*C*H), 72.9 (s, NCH*C*H$_2$), 66.1 (s, N*C*H) ppm.

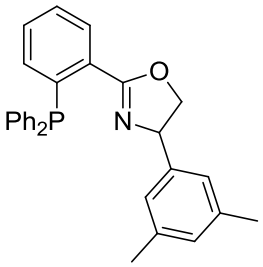
^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ = –4.8 (s) ppm.

IR (NaCl): $\tilde{\nu}$ = 3049m, 2954w, 1653s, 1647s, 1623m, 1560m, 1522m, 1433s, 1349m, 1307m, 1243w, 1182w, 1158w, 1092m, 1051w, 1032m, 963w, 929w, 888m, 839w, 788w, 742s, 731s, 696s, 629w, 544w, 502m, 420w cm^{-1}.

MS (ESI, 200 °C, MeOH/AcOH(5%)): *m/z* (%) = 508 (4, [M+H$^+$]), 546 (100, [M+K$^+$]).

Elemental analysis calc. (%) for $C_{35}H_{26}NOP$: C 82.82, H 5.16, N 2.76; found: C 82.64, H 5.31, N 2.52.

m.p.: 91-95 °C.



4-(3,5-Dimethylphenyl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (27c)

A solution of 2-amino-2-(3,5-dimethylphenyl)ethanol (**30c**) (500 mg, 3.03 mmol, 1.20 eq.), 2-(diphenylphosphino)benzonitrile (726 mg, 2.53 mmol, 1.00 eq.) and $ZnCl_2$ (396 mg, 2.91 mmol, 1.15 eq.) in chlorobenzene (22 mL) was heated to reflux for 6 d. After cooling to RT the suspension was diluted with EtOAc and filtered over celite. After removal of the solvent under reduced pressure, the residue was diluted with chloroform and upon addition of TBME the dichloro-zinc **33c** complex of the desired ligand precipitated as a light yellow solid which was filtered off (1.01 g, 70%). 500 mg of this solid (874 µmol, 1.00 eq.) were dissolved in chloroform (7 mL) and 2,2'-bipyridine (136 mg, 874 µmol, 1.00 eq.) was added. The solution was stirred for 1.5 h at RT and then filtered over a plug of SiO_2. Removal of the solvent under reduced pressure gave the title compound **27c** as a white solid (221 mg, 58%, 41% over 2 steps).

$C_{29}H_{26}NOP$ (435.00 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00 (ddd, J_{HH} = 7.4 Hz, J_{HH} = 3.6 Hz, J_{HH} = 1.5 Hz, 1H, Ar-C*H*), 7.38-7.30 (m, 12H, Ar-C*H*), 6.92 (ddd, J_{HH} = 7.7 Hz, J_{HH} = 4.3 Hz, J_{HH} = 1.3 Hz, 1H, Ar-C*H*), 6.85 (s, 1H, Ar-C*H*), 6.66 (s, 2H, Ar-C*H*), 5.13 (t, $^{3}J_{HH}$ = 9.8 Hz, 1H, NC*H*),

4.50 (dd, $^{3}J_{HH}$ = 10.1 Hz, $^{3}J_{HH}$ = 8.2 Hz, 1H, NCHC*H*H), 3.88 (dd, $^{3}J_{HH}$ = 9.4 Hz, $^{3}J_{HH}$ = 8.2 Hz, 1H, NCHCH*H*), 2.24 (s, 6H, CH_3) ppm.

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ = 164.8 (s, N*C*O), 141.9 (s, NCH*C*), 139.3 (d, $^{2}J_{CP}$ = 25.4 Hz, PC*C*), 138.3 (d, $^{1}J_{CP}$ = 11.9 Hz, PPh-*C*), 138.1 (s, CH_3*C*CH*C*CH_3), 137.9 (d, $^{1}J_{CP}$ = 10.4 Hz, PPh'-*C*), 134.3 (d, $^{2}J_{CP}$ = 21.2 Hz, PPh-C*C*H), 134.1 (d, $^{2}J_{CP}$ = 21.1 Hz, PPh'-C*C*H), 134.0 (s, CC(P)*C*H), 131.8 (d, $^{1}J_{CP}$ =19.4 Hz, P*C*C), 130.8 (s, Ar-*C*H), 130.5 (d, J_{CP} = 3.3 Hz, Ar-*C*H), 129.1 (s, Ar-*C*H), 128.8 (s, Ar-*C*H), 128.8 (s, Ar-*C*H), 128.6 (d, J_{CP} = 7.1 Hz, Ar-*C*H), 128.5 (d, J_{CP} = 7.4 Hz, Ar-*C*H), 128.2 (s, CH_3C*C*HCCH_3), 124.56 (s, NCHC*C*H), 74.6 (s, NCH*C*H_2), 70.2 (s, N*C*H), 21.4 (s, *C*H_3) ppm.

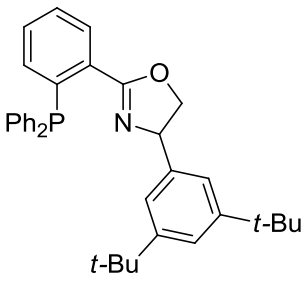
^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ = –4.9 (s) ppm.

IR (NaCl): $\tilde{\nu}$ = 3065w, 3049w, 3000w, 2979w, 2913w, 2892w, 2852w, 1646m, 1644m, 1633w, 1604m, 1583w, 1583w, 1474m, 1459m, 1455, 1432s, 1351m, 1331w, 1301m, 1253w, 1242w, 1199w, 1180w, 1133w, 1120w, 1089s, 1033s, 1027s, 998w, 960m, 940w, 901m, 880w, 847s, 775w, 742s, 719w, 693s cm^{-1}.

MS (FAB, NBA): *m/z* (%) = 453 (11), 452 (26), 437 (24), 436 (79), 435 (37), 305 (23), 304 (100), 303 (10), 302 (25), 289 (14), 288 (16), 183 (13), 119 (18).

Elemental analysis calc. (%) for $C_{29}H_{26}NOP$: C 79.98, H 6.02, N 3.22; found: C 80.21, H 6.24, N 3.13.

m.p.: 112-115 °C.



4-(3,5-Di-*tert*-butylphenyl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (27d)

A solution of 2-amino-2-(3,5-di-*tert*-butylphenyl)ethanol (**30d**) (300 mg, 1.20 mmol, 1.20 eq.), 2-(diphenylphosphino)-benzonitrile (287 mg, 1.00 mmol, 1.00 eq.) and $ZnCl_2$ (156 mg, 1.15 mmol, 1.15 eq.) in chlorobenzene (9 mL) was heated at reflux for 6 d. After cooling to RT the suspension was diluted with EtOAc and filtered over celite. After removal of the solvent under reduced pressure, the dichloro-zinc complex **33d** of the desired ligand was obtained as a yellow solid (650 g, 99%). 300 mg of this solid (457 µmol, 1.00 eq.) were dissolved in chloroform (4 mL) and 2,2'-bipyridine (71.3 mg, 457 µmol, 1.00 eq.) was added. The solution was stirred for 1.5 h at RT and then filtered over a plug of SiO_2. Removal of the solvent under

reduced pressure gave the title compound **27d** as a slightly yellow solid (178 mg, 75%, 74% over 2 steps).

$C_{35}H_{38}NOP$ (519.66 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96 (ddd, J_{HH} = 7.6 Hz, J_{HH} = 3.5 Hz, J_{HH} = 1.5 Hz, 1H, Ar-C*H*), 7.40-7.32 (m, 13H, Ar-C*H*), 7.13 (d, J_{HH} = 1.5 Hz, 2H, Ar-C*H*), 6.96 (ddd, J_{HH} = 7.4 Hz, J_{HH} = 4.0 Hz, J_{HH} = 0.9 Hz, 1H, Ar-C*H*), 5.15 (t, $^{3}J_{HH}$ = 9.8 Hz, 1H, NC*H*), 4.46 (dd, $^{3}J_{HH}$ = 10.1 Hz, $^{3}J_{HH}$ = 8.3 Hz, 1H, NCHC*H*H), 4.08 (7, $^{3}J_{HH}$ = 8.4 Hz, 1H, NCHCH*H*), 1.31 (s, 18H, CH_3) ppm.

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ = 164.9 (s, N*C*O), 151.0 (s, $(CH_3)_3$C*C*), 141.3 (s, PC*C*), 138.9 (d, $^{2}J_{CP}$ = 24.5 Hz, NCH*C*), 138.1 (d, $^{1}J_{CP}$ = 11.1 Hz, PPh-*C*), 138.0 (d, $^{1}J_{CP}$ = 11.9 Hz, PPh'-*C*), 134.2 (d, $^{2}J_{CP}$ = 13.0 Hz, PPh-C*C*H), 134.1 (d, $^{2}J_{CP}$ = 12.7 Hz, PPh'-C*C*H), 134.0 (s, CC(P)*C*H), 132.7 (d, $^{1}J_{CP}$ = 21.7 Hz, P*C*C), 130.7 (s, Ar-*C*H), 130.2 (d, J_{CP} = 3.5 Hz, Ar-*C*H), 128.7 (s, Ar-*C*H), 128.7 (s, Ar-*C*H), 128.6 (s, Ar-*C*H), 128.5 (s, Ar-*C*H), 128.3 (s, Ar-*C*H), 121.6 (s, $(CH_3)_3$CC*C*HCC$(CH_3)_3$), 121.2 (s, NCHC*C*H), 74.7 (s, NCH*C*H_2), 70.8 (s, N*C*H), 35.1 (s, *C*$(CH_3)_3$), 31.7 (s, *C*H_3) ppm.

^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ = –6.0 ppm.

IR (NaCl): $\tilde{\nu}$ = 3054w, 2963s, 2903m, 2866m, 1654s, 1648m, 1599m, 1560m, 1476s, 1456m, 1435m, 1362m, 132w, 1248m, 1201m, 1134w, 1090m, 1037m, 999w, 967w, 894w, 873m, 804w, 743s, 716m, 696s cm^{-1}.

MS (FAB, NBA): *m/z* (%) = 519 (15), 305 (15), 304 (69), 303 (23), 302 (100), 240 (20), 227 (21), 201 (29), 57 (11).

Elemental analysis calc. (%) for $C_{35}H_{38}NOP$: C 80.89, H 7.37, N 2.70; found: C 81.05, H 7.42, N 2.91.

m.p.: 133-136 °C.

HPLC of the corresponding phosphine oxide (Daicel Chiracel AD-H, Hept/*i*-PrOH = 90:10, 0.5 mL/min, 25 °C): t_R = 24.9 min, 32.0 min.

Semipreparative HPLC of the corresponding phosphine oxide (Daicel Chiracel AD, hexane/*i*-PrOH = 93:7, 6 mL/min, 25 °C, 100 µL, 200 mg/mL): t_R = 71 min, 86 min.

7.3.3 ESI-MS Screening of Racemic Catalyst Mixtures

General procedure 1: The precatalyst solution (50 µl, 2.5 mM), prepared from an equimolar mixture of $[Pd(C_3H_5)(MeCN)_2]OTf$ and the corresponding ligand, was mixed with 50 µl of a solution (125 mM) of a 3:1 mixture of quasienantiomers (*R*)-**8a** and (*S*)-**8b** (prepared according to a literature procedure[20]) and 50 µl of a solution (10 mM) of [Na([15]crown-5)][$CEt(CO_2Et)_2$][19]. After 30 s, an aliquot of 5 µl of the reaction mixture was taken, diluted with 1 mL of the corresponding solvent and analyzed by ESI-MS under mild desolvation conditions. The spectra were acquired in the centroid mode and the selectivity was calculated from the ratios of the peak heights of the signals corresponding to the major isotopomers of **36** and **37**.

7.4 New PHOX Containing Catalysts for the Iridium-Catalyzed Asymmetric Hydrogenation

7.4.1 Complexation

To a solution of $[Ir(COD)Cl]_2$ (0.5 eq.) in DCM (15 mM) in a Young-tube a solution of the respective ligand (1.0 eq.) in DCM (25 mM) was added dropwise. The Young-tube was sealed and the mixture stirred at 50 °C for 1 h. After cooling to room temperature $NaBAr_F$ (1.2 eq.) was added and the mixture stirred for 1 h at room temperature. The solvent was removed under reduced pressure. Elution of the side products on a SiO_2-column with TBME and then of the product with DCM afforded the desired complexes **39**.

7.4.2 Hydrogenations

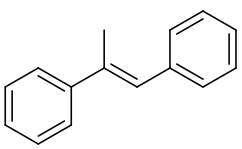
Hydrogenations at elevated pressure

The substrate (0.1 mmol) was dissolved in DCM (1 mL) in a glass vial with a stirring bar and the respective catalyst (1 μmol) was added. Up to four vials were placed in an autoclave (60 mL) which was closed, pressurized with H_2 (50 bar) and placed on a stirring plate for 2 h. After pressure release the solvent was removed under a stream of nitrogen. The residue was filtered over a short plug of SiO_2 eluting with EtOAc. After removal of the solvent under reduced pressure the residue was analyzed by GC and HPLC.

Hydrogenations at ambient pressure

The substrate (0.1 mmol) was dissolved in DCM (1 mL) in a glass vial with a stirring bar and the respective catalyst (1 μmol) was added. The vial was placed in a flask which was closed with a rubber septum. A H_2-filled balloon equipped with a needle was put on the septum, the flask was flushed with H_2 by pulling vacuum and placed on a stirring plate for 2 h.The solvent was removed under a stream of nitrogen and the residue was filtered over a short plug of SiO_2 eluting with EtOAc. After removal of the solvent under reduced pressure the residue was analyzed by GC and HPLC.

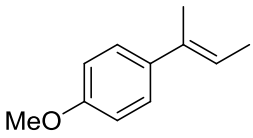
7.4.3 Analytical Data of the Hydrogenation Substrates



(*E*)-Prop-1-ene-1,2-diyldibenzene (40)

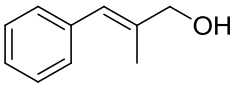
GC (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 µm), 60 kPa He, (100 °C, 2 min, 7 K/min, 250 °C, 10 min)): t_R = 18.2 min (**41**), 21.4 min (**40**).

HPLC (Daicel Chiracel OJ, Hept/*i*-PrOH = 99:1, 0.5 mL/min, 20 °C): t_R = 15.6 min ((*R*)-**41**), 23.8 min ((*S*)-**41**).



(*E*)-1-(But-2-en-2-yl)-4-methoxybenzene (42)

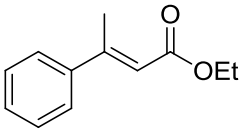
GC (*Chiraldex* γ-cyclodextrin TFA G-TA (30 m × 0.25 mm × 0.12 µm), 60 kPa H_2, (60 °C, 30 min, 5 K/min, 100 °C, 20 K/min, 160 °C, 10 min)): t_R = 38.4 min ((*S*)-**43**), 38.6 min ((*R*)-**43**), 41.2 min (**42**).



(*E*)-2-Methyl-3-phenylprop-2-en-1-ol (44)

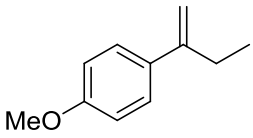
GC (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 µm), 60 kPa He, (100 °C, 2 min, 7 K/min, 250 °C, 10 min)): t_R = 14.6 min (**45**), 16.5 min (**44**).

HPLC (Daicel Chiracel OD-H, Hept/*i*-PrOH = 95:5, 0.5 mL/min, 40 °C): t_R = 15.3 min ((*R*)-**45**), 17.5 min ((*S*)-**45**).



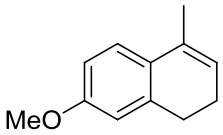
(*E*)-Ethyl 3-phenylbut-2-enoate (46)

GC (*Chiraldex* γ-cyclodextrin TFA G-TA (30 m × 0.25 mm × 0.12 µm), 60 kPa H_2, (85 °C, 50 min, 10 K/min, 160 °C)): t_R = 42.9 min ((*R*)-**47**), 44.9 min ((*S*)-**47**), 57.0 min (**46**).



1-(But-1-en-2-yl)-4-methoxybenzene (48)

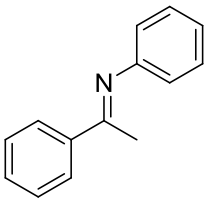
GC (*Chiraldex* γ-cyclodextrin TFA G-TA (30 m × 0.25 mm × 0.12 µm), 60 kPa H_2, (60 °C, 30 min, 5 K/min, 100 °C, 20 K/min, 160 °C, 10 min)): t_R = 38.4 min ((*S*)-**49**), 38.6 min ((*R*)-**49**), 40.3 min (**48**).



7-Methoxy-4-methyl-1,2-dihydronaphthalene (50)

GC (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm), 60 kPa He, (100 °C, 2 min, 7 K/min, 250 °C, 10 min)): t_R = 17.0 min (**51**), 19.7 min (**50**).

HPLC (Daicel Chiracel OD-H, Hept, 0.5 mL/min, 20 °C): t_R = 20.4 min ((*R*)-**51**), 27.0 min ((*S*)-**51**).



(*E*)-N-(1-Phenylethylidene)aniline (52)

GC (Macherey-Nagel Optima 5-Amin (30 m × 0.25 mm × 0.5 μm), 60 kPa He, (150 °C, 10 K/min, 250 °C, 10 min)): t_R = 12.8 min (**53**), 13.2 min (**52**).

HPLC (Daicel Chiracel OD-H, Hept/*i*-PrOH = 99:1, 0.5 mL/min, 20 °C): t_R = 24.6 min ((*S*)-**53**), 33.0 min ((*R*)-**53**).

7.5 Secondary Phosphinoxide Containing Ligands in the Palladium Catalyzed Allylic Substitution

7.5.1 Palladium Catalyzed Allylic Alkylation

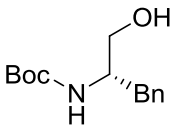
General procedure 2: A solution of $[Pd(C_3H_5)(MeCN)_2]OTf$ (2.37 mg, 6.25 μmol, 2 mol%) and the respective chiral ligand (2 mol%) in the corresponding solvent (2.5 mL, 2.5 mM) was degassed in a Young tube by three freeze-pump-thaw cycles and afterwards stirred at room temperature for 1 h. In a second Young tube (*E*)-di-arylallyl benzoate (**7**) (107 mg, 313 μmol, 2 mol%) was dissolved in the corresponding solvent (1.7 mL, 0.2 M). To this solution BSA (191 mg, 939 μmol, 3.00 eq.), pentane-2,4-dione (93.9 mg, 939 μmol, 3.00 eq.) and catalytic amounts of KOAc were added. After three freeze-pump-thaw cycles the catalyst solution was added via syringe and the resulting mixture was stirred at the given temperature for the given time. Then the reaction was diluted with Et_2O and washed with ice-cold sat. aq. NH_4Cl-solution. The aqueous phase was extracted with Et_2O twice, the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by column chromatography (SiO_2, 3 × 20 cm, hexanes/EtOAc/NEt_3 = 18:1:1) and the enantiomeric excess was determined by HPLC on a chiral stationary phase. The analytical data match the literature values.[20]

7.5.2 Determination of Complexation Pattern by ESI-MS

An equimolar mixture of $[Pd(C_3H_5)(MeCN)_2]OTf$ and the respective chiral ligand was dissolved in DCM (0.5 mM) and the solution was stirred at room temperature for 1 h. Then an aliquot of 5 μl of the mixture was taken, diluted with 1 mL of DCM and analyzed by ESI-MS under mild desolvation conditions. The spectra were acquired in the centroid mode.

7.6 Organo-Catalyzed Transfer-Hydrogenation of α,β-Unsaturated Carbonyl Compounds

7.6.1 Catalyst Synthesis



(*S*)-*tert*-Butyl (1-hydroxy-3-phenylpropan-2-yl)carbamate (71a)

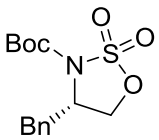
To a solution of phenyl alaninol (**70a**) (6.04 g, 40.0 mmol, 1.00 eq.) and triethyl amine (5.56 mL, 40.0 mmol, 1.00 eq.) in THF (120 mL), Boc-anhydride (8.72 g, 40 mmol, 1.00 eq) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1.5 h. Afterwards the solvent was removed under high vacuum and the residue dissolved in EtOAc (100 mL). The organic phase was washed with water (2 × 100 mL) and brine (1 × 100 mL). After drying over $MgSO_4$ the solvent was removed under reduced pressure to yield the desired Boc-protected aminoalcohol **71a** as a colorless solid (9.55 g, 96%). The analytical data match the literature values.[138]

$C_{14}H_{21}NO_3$ (251.32 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.31-7.26 (m, 2H, Ar-C*H*), 7.23-7.20 (m, 3H, Ar-C*H*), 4.83 (s br, 1H, N*H*), 3.90-3.80 (m, 1H, NHC*H*Bn), 3.67-3.62 (m, 1H, C*H*HOH), 3.56-3.51 (m, 1H, CH*H*OH), 2.84 (d, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2Ph), 2.64 (s br, 1H, O*H*), 1.41 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 156.3 (s, NH*C*(O)O), 138.0 (s, Ar-*C*), 129.4 (s, Ar-*C*H), 128.7 (s, Ar-*C*H), 126.6 (Ar-*C*H), 79.8 (s, *C*(CH$_3$)$_3$), 64.4 (s, *C*H$_2$OH), 53.8 (s, NH*C*HBn), 37.6 (s, CH*C*H$_2$Ph), 28.5 (s, C(*C*H$_3$)$_3$) ppm.

MS (ESI, 200 °C, DCM): *m/z* = 286 [M+Cl$^-$].



(*S*)-*tert*-Butyl-4-benzyl-1,2,3-oxathiazolidine-3-carboxylate-2,2-dioxide (72a)

To a solution of imidazole (2.17 g, 31.0 mmol, 4.00 eq.) in DCM (80 mL) triethyl amine (2.44 mL, 17.5 mmol, 2.20 eq.) and (*S*)-*tert*-butyl (1-hydroxy-3-phenylpropan-2-yl)carbamate (**71a**) (2.00 g, 7.97 mmol, 1.00 eq.) were added. The solution was cooled to 0 °C and $SOCl_2$ (638 µL, 8.77 mmol, 1.10 eq.) was added drop wise. The reaction mixture was warmed to room temperature and stirred overnight. To the resulting greenish solution water was added (50 mL), the layers were separated, the aqueous layer was extracted with DCM (2 × 20 mL) and the combined organic layers were washed with brine (1 × 50 mL). The

organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield a greenish oil.

$NaIO_4$ (6.31 g, 29.5 mmol, 3.70 eq.) was dissolved in water (40 mL). To this solution $RuO_2 \cdot H_2O$ (60.2 mg, 399 µmol, 5 mol%) was added and the mixture was stirred for 5 min at room temperature. The resulting yellow solution was cooled to 0 °C and a solution of the residue from the first step in EtOAc (30 mL) was added. After stirring at 0 °C for 1 h, the layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). and dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 5 × 20 cm, cyclohexane/EtOAc = 2:1) afforded an off-white solid, which was further purified by recrystallization from Et_2O to give the desired compound **72a** as a colorless solid (671 mg, 27%). The title compound is as well commercial available from Strem (MFCD17018793).

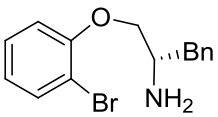
$C_{14}H_{19}NO_5S$ (313.37 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37-7.33 (m, 2H, Ar-C*H*), 7.31-7.28 (m, 1H, Ar-C*H*), 7.24-7.22 (m, 2H, Ar-C*H*), 4.48-4.41 (m, 2H, SOCH_2), 4.34-4.30 (m, 1H, NC*H*Bn), 3.37 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 4.1 Hz, 1H, C*H*HPh), 2.93 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 10.1 Hz, 1H, C*H*HPh), 1.56 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 148.6 (s, N*C*(O)O), 135.3 (s, Ar-), 129.6 (s, Ar-*C*H), 129.2 (s, Ar-*C*H), 127.7 (Ar-*C*H), 85.8 (s, *C*(CH$_3$)$_3$), 68.9 (s, CH*C*H$_2$O), 58.7 (s, Bn*C*HCH$_2$O), 38.0 (s, CH*C*H$_2$Ph), 28.1 (s, C(*C*H$_3$)$_3$) ppm.

MS (ESI, 200 °C, DCM): *m/z* = 348 [M+Cl$^-$].

R$_f$ = 0.61 (SiO_2, cyclohexane/EtOAc = 2:1).



(*S*)-1-(2-Bromophenoxy)-3-phenylpropan-2-amine (73a)

In a flame-dried 2-neck flask 2-bromo phenol (178 µL, 1.54 mmol, 1.20 eq.) was dissolved in DMF (12 mL). To this solution sodium hydride (60%, 61.7 mg, 1.54 mmol, 1.20 eq.) was added and the mixture was stirred at room temperature for 10 min. Then, (*S*)-*tert*-butyl-4-benzyl-1,2,3-oxathiazolidine-3-carboxylate-2,2-dioxide (**72a**) (400 mg, 1.28 mmol, 1.00 eq.) was added and the reaction mixture was stirred at room temperature for 2 days before the solvent was removed under high vacuum. The residue was dissolved in dioxane (8 mL) and conc. sulfuric acid (152 µL) and water (152 µL) were added. After

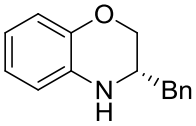
30 min further conc. sulfuric acid (840 µL) was added and the mixture was again stirred for 30 min. After neutralization with sat. aq. $NaHCO_3$-solution the aqueous layer was extracted with DCM (3 × 30 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, cyclohexane/EtOAc = 2:1 → EtOAc pure) gave the desired compound **73a** as a colorless oil (352 mg, 90%). The analytical data match the literature values.[139]

$C_{15}H_{16}BrNO$ (306.20 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.54 (dd, $^3J_{HH}$ = 8.3 Hz, J_{HH} = 1.7 Hz, 1H, Ar-C*H*), 7.33-7.29 (m, 2H, Ar-C*H*), 7.25-7.21 (m, 4H, Ar-C*H*), 6.85-6.81 (m, 2H, Ar-C*H*), 3.98 (dd, $^2J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 4.1 Hz, 1H, OC*H*HCHN), 3.84 (dd, $^2J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.5 Hz, 1H, OCH*H*CHN), 3.52-3.46 (m, 1H, OCH_2CHN), 2.97 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, C*H*HPh), 2.76 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 7.9 Hz, 1H, CH*H*Ph), 1.54 (s br, 2H, NH_2) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 155.2 (s, Ar-*C*), 138.6 (s, Ar-*C*), 133.4 (s, Ar-*C*H), 129.4 (s, Ar-*C*H), 128.7 (s, Ar-*C*H), 128.6 (s, Ar-*C*H), 126.6 (s, Ar-*C*H), 122.2 (s, Ar-*C*H), 113.5 (s, Ar-*C*H), 112.5 (s, Ar-*C*), 73.3 (s, OCH_2CHN), 52.3 (s, OCH_2CHN), 40.8 (s, CH_2Ph) ppm.

R_f = 0.17 (SiO_2, EtOAc).



(*S*)-3-Benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (63a)

In a flame-dried Young-tube a mixture of (*S*)-1-(2-bromophenoxy)-3-phenylpropan-2-amine (**73a**) (170 mg, 478 µmol, 1.00 eq.), $Pd(OAc)_2$ (6.50 mg, 28.7 µmol, 6 mol%), Xantphos (16.6 mg, 28.7 µmol, 6 mol%) and *tert*-BuONa (57.5 mg, 598 µmol, 1.25 eq.) in toluene (5 mL) was stirred at 100 °C overnight. After cooling to room temperature the mixture was diluted with EtOAc (40 mL), washed with water (1 × 40 mL) and brine (1 × 40 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, cyclohexane/EtOAc = 3:1 + 5% NEt_3) gave the desired compound **63a** as a yellow solid (90.0 mg, 69%). The analytical data match the literature values.[140]

$C_{15}H_{15}NO$ (225.29 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, $^3J_{HH}$ = 7.9 Hz, 1H, Ar-C*H*), 7.49 (d, $^3J_{HH}$ = 8.3 Hz, 1H, Ar-C*H*), 7.40-7.35 (m, 3H, Ar-C*H*), 7.33-7.22 (m, 5H, Ar-C*H*), 7.08 (d, $^3J_{HH}$ = 8.8 Hz,

1H, Ar-C*H*), 4.35 (dd, $^{2}J_{HH}$ = 10.5 Hz, $^{3}J_{HH}$ = 2.5 Hz, 1H, OC*H*HCHN), 4.07 (dd br, $^{2}J_{HH}$ = 10.3 Hz, $^{3}J_{HH}$ = 6.6 Hz, 2H, OCH*H*CHN, N*H*), 3.79-3.72 (m, 1H, OCH_2CHN), 2.95 (dd, $^{2}J_{HH}$ = 13.3 Hz, $^{3}J_{HH}$ = 5.6 Hz, 1H, C*H*HPh), 2.86 (dd, $^{2}J_{HH}$ = 13.3 Hz, $^{3}J_{HH}$ = 8.7 Hz, 1H, CH*H*Ph) ppm.

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ = 139.9 (s, Ar-*C*), 137.6 (s, Ar-*C*), 129.8 (s, Ar-*C*), 129.4 (s, Ar-*C*H), 129.0 (s, Ar-*C*H), 128.7 (s, Ar-*C*H), 127.0 (s, Ar-*C*H), 125.4 (s, Ar-*C*H), 125.2 (s, Ar-*C*), 124.4 (s, Ar-*C*), 123.7 (s, Ar-*C*H), 119.2 (s, Ar-*C*H), 118.8 (s, Ar-*C*H), 118.6 (s, Ar-*C*H), 68.9 (s, OCH_2CHN), 51.3 (s, OCH_2CHN), 38.8 (s, CH_2Ph) ppm.

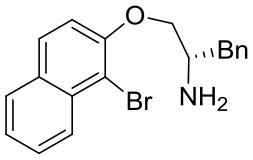
IR (neat): $\tilde{\nu}$ = 3395m, 3035w, 2988w, 2919w, 2863w, 1607m, 1534m, 1500m, 1487m, 1455m, 1433w, 1372w, 1356m, 1313m, 1284s, 1253w, 1203m, 1183w, 1136w, 1079w, 1039m, 1017m, 922w, 879w, 850w, 757s, 739s, 705s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 225 (18), 134 (100), 106 (12).

m.p.: 62-67 °C.

Optical rotation: $[\alpha]_D^{20}$ = –75 (*c* = 0.255, $CHCl_3$).

R_f = 0.46 (SiO_2, cyclohexane/EtOAc = 3:1 + 5% NEt_3).



(*S*)-1-((1-Bromonaphthalen-2-yl)oxy)-3-phenylpropan-2-amine (74a)

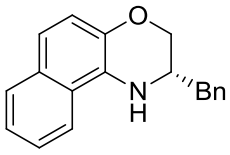
In a flame-dried 2-neck flask 1-bromonaphthalen-2-ol (171 mg, 767 µmol, 1.20 eq.) was dissolved in DMF (6 mL). To this solution sodium hydride (60%, 31.0 mg, 767 µmol, 1.20 eq.) was added and the mixture was stirred at room temperature for 10 min. Then, (*S*)-*tert*-butyl 4-benzyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (**72a**) (200 mg, 639 µmol, 1.00 eq.) was added and the reaction mixture was stirred at room temperature for 2 days before the solvent was removed under high vacuum. The residue was dissolved in dioxane (4 mL) and conc. sulfuric acid (76 µL) and water (76 µL) were added. After 30 min further conc. sulfuric acid (420 µL) was added and the mixture was again stirred for 30 min. After neutralization with sat. aq. $NaHCO_3$-solution the aqueous layer was extracted with DCM (3 × 15 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, EtOAc) gave the desired compound **74a** as a slightly orange oil (187 mg, 82%).

$C_{19}H_{18}BrNO$ (356.26 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, $^3J_{HH}$ = 8.6 Hz, 1H, Ar-C*H*), 7.78 (d, $^3J_{HH}$ = 8.7 Hz, 2H, Ar-C*H*), 7.57 (td, $^3J_{HH}$ = 6.9 Hz, J_{HH} = 0.9 Hz, 1H, Ar-C*H*), 7.40 (td, $^3J_{HH}$ = 7.0 Hz, J_{HH} = 1.0 Hz, 1H, Ar-C*H*), 7.33-7.19 (m, 6H, Ar-C*H*), 4.16-4.13 (m, 1H, OC*H*HCHN), 3.99 (dd, $^2J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 6.5 Hz, 1H, OCH*H*CHN), 3.56-3.50 (m, 1H, OCH_2C*H*N), 3.02 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 5.9 Hz, 1H, C*H*HPh), 2.80 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 7.9 Hz, 1H, CH*H*Ph), 1.62 (s br, 2H, NH_2) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 153.2 (s, Ar-*C*), 138.6 (s, Ar-*C*), 133.3 (s, Ar-*C*), 130.1 (s, Ar-*C*), 129.5 (s, Ar-*C*H), 139.1 (s, Ar-*C*H), 128.7 (s, Ar-*C*H), 128.2 (s, Ar-*C*H), 127.9 (s, Ar-*C*H), 126.6 (s, Ar-*C*H), 126.3 (s, Ar-*C*H), 124.6 (s, Ar-*C*H), 109.7 (s, Ar-*C*), 74.4 (s, O*C*H_2CHN), 52.6 (s, OCH_2*C*HN), 40.8 (s, *C*H_2Ph) ppm.

R_f = 0.15 (SiO_2, EtOAc).



(*S*)-2-Benzyl-2,3-dihydro-1*H*-naphtho[2,1-*b*][1,4]oxazine (75a)

In a flame-dried Young-tube a mixture of (*S*)-1-((1-bromonaphthalen-2-yl)oxy)-3-phenylpropan-2-amine (**74a**) (300 mg, 980 µmol, 1.00 eq.), $Pd(OAc)_2$ (13.2 mg, 58.8 µmol, 6 mol%), Xantphos (34.0 mg, 58.8 µmol, 6 mol%) and *tert*-BuONa (118 mg, 1.23 mmol, 1.25 eq.) in toluene (10 mL) was stirred at 100 °C overnight. After cooling to room temperature the mixture was diluted with EtOAc (80 mL), washed with water (1 × 80 mL) and brine (1 × 80 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, cyclohexane/EtOAc = 3:1 + 5% NEt_3) gave the desired compound **75a** as a slightly orange solid (196 mg, 89%).

$C_{19}H_{17}NO$ (275.34 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37-7.33 (m, 2H, Ar-C*H*), 7.29-7.27 (m, 1H, Ar-C*H*), 7.25-7.22 (m, 2H, Ar-C*H*), 6.79 (d, $^3J_{HH}$ = 7.9 Hz, 1H, Ar-C*H*), 6.76-6.72 (m, 1H, Ar-C*H*), 6.67-6.63 (m, 1H, Ar-C*H*), 6.52-6.50 (m, 1H, Ar-C*H*), 4.25 (dd, $^2J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 2.6 Hz, 1H, OC*H*HCHN), 3.97 (dd, $^2J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, OCH*H*CHN), 3.68 (s br, 1H, N*H*), 3.65-3.59 (m, 1H, OCH_2C*H*N), 2.86 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 5.3 Hz, 1H, C*H*HPh), 2.70 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 9.0 Hz, 1H, CH*H*Ph) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 144.0 (s, Ar-*C*), 137.4 (s, Ar-*C*), 133.2 (s, Ar-*C*), 129.4 (s, Ar-*C*H), 129.0 (s, Ar-*C*H), 127.0 (s, Ar-*C*H), 121.6 (s, Ar-*C*H), 118.9 (s, Ar-*C*H),

116.6 (s, Ar-*C*H), 115.6 (s, Ar-*C*H), 69.2 (s, O*C*H$_2$CHN), 50.9 (s, OCH$_2$*C*HN), 38.7 (s, *C*H$_2$Ph) ppm.

IR (neat): $\tilde{\nu}$ = 3392w, 3030w, 2953w, 2879w, 1580m, 1474m 1398m, 1254m, 1019m, 798s, 744s, 703m cm^{-1}.

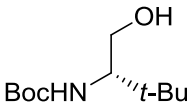
MS (EI, 70 eV): *m/z* (%) =275 (35), 185 (13), 184 (100), 115 (10).

Elemental analysis calc. (%) for $C_{19}H_{17}NO$: C 82.88, H 6.22, N 5.09; found: C 82.74, H 6.17, N 5.01.

m.p.: 126-130 °C.

Optical rotation: $[\alpha]_D^{20}$ = –84.9 (*c* = 0.425, $CHCl_3$).

R$_f$ = 0.64 (SiO_2, cyclohexane/EtOAc = 3:1 + 5% NEt_3).



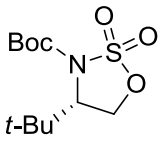
(*S*)-*tert*-Butyl-(1-hydroxy-3,3-dimethylbutan-2-yl)carbamate (71b)

To a solution of *tert*-leucinol (**70b**) (5.00 g, 42.7 mmol, 1.00 eq.) and triethyl amine (6.00 mL, 42.7 mmol, 1.00 eq.) in THF (140 mL), Boc-anhydride (9.31 g, 42.7 mmol, 1.00 eq) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1.5 h. Afterwards the solvent was removed under high vacuum and the residue was dissolved in EtOAc (100 mL). The organic phase was washed with water (2 × 100 mL) and brine (1 × 100 mL). After drying over $MgSO_4$ the solvent was removed under reduced pressure to yield the desired Boc-protected aminoalcohol **71b** as a colorless solid (8.79 g, 95%). The analytical data match the literature values.[141]

$C_{11}H_{23}NO_3$ (217.31 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.69 (s br, 1H, N*H*), 3.86-3.79 (m, 1H, NHC*H*Bn), 3.50-3.44 (m, 2H, C*H*$_2$OH), 2.46 (s br, 1H, O*H*), 1.44 (s, 9H, NHC(C*H*$_3$)$_3$), 0.92 (s, 9H, CHC(C*H*$_3$)$_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 157.3 (s, NH*C*(O)O), 79.7 (s, *C*(CH$_3$)$_3$), 63.2 (s, *C*H$_2$OH), 61.1 (s, NH*C*HC(CH$_3$)$_3$), 33.8 (s, *C*(CH$_3$)$_3$), 28.5 (s, C(*C*H$_3$)$_3$), 26.9 (s, C(*C*H$_3$)$_3$) ppm.



(*S*)-*tert*-Butyl 4-(*tert*-butyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (72b)

To a solution of imidazole (6.27 g, 92.0 mmol, 4.00 eq.) in DCM (230 mL) triethyl amine (7.04 mL, 50.6 mmol, 2.20 eq.) and (*S*)-*tert*-butyl-(1-hydroxy-3,3-dimethylbutan-2-yl)carbamate (**71b**) (4.99 g, 23.0 mmol, 1.00 eq.) were added. The solution was cooled to 0 °C and $SOCl_2$ (1.84 mL, 25.3 mmol, 1.10 eq.) was added drop wise. The reaction mixture was warmed to room temperature and stirred overnight. To the resulting greenish solution water was added (100 mL), the layers were separated, the aqueous layer was extracted with DCM (2 × 50 mL) and the combined organic layers were washed with brine (1 × 50 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield a greenish oil.

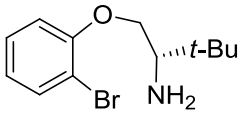
$NaIO_4$ (18.2 g, 85.1 mmol, 3.70 eq.) was dissolved in water (100 mL). To this solution $RuO_2{\times}H_2O$ (174 mg, 1.15 mmol, 5 mol%) was added and the mixture was stirred for 5 min at room temperature. The resulting yellow solution was cooled to 0 °C and a solution of the residue from the first step in EtOAc (80 mL) was added. After stirring at 0 °C for 1 h, the layers were separated, the aqueous layer was extracted with EtOAc (2 × 100 mL) and *iso*-propanol (35 mL) was added to the combined organic layers. The resulting black suspension was filtered over celite where upon a yellow solution was obtained. This was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 5 × 20 cm, EtOAc) gave the desired compound **72b** as a colorless solid (2.39 g, 37%). The analytical data match the literature values.[142]

$C_{11}H_{21}NO_5S$ (279.35 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.58 (dd, $^2J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 6.2 Hz, 1H, NC*H*CH_2O), 4.48 (d, $^3J_{HH}$ = 9.7 Hz, 1H, NCHC*H*HO), 4.16 (d, $^3J_{HH}$ = 6.2 Hz, 1H, NCHCH*H*O), 1.55 (s, 9H, NC(CH_3)$_3$), 1.00 (s, 9H, CHC(CH_3)$_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 150.3 (s, N*C*(O)O), 85.5 (s, N*C*(CH_3)$_3$), 67.8 (s, O*C*H_2CHN), 65.2 (s, OCH$_2$*C*HN), 35.6 (s, CH*C*(CH_3)$_3$), 27.9 (s, NC(*C*H_3)$_3$), 25.9 (s, CHC(*C*H_3)$_3$) ppm.

$\mathbf{R}_f$ = 0.64 (SiO_2, cyclohexane/EtOAc = 2:1).



(*S*)-1-(2-Bromophenoxy)-3,3-dimethylbutan-2-amine (73b)

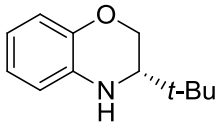
In a flame-dried 2-neck flask 2-bromophenol (499 µL, 4.30 mmol, 1.20 eq.) was dissolved in DMF (40 mL). To this solution sodium hydride (60%, 172 mg, 4.30 mmol, 1.20 eq.) was added and the mixture was stirred at room temperature for 10 min. Then, (*S*)-*tert*-butyl 4-(*tert*-butyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (**72b**) (1.00 g, 3.58 mmol, 1.00 eq.) was added and the reaction mixture was stirred at room temperature overnight before the solvent was removed under high vacuum. The residue was dissolved in dioxane (22 mL) and conc. sulfuric acid (425 µL) and water (425 µL) were added. After 30 min further conc. sulfuric acid (2.35 mL) was added and the mixture was again stirred for 30 min. After neutralization with sat. aq. $NaHCO_3$-solution the aqueous layer was extracted with DCM (3 × 75 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, EtOAc + 5 % NEt_3) gave the desired compound **73b** as a yellow oil (934 mg, 96%).

$C_{12}H_{18}BrNO$ (272.18 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, Ar-C*H*), 7.27-7.22 (m, 1H, Ar-C*H*), 6.89 (dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, Ar-C*H*), 6.83 (td, $^3J_{HH}$ = 7.6 Hz, J_{HH} = 1.4 Hz, 1H, Ar-C*H*), 4.20 (dd, $^2J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, OC*H*HCHN), 3.78 (t, J_{HH} = 8.8 Hz, 1H, OCH*H*CHN), 3.00 (dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, OCH_2CHN), 1.58 (s br, 2 H, NH_2), 1.01 (s, 9H, $C(CH_3)_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 155.4 (s, Ar-*C*), 133.4 (s, Ar-*C*H), 128.6 (s, Ar-*C*H), 122.1 (s, Ar-*C*H), 113.5 (s, Ar-*C*H), 112.5 (s, Ar-*C*), 71.6 (s, OCH_2CHN), 59.2 (s, OCH_2CHN), 33.3 (s, $C(CH_3)_3$), 26.7 (s, $C(CH_3)_3$) ppm.

R_f = 0.52 (SiO_2, EtOAc).



(*S*)-3-(*tert*-Butyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (63b)

In a flame-dried Young-tube a mixture of (*S*)-1-(2-bromophenoxy)-3,3-dimethylbutan-2-amine (**73b**) (920 mg, 3.38 mmol, 1.00 eq.), $Pd(OAc)_2$ (45.7 mg, 203 µmol, 6 mol%), Xantphos (118 mg, 203 µmol, 6 mol%) and *tert*-BuONa (407 mg, 4.23 mmol, 1.25 eq.) in toluene (35 mL) was stirred at 100 °C overnight. After cooling to room temperature the mixture was diluted with EtOAc (250 mL), washed with water (1 × 250 mL) and brine (1 × 250 mL), dried over $MgSO_4$ and concentrated under

reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, cyclohexane/EtOAc = 5:1) gave the desired compound **63b** as a slightly orange solid (484 mg, 75%). The analytical data match the literature values.[143]

$C_{12}H_{17}NO$ (191.27 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.79-6.75 (m, 2H, Ar-C*H*), 6.66-6.62 (m, 2H, Ar-C*H*), 4.30 (td, $^2J_{HH}$ = 10.5 Hz, J_{HH} = 2.2 Hz, 1H, OC*H*HCHN), 3.95 (dd, $^2J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 8.3 Hz, 1H, OCH*H*CHN), 3.78 (s br, 1H, N*H*), 3.13 (td, $^3J_{HH}$ = 8.2 Hz, J_{HH} = 2.1 Hz, 1H, OCH_2CHN), 1.01 (s, 9H, $C(CH_3)_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 144.0 (s, Ar-*C*), 134.5 (s, Ar-*C*), 121.5 (s, Ar-*C*H), 118.4 (s, Ar-*C*H), 116.5 (s, Ar-*C*H), 115.5 (s, Ar-*C*H), 66.7 (s, OCH_2CHN), 58.3 (s, OCH_2CHN), 32.8 (s, $C(CH_3)_3$), 26.2 (s, $C(CH_3)_3$) ppm.

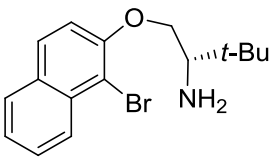
IR (KBr): $\tilde{\nu}$ = 3388m, 2956m, 2868w, 2806w, 1606m, 1592w, 1496s, 1429m, 1398w, 1368m, 1344m, 1309m, 1283s, 1268m, 1244m, 1207s, 1190m, 1132m, 1115m, 1078w, 1043m, 999m, 948w, 915w, 869w, 736s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 191 (23), 134 (100), 106 (16).

m.p.: 40-42 °C.

Optical rotation: $[\alpha]_D^{20}$ = +25.0 (*c* = 0.500, $CHCl_3$).

R$_f$ = 0.61 (SiO_2, cyclohexane/EtOAc = 5:1).



(*S*)-1-((1-Bromonaphthalen-2-yl)oxy)-3,3-dimethylbutan-2-amine (74b)

In a flame-dried 2-neck flask 1-bromonaphthalen-2-ol (959 mg, 4.30 mmol, 1.20 eq.) was dissolved in DMF (40 mL). To this solution sodium hydride (60%, 172 mg, 4.30 mmol, 1.20 eq.) was added and the mixture was stirred at room temperature for 10 min. Then, (*S*)-*tert*-butyl 4-*tert*-butyl-1,2,3-oxathiazolidine-3-carboxylate-2,2-dioxide (**72b**) (1.00 g, 3.58 mmol, 1.00 eq.) was added and the reaction mixture was stirred at room temperature for 2 days before the solvent was removed under high vacuum. The residue was dissolved in dioxane (22 mL) and conc. sulfuric acid (425 µL) and water (425 µL) were added. After 30 min further conc. sulfuric acid (2.35 mL) was added and the mixture was again stirred for 30 min. After neutralization with sat. aq. $NaHCO_3$-solution the aqueous layer

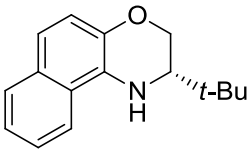
was extracted with DCM (3 × 75 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, EtOAc) gave the desired compound **74b** as a slightly yellow oil (1.12 g, 97%).

$C_{16}H_{20}BrNO$ (322.24 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, $^3J_{HH}$ = 8.5 Hz, 1H, Ar-C*H*), 7.78 (dd, $^3J_{HH}$ = 8.9 Hz, J_{HH} = 6.1 Hz, 2H, Ar-C*H*), 7.58-7.54 (m, 1H, Ar-C*H*), 7.41-7.37 (m, 1H, Ar-C*H*), 7.25 (d, $^3J_{HH}$ = 9.0 Hz, 1H, Ar-C*H*), 4.37 (dd, $^2J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 2.9 Hz, 1H, OC*H*HCHN), 3.91 (d, $^3J_{HH}$ = 8.9 Hz, 1H, OCH*H*CHN), 3.05 (dd, $^3J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 2.9 Hz, 1H, OCH_2CHN), 1.61 (s br, 2H, NH_2), 1.03 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 153.4 (s, Ar-*C*), 133.3 (s, Ar-*C*), 130.1 (s, Ar-*C*), 129.0 (s, Ar-*C*H), 128.2 (s, Ar-*C*H), 127.8 (s, Ar-*C*H), 126.3 (s, Ar-*C*H), 124.6 (s, Ar-*C*H), 115.3 (s, Ar-*C*H), 109.9 (s, Ar-*C*), 72.8 (s, O*C*H_2CHN), 59.4 (s, OCH_2*C*HN), 33.3 (s, *C*$(CH_3)_3$), 26.8 (s, C(*C*H_3)$_3$) ppm.

R_f = 0.50 (SiO_2, EtOAc).



(*S*)-2-(*tert*-Butyl)-2,3-dihydro-1*H*-naphtho[2,1-*b*][1,4]oxazine (75b)

In a flame-dried Young-tube a mixture of (*S*)-1-((1-bromonaphthalen-2-yl)oxy)-3,3-dimethylbutan-2-amine (**74b**) (1.00 g, 3.11 mmol, 1.00 eq.), $Pd(OAc)_2$ (42.1 mg, 187 µmol, 6 mol%), Xantphos (108 mg, 187 µmol, 6 mol%) and *tert*-BuONa (374 mg, 3.89 mmol, 1.25 eq.) in toluene (30 mL) was stirred at 100 °C overnight. After cooling to room temperature the mixture was diluted with EtOAc (200 mL), washed with water (1 × 200 mL) and brine (1 × 200 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, cyclohexane/EtOAc = 10:1) gave the desired compound **75b** as a slightly yellow solid (522 mg, 70%).

$C_{16}H_{19}NO$ (241.32 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.77-7.71 (m, 2H, Ar-C*H*), 7.44 (t, $^3J_{HH}$ = 7.5 Hz, 1H, Ar-C*H*), 7.36-7.32 (m, 1H, Ar-C*H*), 7.23 (d, $^3J_{HH}$ = 8.6 Hz, 1H, Ar-C*H*), 7.06 (d, $^3J_{HH}$ = 8.7 Hz, 1H, Ar-C*H*), 4.42 (dd, $^2J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 2.4 Hz, 1H, OC*H*HCHN), 4.13 (s br, 1H, N*H*),

4.04 (dd, $^{2}J_{HH}$ = 10.4 Hz, $^{3}J_{HH}$ = 8.3 Hz, 1H, OCH*H*CHN), 3.27 (dd, $^{3}J_{HH}$ = 7.8 Hz, $^{3}J_{HH}$ = 1.6 Hz, 1H, OCH$_2$C*H*N), 1.11 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 140.0 (s, Ar-*C*), 129.7 (s, Ar-*C*), 128.8 (s, Ar-*C*H), 126.4 (s, Ar-*C*), 125.3 (s, Ar-*C*H), 124.5 (s, Ar-*C*), 123.6 (s, Ar-*C*H), 118.8 (s, Ar-*C*H), 118.8 (s, Ar-*C*H), 118.5 (s, Ar-*C*H), 66.6 (s, O*C*H$_2$CHN), 58.6 (s, OCH$_2$*C*HN), 33.1 (s, *C*(CH$_3$)$_3$), 26.4 (s, C(*C*H$_3$)$_3$) ppm.

IR (NaCl): $\tilde{\nu}$ = 3388w, 3056w, 2950m, 2868w, 1624w, 1597m, 1583w, 1518w, 1474m, 1400m, 1366m, 1330m, 1315m, 1273m, 1255s, 1204m, 1129m, 1108w, 1063w, 1045m, 1024m, 1000m, 973m, 944w, 924w, 797s, 741s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 241 (30), 185 (13), 184 (100).

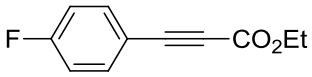
Elemental analysis calc. (%) for $C_{16}H_{19}NO$: C 79.63, H 7.94, N 5.80; found: C 79.65, H 8.00, N 5.74.

m.p.: 49-52 °C.

Optical rotation: $[\alpha]_D^{20}$ = –10.1 (*c* = 0.485, $CHCl_3$).

R$_f$ = 0.53 (SiO_2, cyclohexane/EtOAc = 10:1).

7.6.2 Substrate Synthesis



Ethyl 3-(4-fluorophenyl)propiolate (76c)

A solution of ethyl propiolate (**76b**) (1.58 mL, 15.6 mmol, 1.50 eq.), (4-fluorophenyl)boronic acid (**77d**) (1.46 g, 10.4 mmol, 1.00 eq.), CuI (296 mg, 1.56 mmol, 15 mol%), Ag_2O (4.83 g, 20.8 mmol, 2.00 eq.) and Cs_2CO_3 (6.78 g, 20.8 mmol, 2.00 eq.) in DCE (80 mL) was heated to 80 °C for 36 h under air atmosphere.[93] After cooling to room temperature the suspension was filtered over celite and the resulting solution was washed with water (3 × 100 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, Pent/Et_2O = 10:1) afforded the title compound **76c** as a colorless solid (645 mg, 32%). The analytical data match the literature values.[93]

$C_{11}H_9FO_2$ (192.19 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60-7.55 (m, 2H, Ar-C*H*), 7.09-7.04 (m, 2H, Ar-C*H*), 4.29 (q, $^{3}J_{HH}$ = 7.1 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 1.35 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, CO$_2$CH$_2$C*H*$_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 164.0 (d, $^{1}J_{CF}$ = 253.6 Hz, Ar-*C*F), 154.1 (s, C*C*O_2Et), 125.3 (d, J_{CF} = 8.8 Hz, Ar-*C*H), 116.2 (d, J_{CF} = 22.4 Hz, Ar-*C*H), 115.9 (d, $^{4}J_{CF}$ = 3.6 Hz, Ar-*C*CHCHCF), 85.1 (s, *C*CCO_2Et), 80.8 (s, C*C*CO_2Et), 62.3 (s, CO_2*C*H_2CH_3), 14.2 (s, CO_2CH_2*C*H_3) ppm.

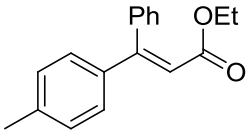
^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ = −106.5 (s, Ar-C*F*) ppm.

MS (EI, 70 eV): *m/z* (%) = 192 (15), 148 (11), 147 (100), 120 (82), 119 (10), 99 (15), 86 (11), 84 (16).

R_f = 0.33 (SiO_2, Pent/Et_2O = 20:1).

Formation of ethyl 3,3-diarylacrylates 78

General procedure 3: In a flame-dried Young-tube ethyl 3-arylpropiolate (**76a**) (1.00 eq.), arylboronic acid (**77**) (3.00 eq.) and CuOAc (2 mol%) were dissolved in MeOH (0.5 M). The solution was degassed by three freeze-pump-thaw cycles and then stirred overnight at room temperature. The resulting suspension was filtered over celite and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 5 × 20 cm, eluent as listed for the R_f-value) afforded the desired ethyl 3,3-diarylacrylate.[92]



(*E*)-Ethyl 3-phenyl-3-(*p*-tolyl)acrylate (78a)

According to general procedure 3, the title compound **78a** was obtained upon reaction of ethyl 3-phenylpropiolate (**76a**) with *p*-tolylboronic acid (**77a**) as a colorless oil (88%). The analytical data match the literature values.[92]

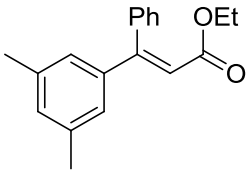
$C_{18}H_{18}O_2$ (266.33 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39-7.38 (m, 3H, Ar-C*H*), 7.22-7.19 (m, 4H, Ar-C*H*), 7.13 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, Ar-C*H*), 6.36 (s, 1H, C*H*CO_2Et), 4.05 (q, $^{3}J_{HH}$ = 7.1 Hz, 2H, CO_2C*H*$_2$CH_3), 2.36 (s, 3H, Ar-CC*H*$_3$), 1.11 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, CO_2CH_2C*H*$_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 166.4 (s, CH*C*O_2Et), 156.7 (s, Ph*C*CH), 139.8 (s, Ar-*C*), 139.3 (s, Ar-*C*), 138.1 (s, Ar-*C*), 129.2 (s, Ar-*C*H), 129.2 (s, Ar-*C*H), 128.4 (s, Ar-*C*H), 128.1 (s, Ar-*C*H), 127.9 (s, Ar-*C*H), 116.6 (s, C*C*HCO_2Et), 60.1 (s, CO_2*C*H_2CH_3), 21.4, (s, Ar-C*C*H_3), 14.1 (s, CO_2CH_2*C*H_3) ppm.

MS (EI, 70 eV): *m/z* (%) = 267 (19), 266 (94), 237 (21), 222 (19), 221 (100), 195 (159, 194 (82), 193 (38), 192 (18), 191 (26), 190 (12), 189 (20), 179 (45), 178 (82), 176 (14), 165 (24), 152 (15), 119 (28), 115 (48), 205 (21), 91 (19), 89 (14), 77 (13), 65 (14), 63 (11), 51 (14).

$\mathbf{R}_f$ = 0.29 (SiO_2, Pent/Et_2O = 10:1).



(*E*)-Ethyl 3-(3,5-dimethylphenyl)-3-phenylacrylate ((*E*)-78b)

According to general procedure 3, the title compound **78b** was obtained upon reaction of ethyl 3-phenylpropiolate (**76a**) with (3,5-dimethylphenyl)boronic acid (**77b**) as a colorless oil (71%).

$C_{19}H_{20}O_2$ (280.36 g mol^{-1})

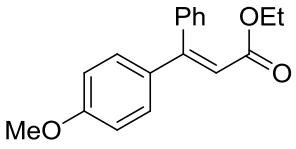
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.42-7.31 (m, 3H, Ar-C*H*), 7.24-7.15 (m, 2H, Ar-C*H*), 6.99 (s, 1H, Ar-C*H*), 6.91 (s, 2H, Ar-C*H*), 6.33 (s, 1H, C*H*CO_2Et), 4.04 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 2.27 (s, 6H, $CH_3CCHCCH_3$), 1.11 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 166.2 (s, CH*C*O_2Et), 156.9 (s, Ph*C*CH), 140.9 (s, Ar-*C*), 139.2 (s, Ar-*C*), 137.9 (s, Ar-*C*), 131.1 (s, Ar-*C*H), 129.1 (s, Ar-*C*H), 128.0 (s, Ar-*C*H), 127.8 (s, Ar-*C*H), 126.2 (s, Ar-*C*H), 117.2 (s, C*C*HCO_2Et), 60.0 (s, $CO_2CH_2CH_3$), 21.3, (s, $CH_3CCHCCH_3$), 14.0 (s, $CO_2CH_2CH_3$) ppm.

IR (NaCl): $\tilde{\nu}$ = 3029m, 2980m, 2919m, 2867m, 1890w, 1723s, 1654w, 1618s, 1597s, 1576m, 1560m, 1541m, 1494m, 1464m, 1444m, 1367s, 1350m, 1280s, 1261s, 1220s, 1159s, 1096m, 1076m, 1044s, 914w, 876m, 852s, 774m, 699s, 668m, 646m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 281 (21), 280 (100), 279 (25), 265 (15), 251 (23), 237 (17), 236 (19), 235 (93), 221 (14), 209 (13), 208 (72), 207 (72), 206 (22), 205 (10), 193 (37), 192 (53), 191 (57), 190 (22), 189 (29), 179 (11), 178 (23), 165 (31), 133 (27), 129 (20), 128 (14), 115 (32), 105 (30), 91 (13), 89 (11), 77 (25), 51 (15).

$\mathbf{R}_f$ = 0.26 (SiO_2, Pent/Et_2O = 50:1).



(*E*)-Ethyl 3-(4-methoxyphenyl)-3-phenylacrylate ((*E*)-78c)

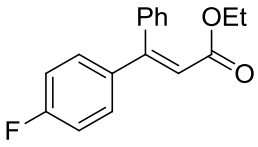
According to general procedure 3, the title compound **78c** was obtained upon reaction of ethyl 3-phenylpropiolate (**76a**) with (4-methoxyphenyl)boronic acid (**77c**) as a colorless oil (81%). The analytical data match the literature values.[92]

$C_{18}H_{18}O_3$ (282.33 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39-7.36 (m, 3H, Ar-C*H*), 7.25-7.23 (m, 2H, Ar-C*H*), 7.22-7.19 (m, 2H, Ar-C*H*), 6.85-6.82 (m, 2H, Ar-C*H*), 6.31 (s, 1H, C*H*CO_2Et), 4.03 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.81 (s, 3H, CH_3O), 1.10 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 166.3 (s, CH*C*O_2Et), 160.8 (s, MeO*C*), 156.3 (s, Ph*C*CH), 139.3 (s, Ph-*C*), 133.1 (s, MeOCCHCH*C*), 129.8 (s, Ar-*C*H), 129.1 (s, Ar-*C*H), 128.0 (s, Ar-*C*H), 127.8 (s, Ar-*C*H), 115.4 (s, C*C*HCO_2Et), 113.8 (s, Ar-*C*H), 59.9 (s, $CO_2CH_2CH_3$), 55.4 (s, CH_3O), 14.01 (s, $CO_2CH_2CH_3$) ppm.

R_f = 0.35 (SiO_2, Pent/Et_2O = 5:1).



(*E*)-Ethyl 3-(4-fluorophenyl)-3-phenylacrylate ((*E*)-78d)

According to general procedure 3, the title compound (*E*)-**78d** was obtained upon reaction of ethyl 3-phenylpropiolate (**76a**) with (4-fluorophenyl)boronic acid (**77d**) as a colorless oil (84%). The analytical data match the literature values.[144]

$C_{17}H_{15}FO_2$ (270.30 g mol^{-1})

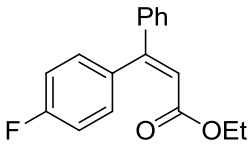
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40-7.37 (m, 3H, Ar-C*H*), 7.30-7.20 (m, 2H, Ar-C*H*), 7.20-7.18 (m, 2H, Ar-C*H*), 7.03-6.97 (m, 2H, Ar-C*H*), 6.31 (s, 1H, C*H*CO_2Et), 4.05 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 1.11 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 166.1 (s, CH*C*O_2Et), 163.6 (d, $^1J_{CF}$ = 250.1 Hz, Ar-*C*F), 155.5 (s, Ph*C*CH), 138.9 (s, Ph-*C*), 137.0 (d, $^4J_{CF}$ = 3.2 Hz, Ar-*C*CHCHCF), 130.3 (d, $^3J_{CF}$ = 8.4 Hz, Ar-CFCH*C*HC), 129.2 (s, Ph-*C*H), 128.4 (s, Ph-CCH*C*H), 128.1 (s, Ph-*C*H), 117.4 (s, C*C*HCO_2Et), 115.5 (d, $^2J_{CF}$ = 21.6 Hz, Ar-CF*C*HCHC), 60.2 (s, $CO_2CH_2CH_3$), 14.1 (s, $CO_2CH_2CH_3$) ppm.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ = –111.9 (s, Ar-C*F*) ppm.

MS (EI, 70 eV): *m/z* (%) = 271 (15), 270 (84), 242 (10), 241 (20), 226 (18), 225 (100), 199 (10), 198 (64), 197 (64), 196 (82), 194 (14), 183 (22), 177 (21), 176 (23), 175 (10), 170 (16), 123 (19), 105 (19), 98 (10), 77 (12), 75 (10), 51 (15).

$\mathbf{R}_f$ = 0.26 (SiO_2, Pent/Et_2O = 10:1).



(*Z*)-Ethyl 3-(4-fluorophenyl)-3-phenylacrylate ((*Z*)-78d)

According to general procedure 3, the title compound (*Z*)-**78d** was obtained upon reaction of Ethyl 3-(4-fluorophenyl)propiolate (**76c**) with phenylboronic acid using 10 mol% CuOAc for 4 h as a colorless solid (53%).

$C_{17}H_{15}FO_2$ (270.30 g mol^{-1})

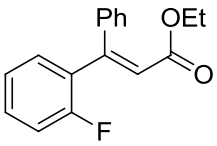
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38-7.26 (m, 5H, Ar-C*H*), 7.22-7.17 (m, 2H, Ar-C*H*), 7.10-7.04 (m, 2H, Ar-C*H*), 6.35 (s, 1H, C*H*CO_2Et), 4.07 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 1.15 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 166.1 (s, CH*C*O_2Et), 162.8 (d, $^1J_{CF}$ = 247.6 Hz, Ar-*C*F), 155.7 (s, Ph*C*CH), 140.9 (s, Ph-*C*), 134.9 (d, $^4J_{CF}$ = 3.5 Hz, Ar-*C*CHCHCF), 131.2 (d, $^3J_{CF}$ = 8.1 Hz, Ar-CFCH*C*HC), 129.7 (s, Ph-*C*H), 128.6 (s, Ph-CCH*C*H), 128.4 (s, Ph-*C*H), 117.9 (s, C*C*HCO$_2$Et), 115.0 (d, $^2J_{CF}$ = 21.6 Hz, Ar-CF*C*HCHC), 60.3 (s, $CO_2CH_2CH_3$), 14.2 (s, $CO_2CH_2CH_3$) ppm.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ = –113.5 (s, Ar-C*F*) ppm.

MS (EI, 70 eV): *m/z* (%) = 271(16), 270 (88), 241 (17), 226 (16), 225 (100), 198 (54), 197 (55), 196 (75), 194 (11), 183 (19), 177 (17), 176 (18), 170 (13), 123 (13), 105 (10), 51 (11).

$\mathbf{R}_f$ = 0.18 (SiO_2, Pent/Et_2O = 20:1).



(*E*)-Ethyl 3-(2-fluorophenyl)-3-phenylacrylate ((*E*)-78e)

According to general procedure 3, the title compound **78e** was obtained upon reaction of ethyl 3-phenylpropiolate (**76a**) with (2-fluorophenyl)boronic acid (**77e**) as a colorless oil (47%). Carrying out the reaction with 10 mol% of CuOAc for 3 h afforded the desired acrylate in 82% yield.

$C_{17}H_{15}FO_2$ (270.30 g mol^{-1})

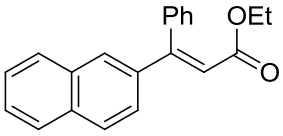
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.36-7.26 (m, 4H, Ar-C*H*), 7.25-7.21 (m, 2H, Ar-C*H*), 7.14-7.04 (m, 3H, Ar-C*H*), 6.33 (s, 1H, C*H*CO_2Et), 4.07 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 1.12 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 166.2 (s, CH*C*O_2Et), 160.3 (d, $^1J_{CF}$ = 251.6 Hz, Ar-*C*F), 150.5 (s, Ph*C*CH), 139.0 (s, Ph-*C*), 131.6 (d, J_{CF} = 2.4 Hz, Ar-*C*H), 130.6 (d, J_{CF} = 8.6 Hz, Ar-*C*H), 129.3 (d, $^2J_{CF}$ = 11.9 Hz, Ar-CF*C*CH), 128.9 (s, Ph-*C*H), 128.4 (s, Ph-*C*H), 128.0 (s, Ph-*C*H), 124.1 (d, J_{CF} = 3.8 Hz, Ar-*C*H), 121.7 (d, J_{CF} = 5.7 Hz, Ar-*C*H), 116.3 (d, $^4J_{CF}$ = 22.6 Hz, PhC*C*HCO$_2$Et), 60.4 (s, $CO_2CH_2CH_3$), 14.1 (s, $CO_2CH_2CH_3$) ppm.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ = –112.9 (s, Ar-C*F*) ppm.

MS (EI, 70 eV): *m/z* (%) = 271 (14), 270 (80), 169 (13), 142 (18), 226 (16), 225 (100), 109 (13), 198 (34), 197 (47), 196 (60), 194 (15), 183 (10), 177 (16), 176 (24).

R$_f$ = 0.21 (SiO_2, Pent/Et_2O = 20:1).



(*E*)-Ethyl 3-(naphthalen-2-yl)-3-phenylacrylate ((*E*)-78f)

According to general procedure 3, the title compound **78f** was obtained upon reaction of ethyl 3-phenylpropiolate (**76a**) with naphthalen-2-ylboronic acid (**77f**) as a colorless solid (40%).

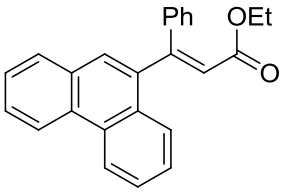
$C_{21}H_{18}O_2$ (302.37 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.81-7.72 (m, 3H, Ar-C*H*), 7.68-7.65 (m, 1H, Ar-C*H*), 7.49-7.38 (m, 6H, Ar-C*H*), 7.27-7.23 (m, 2H, Ar-C*H*), 6.50 (s, 1H, C*H*CO_2Et), 4.07 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 1.12 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 166.3 (s, CH*C*O_2Et), 156.5 (s, Ph*C*CH), 139.1 (s, Ar-*C*), 138.2 (s, Ar-*C*), 133.8 (s, Ar-*C*), 133.1 (s, Ar-*C*), 129.4 (s, Ar-*C*H), 128.9 (s, Ar-*C*H), 128.8 (s, Ar-*C*H), 128.3 (s, Ar-*C*H), 128.2 (s, Ar-*C*H), 128.1 (s, Ar-*C*H), 127.7 (s, Ar-*C*H), 127.1 (s, Ar-*C*H), 126.6 (s, Ar-*C*H), 125.3 (s, Ar-*C*H), 118.0 (s, C*C*HCO$_2$Et), 60.2 (s, $CO_2CH_2CH_3$), 14.1 (s, $CO_2CH_2CH_3$) ppm.

MS (EI, 70 eV): *m/z* (%) = 303 (22), 302 (100), 273 (15), 258 (13), 257 (59), 230 (44), 229 (61), 228 (57), 227 (22), 226 (32), 215 (15), 202 (14), 155 (11), 114 (12).

R$_f$ = 0.18 (SiO_2, Pent/Et_2O = 20:1).



(*E*)-Ethyl 3-(phenantren-9-yl)-3-phenylacrylate ((*E*)-78g)

According to general procedure 3, the title compound **78g** was obtained upon reaction of ethyl 3-phenylpropiolate (**76a**) with phenanthren-9-ylboronic acid (**77g**) in MeOH/DCM (2:1, 0.5 M) as a colorless solid (34%).

$C_{25}H_{20}O_2$ (352.43 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.68 (t, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-C*H*), 7.91 (dd, J_{HH} = 11.0 Hz, $^3J_{HH}$ = 8.4 Hz, 2H, Ar-C*H*), 7.72 (s, 1H, Ar-C*H*), 7.70-7.66 (m, 1H, Ar-C*H*), 7.63-7.58 (m, 2H, Ar-C*H*), 7.46 (t, J_{HH} = 7.6 Hz, 1H, Ar-C*H*), 7.41 (t, J_{HH} = 3.6 Hz, 2H, Ar-C*H*), 7.30-7.28 (m, 3H, Ar-C*H*), 6.30 (s, 1H, C*H*CO_2Et), 4.18 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 1.21 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$) ppm.

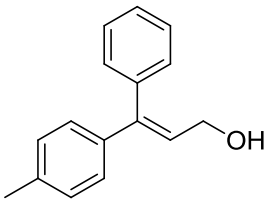
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 166.5 (s, CH*C*O_2Et), 155.4 (s, Ph*C*CH), 139.0 (s, Ar-*C*), 138.6 (s, Ar-*C*), 131.2 (s, Ar-*C*), 130.9 (s, Ar-*C*), 130.6 (s, Ar-*C*), 130.3 (s, Ar-*C*), 129.2 (s, Ar-*C*H), 129.1 (s, Ar-*C*H), 128.8 (s, Ar-*C*H), 128.1 (s, Ar-*C*H), 128.0 (s, Ar-*C*H), 127.3 (s, Ar-*C*H), 127.1 (s, Ar-*C*H), 127.0 (s, Ar-*C*H), 126.9 (s, Ar-*C*H), 126.7 (s, Ar-*C*H), 123.0 (s, Ar-*C*H), 122.7 (s, Ar-*C*H), 121.4 (s, Ar-*C*H), 60.5 2 (s, $CO_2CH_2CH_3$), 14.2 (s, $CO_2CH_2CH_3$) ppm.

MS (EI, 70 eV): *m/z* (%) = 352 (23), 280 (21), 279 (100), 278 (81), 277 (22), 276 (25), 202 (10).

R_f = 0.22 (SiO_2, Pent/Et_2O = 20:1).

Formation of allylic alcohol 79

General procedure 4: In a flame-dried two-neck flask with attached reflux condenser a solution of ethyl 3,3-diarylacrylate (**78**) (1.00 eq.), $NaBH_4$ (4.00 eq.), $ZnCl_2$ (2.00 eq.) and NEt_3 (2.00 eq.) in THF (0.3 M) was stirred at reflux for 3 h. Afterwards the reaction mixture was cooled to 0 °C and a mixture of aq. HCl (10%) and Et_2O (1:2) was added in the threefold amount as THF was used before, whereupon gas evolution was observed. After phase separation the organic layer was washed with sat. aq. $NaHCO_3$-solution, water and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, eluent as listed for the R_f -value) afforded the desired 3,3-diaryl allylic alcohols.



(*E*)-3-Phenyl-3-(*p*-tolyl)prop-2-en-1-ol ((*E*)-79a)

According to general procedure 4, the title compound **79a** was obtained upon reduction of (*E*)-ethyl 3-phenyl-3-(*p*-tolyl)acrylate ((*E*)-**78a**) as a colorless solid (91%).

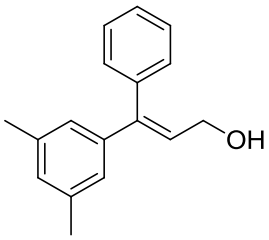
$C_{16}H_{16}O$ (224.12 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40-7.33 (m, 3H, Ar-C*H*), 7.18-7.15 (m, 4H, Ar-C*H*), 7.11-7.09 (m, 2H, Ar-C*H*), 6.22 (t, $^3J_{HH}$ = 6.9 Hz, 1H, C*H*CH$_2$OH), 4.25-4.19 (m, 2H, CHC*H*$_2$OH), 2.34 (s, 3H, Ar-CC*H*$_3$), 1.45 (s br, 1H, O*H*) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 144.3 (s, Ar-*C*), 139.3 (s, Ar-*C*), 139.1 (s, Ar-*C*), 137.6 (s, Ph*C*CH), 129.9 (s, Ar-*C*H), 129.0 (s, Ar-*C*H), 128.3 (s, Ar-*C*H), 127.6 (s, Ar-*C*H), 127.6 (s, Ar-*C*H), 126.7 (s, *C*HCH$_2$OH), 60.9 (s, CH*C*H$_2$OH), 21.2 (s, Ar-C*C*H$_3$) ppm.

MS (EI, 70 eV): *m/z* (%) = 225 (12), 224 (69), 210 (10), 209 (58), 208 (10), 207 (16), 206 (36), 194 (20), 191 (18), 182 (17), 181 (100), 179 (18), 178 (28), 166 (26), 165 (43), 131 (11), 119 (21), 117 (19), 115 (18), 105 (22), 103 (30), 91 (16), 89 (11), 77 (11).

R$_f$ = 0.29 (SiO_2, Pent/EtOAc = 3:1).



(*E*)-3-(3,5-Dimethylphenyl)-3-phenylprop-2-en-1-ol ((*E*)-79b)

According to general procedure 4, the title compound **79b** was obtained upon reduction of (*E*)-ethyl 3-(3,5-dimethylphenyl)-3-phenylacrylate ((*E*)-**78b**) as a colorless solid (70%).

$C_{17}H_{18}O$ (238.32 g mol^{-1})

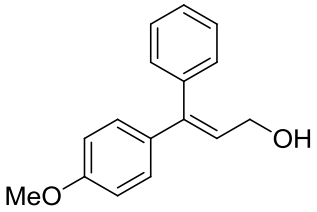
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40-7.32 (m, 3H, Ar-C*H*), 7.17-7.15 (m, 2H, Ar-C*H*), 6.92 (s, 1H, Ar-C*H*), 6.88 (s, 2H, Ar-C*H*), 6.22 (t, $^3J_{HH}$ = 6.9 Hz, 1H, C*H*CH$_2$OH), 4.20 (d, $^3J_{HH}$ = 6.9 Hz, 2H, CHC*H*$_2$OH), 2.27 (s, 6H, C*H*$_3$CCHCC*H*$_3$), 1.36 (s br, 1H, O*H*) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 144.6 (s, Ar-*C*), 142.0 (s, Ar-*C*), 139.4 (s, Ph*C*CH), 137.8 (s, CH$_3$*C*CH*C*CH$_3$), 129.9 (s, Ar-*C*H), 129.5 (s, Ar-*C*H), 128.3 (s, Ar-*C*H), 127.6 (s, Ar-*C*H), 127.4 (s, Ar-*C*H), 125.7 (s, *C*H *C*HCH$_2$OH), 60.9 (s, CH*C*H$_2$OH), 21.4 (s, Ar-C*C*H$_3$) ppm.

IR (NaCl): $\tilde{\nu}$ = 3422s, 1702m, 1655s, 1561s, 1561s, 1543m, 1509s, 1459m, 839w, 671w cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 239 (18), 238 (100), 223 (34), 221 (15), 220 (44), 208 (18), 205 (26), 203 (10), 202 (10), 196 (17), 195 (51), 190 (16), 189 (18), 181 (14), 180 (19), 179 (23), 178 (33), 165 (28), 152 810), 133 (24), 131 (27), 128 (10), 119 (28), 115 (25), 105 (15), 104 (17), 103 (69), 91 (26), 89 (12), 77 (24), 51 (10).

$\mathbf{R}_f$ = 0.11 (SiO_2, petrol ether/EtOAc = 9:1).



(*E*)-3-(4-Methoxyphenyl)-3-phenylprop-2-en-1-ol ((*E*)-79c)

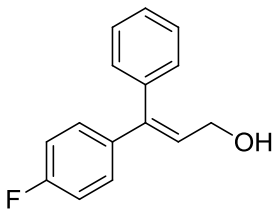
According to general procedure 4, the title compound **79c** was obtained upon reduction of (*E*)-ethyl 3-(4-methoxyphenyl)-3-phenylacrylate ((*E*)-**78c**) as a colorless oil (88%). The analytical data match the literature values.[99,145]

$C_{16}H_{16}O_2$ (240.30 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39-7.31 (m, 3H, Ar-C*H*), 7.20-7.15 (m, 4H, Ar-C*H*), 6.82 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar-C*H*), 6.17 (t, $^3J_{HH}$ = 6.9 Hz, 1H, C*H*CH_2OH), 4.19 (d, $^3J_{HH}$ = 6.8 Hz, 2H, CHC*H*$_2$OH), 3.80 (s, 3H, C*H*$_3$O), 1.53 (s br, 1H, O*H*) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 159.4 (s, CH_3O*C*), 144.0 (s, Ar-*C*), 139.4 (s, Ph*C*CH), 134.5 (s, Ar-*C*), 129.9 (s, Ar-*C*H), 128.9 (s, Ar-*C*H), 128.3 (s, Ar-*C*H), 127.6 (s, Ar-*C*H), 125.8 (s, *C*HCH$_2$OH), 113.7 (s, Ar-*C*H), 60.9 (s, CH*C*H$_2$OH), 55.4 (s, *C*H$_3$O) ppm.

$\mathbf{R}_f$ = 0.27 (SiO_2, Pent/EtOAc = 3:1).



(*E*)-3-(4-Fluorophenyl)-3-phenylprop-2-en-1-ol ((*E*)-79d)

According to general procedure 4, the title compound **79d** was obtained upon reduction of (*E*)-ethyl 3-(4-fluorophenyl)-3-phenylacrylate ((*E*)-**78d**) as a colorless oil (95%).

$C_{15}H_{13}FO$ (228.10 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40-7.32 (m, 3H, Ar-C*H*), 7.23-7.20 (m, 2H, Ar-C*H*), 7.16-7.14 (m, 2H, Ar-C*H*), 6.99-6.94 (m, 2H, Ar-C*H*), 6.18 (t, $^3J_{HH}$ = 6.8 Hz, 1H, C*H*CH_2OH), 4.22-4.19 (m, 2H, CHC*H*$_2$OH), 1.51 (t br, 1H, $^3J_{HH}$ = 4.9 Hz, O*H*) ppm.

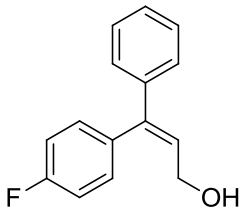
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 162.5 (d, $^1J_{CF}$ = 247.2 Hz, Ar-*C*F), 143.4 (s, Ph-*C*), 139.0 (s, Ph*C*CHCH$_2$), 138.1 (d, $^4J_{CF}$ = 3.2 Hz, FCCHCH*C*), 129.8 (s, Ph-*C*H),

129.4 (d, $^{3}J_{CF}$ = 8.0 Hz, FCCH*C*HC), 128.4 (s, Ph-*C*H), 127.9 (s, Ph-CCHCH*C*H), 127.4 (s, *C*HCH$_2$OH), 115.2 (d, $^{2}J_{CF}$ = 21.0 Hz, FC*C*HCHC), 60.8 (s, CH*C*H$_2$OH) ppm.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ = –115.1 (s, Ar-C*F*) ppm.

MS (EI, 70 eV): *m/z* (%) = 228 (65), 227 (10), 219 (49), 109 (16), 196 (17), 186 (18), 185 (100), 184 (11), 183 (45), 165 (14), 133 (12), 123 (14), 121 (16), 109 (15), 105 (29), 103 (14), 91 (10).

R$_f$ = 0.22 (SiO_2, Pent/EtOAc = 3:1).



(*Z*)-3-(4-Fluorophenyl)-3-phenylprop-2-en-1-ol ((*Z*)-79d)

According to general procedure 4, the title compound **78d** was obtained upon reduction of (*Z*-ethyl 3-(4-fluorophenyl)-3-phenylacrylate ((*Z*)-**79d**) as a colorless oil (46%).

$C_{15}H_{13}FO$ (228.10 g mol^{-1})

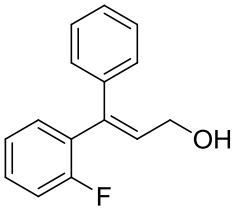
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.31-7.22 (m, 5H, Ar-C*H*), 7.17-7.12 (m, 2H, Ar-C*H*), 7.09-7.03 (m, 2H, Ar-C*H*), 6.23 (t, $^{3}J_{HH}$ = 6.9 Hz, 1H, C*H*CH$_2$OH), 4.21 (d, $^{3}J_{HH}$ = 6.9 Hz, 2H, CHC*H*$_2$OH), 1.56 (s br, 1H, O*H*) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 162.4 (d, $^{1}J_{CF}$ = 246.7 Hz, Ar-*C*F), 143.4 (s, Ph-*C*), 141.8 (s, Ph*C*CHCH$_2$), 135.1 (d, $^{4}J_{CF}$ = 3.5 Hz, FCCHCH*C*), 131.6 (d, $^{3}J_{CF}$ = 8.0 Hz, FCCH*C*HC), 128.4 (s, Ph-*C*H), 127.9 (s, Ph-*C*H), 127.7 (s, Ph-*C*H), 127.7 (s, *C*HCH$_2$OH), 115.3 (d, $^{2}J_{CF}$ = 21.6 Hz, FC*C*HCHC), 60.8 (s, CH*C*H$_2$OH) ppm.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ = –114.4 (s, Ar-C*F*) ppm.

MS (EI, 70 eV): *m/z* (%) = 229 (12), 228 (67), 227 (13), 226 (14), 225 (19), 212 (19), 211 (13), 210 (62), 209 (23), 197 (12), 196 (28), 186 (20), 185 (100), 184 (17), 183 (62), 170 (13), 165 (24), 133 (19), 131 (10), 123 (19), 121 (24), 120 (10), 115 (10), 109 (19), 105 (33), 104 (10), 103 (23), 102 (10), 101 (15), 91 (16), 84 (11), 77 (20), 75 (11), 51 (15).

R$_f$ = 0.31 (SiO_2, Pent/EtOAc = 3:1).



(*E*)-3-(2-Fluorophenyl)-3-phenylprop-2-en-1-ol ((*E*)-79e)

According to general procedure 4, the title compound **79e** was obtained upon reduction of (*E*)-ethyl 3-(2-fluorophenyl)-3-phenylacrylate ((*E*)-**78e**) as a colorless solid (94%).

$C_{15}H_{13}FO$ (228.10 g mol^{-1})

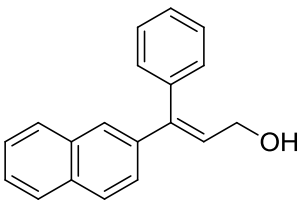
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.36-7.29 (m, 3H, Ar-C*H*), 7.27-7.23 (m, 1H, Ar-C*H*), 7.20-7.15 (m, 3H, Ar-C*H*), 7.08 (td, $^3J_{HH}$ = 7.5 Hz, J_{HF} = 1.2 Hz, 1H, Ar-C*H*), 7.02 (ddd, $^3J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 8.2 Hz, J_{HF} = 1.1 Hz, Ar-C*H*), 6.18 (t, $^3J_{HH}$ = 6.8 Hz, 1H, C*H*CH$_2$OH), 4.32-4.30 (m, 2H, CHC*H*$_2$OH), 1.51 (s br, 1H, O*H*) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 160.3 (d, $^1J_{CF}$ = 248.7 Hz, Ar-*C*F), 139.1 (s, Ar-*C*), 138.9 (s, Ph*C*CHCH$_2$), 131.7 (d, J_{CF} = 3.6 Hz, Ar-*C*H), 131.4 (d, J_{CF} = 3.4 Hz, Ar-*C*H), 130.3 (d, J_{CF} = 13.0 Hz, Ar-*C*), 129.3 (s, Ar-*C*H), 129.2 (s, Ar-*C*H), 128.3 (s, Ar-*C*H), 127.7 (s, Ar-*C*H), 124.0 (d, J_{CF} = 3.6 Hz, Ar-*C*H), 116.2 (s, Ar-*C*H), 115.9 (s, *C*HCH$_2$OH), 60.5 (s, CH*C*H$_2$OH) ppm.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ = –114.1 (s, Ar-C*F*) ppm.

MS (EI, 70 eV): *m/z* (%) = 229 (12), 228 (79), 227 (15), 211 (13), 210 (63), 109 (18), 199 (11), 196 (17), 186 (30), 185 (100), 184 (13), 183 (50), 165 (20), 133 (15), 123 (13), 122 (13), 121 (29), 109 (13), 105 (51), 103 (17), 101 (12), 91 (18), 77 (12).

R$_f$ = 0.22 (SiO_2, Pent/EtOAc = 3:1).



(*E*)-3-(Naphthalen-2-yl)-3-phenylprop-2-en-1-ol ((*E*)-79f)

According to general procedure 4, the title compound **79f** was obtained upon reduction of (*E*)-ethyl 3-(naphthalen-2-yl)-3-phenylacrylate ((*E*)-**78f**) as a colorless solid (50%).

$C_{19}H_{16}O$ (260.12 g mol^{-1})

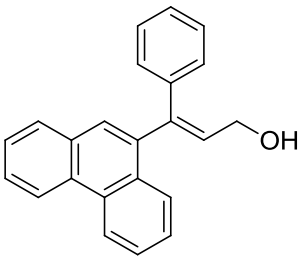
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.81-7.70 (m, 3H, Ar-C*H*), 7.62-7.60 (m, 1H, Ar-C*H*), 7.49-7.34 (m, 6H, Ar-C*H*), 7.23-7.20 (m, 2H, Ar-C*H*), 6.38 (t, $^3J_{HH}$ = 6.8 Hz, 1H, C*H*CH$_2$OH), 4.27 (d, $^3J_{HH}$ = 6.8 Hz, 2H, CHC*H*$_2$OH), 1.59 (s br, 1H, O*H*) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 144.3 (s, Ar-*C*), 139.3 (s, Ar-*C*), 139.2 (s, Ph*C*CH), 133.4 (s, Ar-*C*), 133.0 (s, Ar-*C*), 130.0 (s, Ar-*C*H), 128.4 (s, Ar-*C*H), 128.4 (s, Ar-*C*H), 128.2

(s, Ar-*C*H), 127.9 (s, Ar-*C*H), 127.8 (s, Ar-*C*H), 127.7 (s, Ar-*C*H), 127.2 (s, Ar-*C*H), 126.3 (s, Ar-*C*H), 126.2 (s, Ar-*C*H), 125.6 (s, *C*HCH$_2$OH), 60.9 (s, CH*C*H$_2$OH) ppm.

MS (EI, 70 eV): *m/z* (%) = 261 (17), 260 (81), 259 (10), 243 (10), 242 (33), 241 (16), 228 (14), 226 (13), 218 (38), 217 (100), 216 (18), 215 (40), 202 (19), 165 (11), 155 (16), 153 (16), 152 (10), 141 (15), 128 (15), 121 (13), 115 (10), 103 (29).

R$_f$ = 0.47 (SiO$_2$, Pent/EtOAc = 2:1).



(*E*)-3-(Phenanthren-9-yl)-3-phenylprop-2-en-1-ol ((*E*)-79g)

According to general procedure 4, the title compound **79g** was obtained upon reduction of (*E*)-ethyl 3-(phenanthren-9-yl)-3-phenylacrylate ((*E*)-**78g**) as a colorless solid (83%).

$C_{23}H_{18}O$ (310.14 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.67 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 5.4 Hz, 2H, Ar-C*H*), 7.91-7.86 (m, 2H, Ar-C*H*), 7.74 (s, 1H, Ar-C*H*), 7.67-7.54 (m, 3H, Ar-C*H*), 7.42 (t, $^3J_{HH}$ = 7.3 Hz, 1H, Ar-C*H*), 7.29-7.24 (m, 5H, Ar-C*H*), 6.18 (t, $^3J_{HH}$ = 6.7 Hz, 1H, C*H*CH$_2$OH), 4.57-4.52 (m, 2H, CHC*H*$_2$OH), 1.66 (s br, 1H, O*H*) ppm.

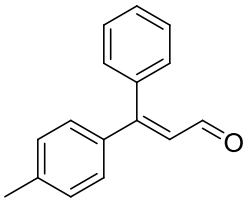
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 143.6 (s, Ar-*C*), 139.5 (s, Ph*C*CH), 139.4 (s, Ar-*C*), 131.7 (s, Ar-*C*), 131.3 (s, Ar-*C*H), 131.1 (s, Ar-*C*), 130.8 (s, Ar-*C*), 130.4 (s, Ar-*C*), 129.1 (s, Ph-*C*H), 128.8 (s, Ar-*C*H), 128.4 (s, Ph-*C*H), 128.2 (s, Ar-*C*H), 127.8 (s, Ar-*C*H), 127.2 (s, Ar-*C*H), 126.9 (s, Ar-*C*H), 126.8 (s, Ar-*C*H), 126.6 (s, Ar-*C*H), 126.4 (s, Ar-*C*H), 122.9 (s, Ar-*C*H), 122.7 (s, *C*HCH$_2$OH), 60.5 (s, CH*C*H$_2$OH) ppm.

MS (EI, 70 eV): *m/z* (%) = 310 (35), 293 (19), 292 (74), 291 (74), 289 (11), 280 (26), 279 (100), 278 (17), 277 (14), 276 (18), 267 (17), 265 (25), 263 (11), 252 (10), 216 (10), 215 (54), 203 (12), 202 (17), 178 (12), 146 (10), 103 (13).

R$_f$ = 0.43 (SiO$_2$, Pent/EtOAc = 2:1).

Formation of 3,3-diaryl acrylaldehydes 64

General procedure 5: To a solution of 3,3-diaryl allylic alcohol (1.00 eq.) in $CHCl_3$ (0.3 M), MnO_2 (4.00 eq.) was added and the mixture was stirred at room temperature for 3 d. After filtration over celite the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, 3 × 20 cm, eluent as listed for the R_f -value) afforded the desired 3,3-diaryl acrylaldehydes.



(*E*)-3-Phenyl-3-(*p*-tolyl)acrylaldehyde ((*E*)-64a)

According to general procedure 5, the title compound **64a** was afforded upon oxidation of (*E*)-3-phenyl-3-(*p*-tolyl)prop-2-en-1-ol ((*E*)-**79a**) as a slightly yellow oil (80%). The analytical data match the literature values.[146]

$C_{16}H_{14}O$ (222.28 g mol^{-1})

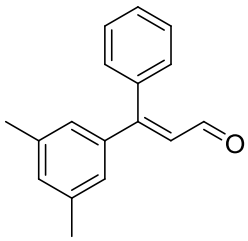
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.50 (d, $^3J_{HH}$ = 8.0 Hz, 1H, CHC(O)*H*), 7.50-7.42 (m, 3H, Ar-C*H*), 7.32-7.25 (m, 4H, Ar-C*H*), 7.19-7.17 (m, 2H, Ar-C*H*), 6.59 (d, $^3J_{HH}$ = 8.0 Hz, 1H, C*H*C(O)H), 2.39 (s, 3H, Ar-CCH_3) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 193.8 (s, CH*C*(O)H), 162.5 (s, Ph*C*CH), 141.2 (s, Ar-*C*), 137.0 (s, Ar-*C*), 137.0 (s, Ar-*C*), 130.9 (s, Ar-*C*H), 129.5 (s, Ar-*C*H), 128.8 (s, Ar-*C*H), 128.4 (s, Ar-*C*H), 126.7 (s, *C*HC(O)H), 21.5 (s, Ar-C*C*H_3) ppm.

IR (NaCl): $\tilde{\nu}$ = 3046s, 2833m, 1666s, 1588m, 1508w, 1442w, 1385w, 1340m, 1240w, 1189m, 1154m, 1128s, 868w, 819s, 782m, 734m, 702m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 222 (31), 221 (46), 208 (14), 207 (100), 191 (10), 189 (16), 179 (28), 178 (52), 176 (12), 165 (19), 152 (18), 116 (29), 115 (56), 102 (36), 91 (25), 89 (19), 78 (18), 77 (36), 76 (19), 75 (18), 74 (14), 65 (25), 63 (37), 52 (17), 51 (63), 50 (29).

R_f = 0.33 (SiO_2, Pent/EtOAc = 10:1).



(*E*)-3-(3,5-Dimethylphenyl)-3-phenylacrylaldehyde ((*E*)-64b)

According to general procedure 5, the title compound **64b** was afforded upon oxidation of (*E*)-3-(3,5-dimethylphenyl)-3-phenylprop-2-en-1-ol ((*E*)-**79b**) as a slightly yellow solid (73%).

$C_{17}H_{16}O$ (236.12 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.50 (d, $^3J_{HH}$ = 8.0 Hz, 1H, CHC(O)*H*), 7.47-7.41 (m, 3H, Ar-C*H*), 7.32-7.28 (m, 2H, Ar-C*H*), 7.07 (s, 1H, Ar-C*H*), 6.96 (s, 2H, Ar-C*H*), 6.57 (d, $^3J_{HH}$ = 8.0 Hz, 1H, C*H*C(O)H), 2.30 (s, 6H, *C*H$_3$CCHCC*H*$_3$) ppm.

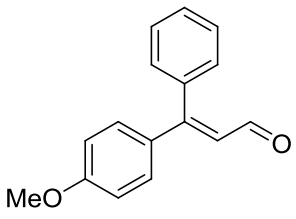
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 193.8 (s, CH*C*(O)H), 162.9 (s, Ph*C*CH),139.9 (s, Ar-*C*), 138.3 (s, CH$_3$*C*CH*C*CH$_3$), 137.0 (s, Ar-*C*), 132.4 (s, Ar-*C*H), 130.9 (s, Ar-*C*H), 129.5 (s, Ar-*C*H), 128.4 (s, Ar-*C*H), 127.3 (s, *C*HC(O)H), 126.7 (s, Ar-*C*H), 21.4 (s, *C*H$_3$CCHC*C*H$_3$) ppm.

IR (KBr): $\tilde{\nu}$ = 2926m, 2840m, 2742m, 1661s, 1578s, 1440m, 1380m, 1338m, 1214m, 1580w, 1146m, 1130s, 1028m, 911w, 893w, 872w, 854s, 784m, 712s, 703s, 664m, 614m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 236 (40), 235 (25), 222 (17), 221 (100), 193 (11), 192 (12), 191 (16), 189 (11), 178 (23), 165 (11), 115 (15), 102 (15), 91 (10), 77 (10).

HRMS (ESI-MS) calc. (*m/z*) for $C_{17}H_{17}O$: 237.1274 [M+H$^+$]; found: 237.1267.

R$_f$ = 0.23 (SiO_2, petrol ether/EtOAc = 10:1).



(*E*)-3-(4-Methoxyphenyl)-3-phenylacrylaldehyde ((*E*)-64c)

According to general procedure 5, the title compound **64c** was afforded upon oxidation of (*E*)-3-(4-methoxyphenyl)-3-phenylprop-2-en-1-ol ((*E*)-**79c**) as a slightly yellow solid (87%).

$C_{16}H_{14}O_2$ (238.28 g mol^{-1})

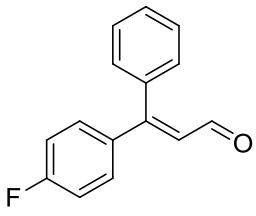
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.45 (d, $^3J_{HH}$ = 8.1 Hz, 1H, CHC(O)*H*), 7.49-7.42 (m, 3H, Ar-C*H*), 7.33-7.29 (m, 4H, Ar-C*H*), 6.91-6.87 (m, 2H, Ar-C*H*), 6.56 (d, $^3J_{HH}$ = 8.1 Hz, 1H, C*H*C(O)H), 3.84 (s, 3H, OC*H*$_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 193.7 (s, CH*C*(O)H), 162.1 (s, Ph*C*CH), 161.8 (s, Ar-*C*), 137.0 (s, Ar-*C*), 132.0 (s, Ar-*C*), 130.8 (s, Ar-*C*H), 130.4 (s, Ar-*C*H), 129.4 (s, Ar-*C*H), 128.4 (s, Ar-*C*H), 125.7 (s, *C*HC(O)H), 55.5 (s, O*C*H_3) ppm.

MS (EI, 70 eV): *m/z* (%) = 239 (17), 238 (100), 237 (79), 223 (16), 219 (15), 209 (13), 207 (44), 195 (18), 194 815), 179 (13), 178 (18), 167 (13), 166 (18), 165 (58), 152 (18), 139 (12), 135 (18), 132 (19), 108 (12), 105 (12), 102 (36), 89 (17), 78 (10), 77 (14), 76 (10), 63 (18), 51 (16).

HRMS (ESI-MS) calc. (*m*/*z*) for $C_{16}H_{15}O_2$: 239.1072 [M+H^+]; found: 239.1062.

R_f = 0.15 (SiO_2, Pent/EtOAc = 10:1).



(*E*)-3-(4-Fluorophenyl)-3-phenylacrylaldehyde ((*E*)-64d)

According to general procedure 5, the title compound **64d** was afforded upon oxidation of (*E*)-3-(4-fluorophenyl)-3-phenylprop-2-en-1-ol ((*E*)-**79d**) as a slightly yellow solid (90%).

$C_{15}H_{11}FO$ (226.08 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.50 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, CHC(O)*H*), 7.51-7.43 (m, 3H, Ar-C*H*), 7.37-7.28 (m, 4H, Ar-C*H*), 7.09-7.05 (m, 2H, Ar-C*H*), 6.55 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, C*H*C(O)H) ppm.

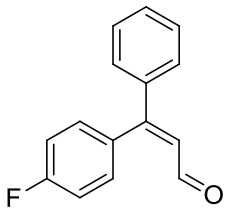
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 193.5 (s, CH*C*(O)H), 164.3 (d, $^{1}J_{CF}$ = 252.0 Hz, Ar-*C*F), 161.2 (s, Ph*C*CH), 136.6 (s, Ph-*C*), 136.0 (d, $^{4}J_{CF}$ = 3.2 Hz, Ar-CFCHCH*C*), 130.8 (s, Ph-*C*H), 130.8 (d, $^{3}J_{CF}$ = 8.6 Hz, Ar-CFCH*C*HC), 129.8 (s, Ph-*C*H), 128.6 (s, Ph-*C*H), 127.2 (d, $^{6}J_{CF}$ = 1.2 Hz, *C*HC(O)H), 115.9 (d, $^{2}J_{CF}$ = 21.8 Hz, Ar-CF*C*HCHC) ppm.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ = –109.9 (s, Ar-C*F*) ppm.

MS (EI, 70 eV): *m/z* (%) = 227 (11), 226 (73), 225 (100), 197 (29), 196 (41), 183 (17), 177 (14), 176 (14), 170 (11), 120 (30), 102 (28), 75 (12), 51 (17).

HRMS (ESI-MS) calc. (*m*/*z*) for $C_{15}H_{12}FO$: 227.0867 [M+H^+]; found: 227.0865.

R_f = 0.25 (SiO_2, Pent/EtOAc = 10:1).



(*Z*)-3-(4-Fluorophenyl)-3-phenylacrylaldehyde ((*Z*)-64d)

According to general procedure 5, the title compound **64d** was afforded upon oxidation of (*Z*)-3-(4-fluorophenyl)-3-phenylprop-2-en-1-ol ((*Z*)-**79d**) as a slightly yellow oil (76%).

$C_{15}H_{11}FO$ (226.08 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.53 (d, $^3J_{HH}$ = 8.0 Hz, 1H, CHC(O)*H*), 7.48-7.28 (m, 7H, Ar-C*H*), 7.18-7.13 (m, 2H, Ar-C*H*), 7.09-7.05 (m, 2H, Ar-C*H*), 6.59 (d, $^3J_{HH}$ = 8.0 Hz, 1H, C*H*C(O)H) ppm.

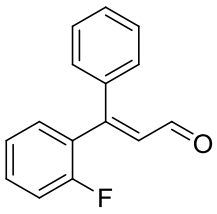
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 193.2 (s, CH*C*(O)H), 163.6 (d, $^1J_{CF}$ = 250.0 Hz, Ar-*C*F), 161.2 (s, Ph*C*CH), 139.8 (s, Ar-*C*), 132.8 (s, Ar-*C*), 132.8 (d, $^3J_{CF}$ = 8.6 Hz, Ar-CFCH*C*HC), 130.8 (s, Ph-*C*H), 128.8 (s, Ph-*C*H), 127.7 (s, Ar-*C*H), 115.7 (d, $^2J_{CF}$ = 21.6 Hz, Ar-CF*C*HCHC) ppm.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ = –111.0 (s, Ar-C*F*) ppm.

MS (EI, 70 eV): *m/z* (%) = 227 (11), 226 (78), 225 (100), 197 (27), 196 (40), 183 (16), 177 (10), 176 (12), 170 (10), 120 (26), 102 (25), 51 (11).

HRMS (ESI-MS) calc. (*m*/*z*) for $C_{15}H_{12}FO$: 227.0867 [M+H$^+$]; found: 227.0864.

R$_f$ = 0.33 (SiO_2, Pent/EtOAc = 10:1).



(*E*)-3-(2-Fluorophenyl)-3-phenylacrylaldehyde ((*E*)-64e)

According to general procedure 5, the title compound **64e** was afforded upon oxidation of (*E*)-3-(2-fluorophenyl)-3-phenylprop-2-en-1-ol ((*E*)-**79e**) as a slightly yellow oil (89%).

$C_{15}H_{11}FO$ (226.08 g mol^{-1})

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.62 (d, $^3J_{HH}$ = 7.9 Hz, 1H, CHC(O)*H*), 7.48-7.37 (m, 4H, Ar-C*H*), 7.32-7.29 (m, 2H, Ar-C*H*), 7.17-7.10 (m, 3H, Ar-C*H*), 6.56 (dd, $^3J_{HH}$ = 7.9 Hz, $^5J_{HF}$ = 1.1 Hz, 1H, C*H*C(O)H) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 193.4 (s, CH*C*(O)H), 160.5 (d, $^1J_{CF}$ = 253.0 Hz, Ar-*C*F), 156.7 (s, Ph*C*CH), 137.0 (s, Ph-*C*), 131.7 (d, J_{CF} = 8.6 Hz, Ar-*C*H), 131.7 (d, J_{CF} = 2.1 Hz, Ar-*C*H), 131.0 (d, J_{CF} = 5.7 Hz, Ar-*C*H), 130.4 (s, Ph-*C*H), 129.7 (s, Ph-*C*H), 128.5

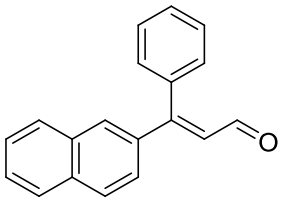
(s, Ph-*C*H), 128.2 (s, Ph-*C*), 124.4 (d, $^{4}J_{CF}$ = 3.6 Hz, *C*HC(O)H), 116.6 (d, $^{2}J_{CF}$ = 22.6 Hz, Ar-CF*C*H) ppm.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ = –111.6 (s, Ar-C*F*) ppm.

MS (EI, 70 eV): *m/z* (%) = 227 (13), 226 (85), 225 (100), 197 (30), 196 (36), 183 (15), 178 (12), 177 (17), 176 (21), 170 (10), 120 (33), 102 (30), 77 812), 76 (10), 75 (12), 51 (20), 50 (10).

HRMS (ESI-MS) calc. (*m*/*z*) for $C_{15}H_{12}FO$: 227.0867 [M+H$^+$]; found: 227.0864.

R$_f$ = 0.35 (SiO_2, Pent/EtOAc = 10:1).



(*E*)-3-(Naphthalen-2-yl)-3-phenylacrylaldehyde ((*E*)-64f)

According to general procedure 5, the title compound **64f** was afforded upon oxidation of (*E*)-3-(naphthalen-2-yl)-3-phenylprop-2-en-1-ol ((*E*)-**79f**) as a slightly yellow solid (81%).

$C_{19}H_{14}O$ (258.31 g mol^{-1})

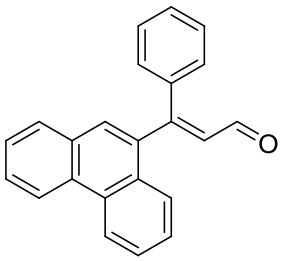
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.57 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H, CHC(O)*H*), 7.85 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H, Ar-C*H*), 7.79 (d, $^{3}J_{HH}$ = 8.5 Hz, 1H, Ar-C*H*),, 7.75 (s, 1H, Ar-C*H*), 7.56-7.47 (m, 6H, Ar-C*H*), 7.39-7.36 (m, 2H, Ar-C*H*), 6.74 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H, C*H*C(O)H) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 193.7 (s, CH*C*(O)H), 162.3 (s, Ph*C*CH), 137.2 (s, Ar-*C*), 126.9 (s, Ar-*C*), 134.4 (s, Ar-*C*), 133.1 (s, Ar-*C*), 131.0 (s, Ar-*C*H), 129.8 (s, Ar-*C*H), 129.7 (s, Ar-*C*H), 129.0 (s, Ar-*C*H), 128.6 (s, Ar-*C*H), 127.8 (s, Ar-*C*H), 127.8 (s, Ar-*C*H), 127.7 (s, Ar-*C*H), 126.9 (s, Ar-*C*H), 125.2 (s, *C*HC(O)H) ppm.

MS (EI, 70 eV): *m/z* (%) = 259 (19), 258 (100), 257 (79), 230 (16), 229 (56), 228 (44), 227 (20), 226 (32), 215 (18), 202 (15), 181 (28), 152 (30), 151 (12), 128 (34), 127 (10), 114 (11), 113 (11), 102 (32), 101 (13), 77 (11).

HRMS (ESI-MS) calc. (*m*/*z*) for $C_{19}H_{15}O$: 259.1117 [M+H$^+$]; found: 259.1114.

R$_f$ = 0.51 (SiO_2, Pent/EtOAc = 5:1).



(*E*)-3-(Phenanthren-9-yl)-3-phenylacrylaldehyde ((*E*)-64g)

According to general procedure 5, the title compound **64g** was afforded upon oxidation of (*E*)-3-(phenanthren-9-yl)-3-phenylprop-2-en-1-ol ((*E*)-**79g**) as a slightly yellow solid (98%).

$C_{23}H_{16}O$ (308.37 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.93 (d, $^3J_{HH}$ = 8.0 Hz, 1H, CHC(O)*H*), 8.71 (dd, J_{HH} = 11.7 Hz, J_{HH} = 8.4 Hz, 2H, Ar-C*H*), 7.91 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar-C*H*), 7.84 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Ar-C*H*), 7.74-7.70 (m, 2H, Ar-C*H*), 7.66-7.61 (m, 2H, Ar-C*H*), 7.49-7.37 (m, 6H, Ar-C*H*), 6.57 (d, $^3J_{HH}$ = 8.0 Hz, 1H, C*H*C(O)H) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 193.5 (s, CH*C*(O)H), 162.2 (s, Ph*C*CH), 137.8 (s, Ar-*C*), 137.7 (s, Ar-*C*), 131.3 (s, Ar-*C*H), 131.0 (s, Ar-*C*), 130.9 (s, Ar-*C*), 130.5 (s, Ar-*C*H), 130.1 (s, Ar-*C*H), 129.9 (s, Ar-*C*), 129.3 (s, Ar-*C*H), 128.8 (s, Ar-*C*H), 128.7 (s, Ar-*C*H), 127.8 (s, Ar-*C*H), 127.3 (s, Ar-*C*H), 127.0 (s, Ar-*C*H), 127.0 (s, Ar-*C*H), 126.8 (s, Ar-*C*H), 123.2 (s, Ar-*C*H), 122.8 (s, *C*HC(O)H) ppm.

MS (EI, 70 eV): *m/z* (%) = 309 (23), 308 (100), 307 (66), 291 (23), 289 (12), 280 (21), 279 (79), 278 (26), 277 (28), 276 (36), 252 (10), 232 (10), 231 (56), 203 (11), 202 (35), 201 (15), 200 (15), 178 (26), 176 (10), 138 (13), 102 (20).

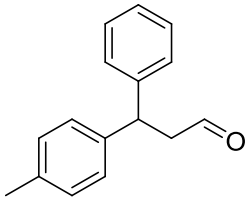
HRMS (ESI-MS) calc. (*m*/*z*) for $C_{23}H_{17}O$: 309.1274 [M+H$^+$]; found: 309.1267.

R$_f$ = 0.51 (SiO_2, Pent/EtOAc = 5:1).

7.6.3 Organocatalyzed Transfer Hydrogenation

General procedure 6: To a solution of acrylaldehyde (**64**) (1.00 eq.), Hantzsch-ester (**66**) (1.20 eq.) and organocatalyst (20 mol%) in $CHCl_3$ (0.2 M) was added TFA (4 mol%) at –20 °C. The conversion was followed by GC-MS analysis of an aliquot of the reaction mixture. After full conversion or conversion being constant, the solvent was removed under reduced pressure and the residue purified by column chromatography (SiO_2, 2 × 20 cm, eluent as listed for the R$_f$ -value). The enantiomeric excess of 3,3-diaryl aldehydes was determined by chiral HPLC analysis of the corresponding alcohol. Therefore the aldehyde was dissolved in MeOH (0.1 M) and the solution was cooled to 0 °C. Afterwards $NaBH_4$ (5.00 eq.) was added and the mixture stirred for 1 h before it was quenched with sat. aq. NH_4Cl-solution. After extraction with EtOAc, drying over $MgSO_4$ and removal of the solvent under reduced

pressure, the residue was diluted in *i*-PrOH and analyzed by chiral stationary phase HPLC. Racemic reference samples were obtained by hydrogenation (1 bar) of the corresponding allylic alcohol **78** upon use of Pd on charcoal in EtOAc.



3-Phenyl-3-(*p*-tolyl)propanal (69a)

According to general procedure 6, the title compound **69a** was obtained upon reduction of (*E*)-3-phenyl-3-(*p*-tolyl)acrylaldehyde ((*E*)-**64a**) (76%). The analytical data match the literature values.[147]

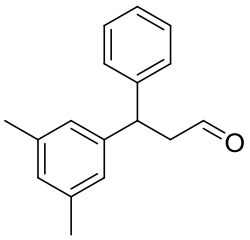
$C_{16}H_{16}O$ (224.30 g mol^{-1})

MS (EI, 70 eV): *m/z* (%) = 224 (48), 209 (29), 206 (51), 191 (15), 182 (20), 181 (92), 180 (10), 179 (24), 178 (31), 167 (16), 166 (63), 165 (97), 153 (10), 152 (20), 128 (12), 119 (19), 118 (11), 117 (20), 115 (48), 105 (29), 194 (18), 103 (29), 102 (22), 92 (12), 91 (70), 90 (10), 89 (35), 79 815), 78 (49), 77 (84), 76 (24), 75 (15), 74 (12), 65 (56), 64 (12), 63 (58), 62 (14), 53 (12), 52 (21), 51 (100), 50 (51), 44 (11), 42 (29), 41 (21).

GC (Macherey-Nagel Optima 5 PhMeSi (25 m × 0.2 mm × 0.35 µm), 140 kPa He, (100 °C, 2 min, 10 K/min, 270 °C, 10 min)): t_R = 15.5 min (**69a**), 16.9 min ((*E*)-**64a**).

HPLC of the corresponding alcohol (Daicel Chiracel AD-H, Hept/*i*-PrOH = 95:5, 0.5 mL/min, 20 °C): t_R = 27.2 min ((–)-**80a**), 29.8 min ((+)-**80a**).

R$_f$ = 0.45 (SiO_2, Pent/Et_2O = 10:1).



3-(3,5-Dimethylphenyl)-3-phenylpropanal (69b)

According to general procedure 6, the title compound **69b** was obtained upon reduction of (*E*)-3-(3,5-dimethylphenyl)-3-phenylacrylaldehyde ((*E*)-**64b**) (46%). The analytical data match the literature values.[101]

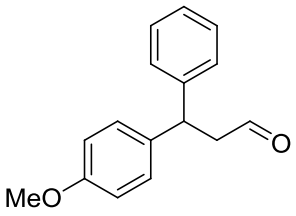
$C_{17}H_{18}O$ (238.32 g mol^{-1})

MS (EI, 70 eV): *m/z* (%) = 239 (18), 238 (100), 223 (19), 220 (21), 196 (23), 195 (74), 181 (25), 180 (45), 179 (30), 178 (33), 166 (13), 165 (64), 133 (12), 119 (30), 115 (15), 106 (11), 104 (16), 103 (27), 91 (19), 89 (11), 77 (19).

GC (Macherey-Nagel Optima 5 PhMeSi (15 m × 0.2 mm × 0.35 µm), 140 kPa He, (100 °C, 2 min, 10 K/min, 270 °C, 10 min)): t_R = 11.2 min (**69b**), 12.3 min ((*E*)-**64b**).

HPLC of the corresponding alcohol (Daicel Chiracel AS, Hept/*i*-PrOH = 98:2, 0.5 mL/min, 20 °C): t_R = 35.9 min ((*R*)- **80b**), 43.3 min ((*S*)- **80b**).

R$_f$ = 0.49 (SiO_2, Pent/EtOAc = 3:1).



3-(4-Methoxyphenyl)-3-phenylpropanal (69c)

According to general procedure 6, the title compound **69c** was obtained upon reduction of (*E*)-3-(4-methoxyphenyl)-3-phenylacrylaldehyde ((*E*)-**64c**). The analytical data match the literature values.[101] This time the aldehyde was reduced to the alcohol prior to purification by column chromatography. The alcohol was isolated in 52% yield.

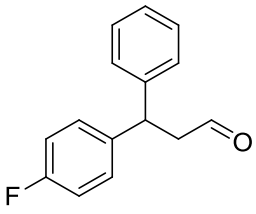
$C_{16}H_{16}O_2$ (240.30 g mol^{-1})

MS (EI, 70 eV): *m/z* (%) = 240 (33), 198 (16), 197 (100), 166 (10), 165 824), 154 (11), 153 (21), 152 (16), 77 (12).

GC (Macherey-Nagel Optima 5 PhMeSi (25 m × 0.2 mm × 0.35 µm), 140 kPa He, (100 °C, 2 min, 10 K/min, 270 °C, 10 min)): t_R = 17.1 min (**69c**), 18.5 min ((*E*)-**64c**).

HPLC of the corresponding alcohol (Daicel Chiracel AD-H, Hept/*i*-PrOH = 90:10, 1.0 mL/min, 20 °C): t_R = 12.8 min ((*R*)-**80c**), 14.4 min ((*S*)-**80c**).

R$_f$ of the corresponding alcohol = 0.33 (SiO_2, Pent/EtOAc = 2:1).



3-(4-Fluorophenyl)-3-phenylpropanal (69d)

According to general procedure 6, the title compound **69d** was obtained upon reduction of (*E*)- or (*Z*)-3-(4-fluorophenyl)-3-phenylacrylaldehyde (**64d**) (84% for the reduction of (*E*)-**64d**, 75% for the reduction of (*Z*)-**64d**). The analytical data match the literature values.[101]

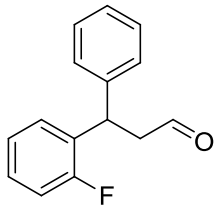
$C_{15}H_{13}FO$ (228.26 g mol^{-1})

MS (EI, 70 eV): *m/z* (%) = 228 (61), 210 (30), 186 (24), 185 (100), 183 (59), 170 (15), 165 (67), 121 (139, 105 (28), 104 (10), 103 (14), 101 (10), 91 (10), 77 (17), 75 (10), 63 (12), 51 (25), 50 (11).

GC (Macherey-Nagel Optima 5 PhMeSi (25 m × 0.2 mm × 0.35 µm), 140 kPa He, (100 °C, 2 min, 10 K/min, 270 °C, 10 min)): 14.2 min (**69d**), 15.3 min ((*E*)-**64d**), t_R = 15.4 min ((*Z*)-**64d**).

HPLC of the corresponding alcohol (Daicel Chiracel OD-H, Hept/*i*-PrOH = 95:5, 0.5 mL/min, 40 °C): t_R = 32.7 min ((*R*)- **80d**), 37.2 min ((*S*)- **80d**).

R$_f$ = 0.21 (SiO_2, Pent/Et_2O = 5:1).



3-(2-Fluorophenyl)-3-phenylpropanal (69e)

According to general procedure 6, the title compound **69e** was obtained upon reduction of (*E*)-3-(2-fluorophenyl)-3-phenylacrylaldehyde ((*E*)-**64e**) (71%).

$C_{15}H_{13}FO$ (228.26 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.74 (t, $^3J_{HH}$ = 1.7 Hz, 1H, C(O)*H*), 7.38-7.37 (m, 1H, Ar-C*H*), 7.32-7.25 (m, 4H, Ar-C*H*), 7.23-7.17 (m, 2H, Ar-C*H*), 7.10-6.99 (m, 2H, Ar-C*H*), 4.92 (t, $^3J_{HH}$ = 7.8 Hz, 1H, PhC*H*CH_2), 3.19 (td, $^3J_{HH}$ = 7.8 Hz. $^3J_{HH}$ = 1.7 Hz, 2H, CHC*H*$_2$C(O)H) ppm.

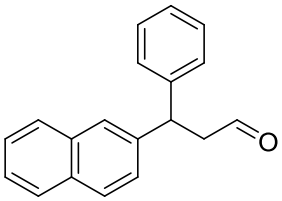
^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ = −116.9 (s, Ar-C*F*) ppm.

MS (EI, 70 eV): *m/z* (%) = 229 (10), 228 (62), 210 (31), 186 (26), 185 (100), 184 (17), 183 (59), 170 (16), 165 (59), 133 (10), 123 (11), 122 (17), 121 (20), 109 (12), 105 (44), 104 (11), 103 (15), 101 (15), 91 (19), 77 (22), 75 (10), 51 (14).

GC (Macherey-Nagel Optima 5 Me_2Si (15 m × 0.2 mm × 0.35 µm), 140 kPa He, (100 °C, 2 min, 5 K/min, 270 °C, 10 min)): t_R = 21.5 min (**69e**), 23.3 min ((*E*)-**64e**).

HPLC of the corresponding alcohol (Daicel Chiracel OD-H, Hept/*i*-PrOH = 97:3, 0.5 mL/min, 40 °C): t_R = 46.9 min ((+)-**80e**), 52.6 min ((−)-**80e**).

R$_f$ = 0.33 (SiO_2, Pent/EtOAc = 5:1).



3-(Naphthalen-2-yl)-3-phenylpropanal (69f)

According to general procedure 6, the title compound **69f** was obtained upon reduction of (*E*)-3-(naphthalen-2-yl)-3-phenylacrylaldehyde ((*E*)-**64f**) (66%). The analytical data match the literature values.[101]

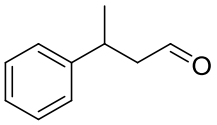
$C_{19}H_{16}O$ (260.33 g mol^{-1})

MS (EI, 70 eV): *m/z* (%) = 261 (10), 260 (50), 242 (15), 218 (34), 217 (100), 216 (22), 215 (56), 203 (11), 202 (48), 153 (10), 152 (11), 128 (14), 108 (11), 107 (11), 103 (11), 77 (10).

GC (Macherey-Nagel Optima 5 Me_2Si (15 m × 0.2 mm × 0.35 µm), 140 kPa He, (100 °C, 2 min, 10 K/min, 270 °C, 10 min)): t_R = 14.8 min (**69f**), 16.1 min ((*E*)-**64f**).

HPLC of the corresponding alcohol (Daicel Chiracel AD-H, Hept/*i*-PrOH = 90:10, 0.3 mL/min, 20 °C): t_R = 37.1 min ((*R*)-**80f**), 40.4 min ((*S*)-**80f**).

R$_f$ = 0.40 (SiO_2, Pent/Et_2O = 2:1).



3-Phenylbutanal (69h)

According to general procedure 6, the title compound **69h** was obtained upon reduction of (*E*)-3-phenylbut-2-enal ((*E*)-**64h**) (68%). The analytical data match the literature values.[147]

$C_{10}H_{12}O$ (148.20 g mol^{-1})

MS (EI, 70 eV): *m/z* (%) = 148 (32), 133 (30), 130 (15), 115 (13), 106 (30), 105 (100), 104 (16), 103 (25), 91 (58), 79 (37), 78 (34), 77 (52), 65 (12), 63 (11), 55 (10), 51 (36), 41 (22).

GC (Macherey-Nagel Optima 5 PhMeSi (25 m × 0.2 mm × 0.35 µm), 140 kPa He, (100 °C, 2 min, 10 K/min, 270 °C, 10 min)): t_R = 6.7 min (**69h**), 9.3 min ((*E*)-**64h**).

GC (Chiraldex G-TA, 60 kPa, 90 °C, 30 min, 10 K/min, 160 °C, 5 min): t_R = 29.3 min ((*S*)-**69h**), 30.5 min ((*R*)-**69h**).

R$_f$ = 0.24 (SiO_2, Pent/Et_2O = 5:1).

7.7 Mechanistic Investigations on the Organo-Catalyzed Conjugate Addition Reaction

7.7.1 ESI-MS Analysis of the Forward Reaction

10 μL of a 0.1 M solution of the organocatalyst **89** in the corresponding solvent was mixed with 10 μL of a 1 M solution of 3-phenylpropanal (**88a**) and 10 μL of a 1 M solution of (*E*)-(2-nitrovinyl)benzene (**91**) in the same solvent. The mixture was shaken for 1 min and then diluted with 1 mL of the corresponding solvent. This mixture was analyzed by ESI-MS under mild desolvation conditions. The spectra were acquired in the centroid mode.

7.7.2 ESI-MS Analysis of the Back Reaction

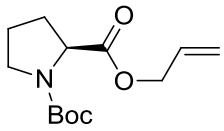
10 μL of a 0.1 M solution of the organocatalyst **89** in the corresponding solvent was mixed with 10 μL of a 1 M solution of 2-benzyl-4-nitro-3-phenylbutanal (**93a**) in the same solvent. The mixture was shaken for 1 min and then diluted with 1 mL of the corresponding solvent. This mixture was analyzed by ESI-MS under mild desolvation conditions. The spectra were acquired in the centroid mode.

7.7.3 Selectivity Determination by ESI-MS Screening of the Back Reaction

10 μL of a 0.1 M solution of the organocatalyst **89** in the corresponding solvent was mixed with 10 μL of a 1 M solution of an euqimolar mixture of (2*S*)-2-(4-methylbenzyl)-4-nitro-3-phenylbutanal ((*S*)-**93b**) and (2*R*)-2-(4-ethylbenzyl)-4-nitro-3-phenylbutanal ((*R*)-**93c**) in the same solvent. The mixture was shaken for 1 min and then diluted with 1 mL of the corresponding solvent. This mixture was analyzed by ESI-MS under mild desolvation conditions. The spectra were acquired in the centroid mode.

7.8 α-Allylation of Carbonyl Compounds by Palladium-Enamine Tandem Catalysis

7.8.1 Catalyst Synthesis



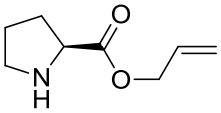
(*S*)-2-allyl 1-*tert*-butyl pyrrolidine-1,2-dicarboxylate (100)

A mixture of (*L*)-Boc proline (**99**) (4.30 g, 20.0 mmol, 1.00 eq.), allyl bromide (2.54 mL, 30.0 mmol, 1.50 eq.) and K_2CO_3 (8.28 g, 60.0 mmol, 3.00 eq.) in acetone (50 mL) was heated to reflux for 6 h. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in Et_2O (40 mL). After washing with brine (2 × 40 mL), the organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the allyl ester **100** as a slightly yellow oil (5.05 g, 99%). The analytical data match the literature values.[120c]

$C_{13}H_{21}NO_4$ (255.31 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.94-5.83 (m, 1H, OCH_2CHCH_2 rotamer 1+2), 5.33-5.28 (m, 1H, $OCH_2CHCH_{trans}H$ rotamer 1+2), 5.23-5.18 (m, 1H, OCH_2CHCHH_{cis} rotamer 1+2), 4.67-4.53 (m, 2H, OCH_2CHCH_2 rotamer 1+2), 4.32 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 2.9 Hz, 1H $NCHCO_2$allyl rotamer 1), 4.22 (dd, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 3.7 Hz, 1H, $NCHCO_2$allyl rotamer 2), 3.56-3.33 (m, 2H, $CHNCH_2$ rotamer 1+2), 2.26-2.11 (m, 1H, $NCHCHHCH_2$, rotamer 1+2), 2.00-1.78 (m, 3H, $NCHCHHCH_2$, rotamer 1+2), 1.43 (s, 9H, $C(CH_3)_3$ rotamer 1), 1.38 (s, 9H, $C(CH_3)_3$ rotamer 2) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 173.0 (s, CO_2allyl rotamer 2), 172.7 (s, CO_2allyl rotamer 1), 154.5 (s, NCO_2, rotamer 1), 153.9 (s, NCO_2, rotamer 2), 132.1 (s, allyl-OCH_2CHCH_2 rotamer 1), 131.9 (s, allyl-OCH_2CHCH_2 rotamer 2), 118.7 (s, allyl-OCH_2CHCH_2 rotamer 2), 118.2 (s, allyl-OCH_2CHCH_2 rotamer 1), 80.0 (s, $OC(CH_3)_3$ rotamer 2), 79.8 (s, $OC(CH_3)_3$ rotamer 1), 65.5 (s, allyl-OCH_2CHCH_2 rotamer 1+2), 59.2 (s, $NCHCO_2$allyl rotamer 2), 58.9 (s, $NCHCO_2$allyl rotamer 1), 46.6 (s, $CHNCH_2$ rotamer 1), 46.4 (s, $CHNCH_2$ rotamer 2), 31.0 (s, $NCHCH_2CH_2$ rotamer 2), 30.0 (s, $NCHCH_2CH_2$ rotamer 1), 28.5 (s, $C(CH_3)_3$ rotamer 1), 28.4 (s, $C(CH_3)_3$ rotamer 2), 24.4 (s, $NCHCH_2CH_2$ rotamer 1), 23.7 (s, $NCHCH_2CH_2$ rotamer 2) ppm.



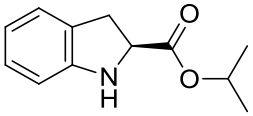
(*S*)-allyl pyrrolidine-2-carboxylate (96)

(*S*)-2-allyl 1-*tert*-butyl pyrrolidine-1,2-dicarboxylate (**100**) (2.00 g, 7.84 mmol, 1.00 eq.) was dissolved in DCM (16 mL). To this solution TFA (4 mL) was added and the mixture was stirred at room temperature for 4 h. The solvent was removed under high vacuum and the resulting brownish oil was dissolved in NaOH-solution (1 M, 60 mL). The aqueous phase was washed with DCM (5 × 30 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Drying under high vacuum afforded the title compound **96** as a slightly yellow oil (1.01 g, 83%). The analytical data match the literature values.[120c]

$C_8H_{13}NO_2$ (155.19 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.95-5.85 (m, 1H, allyl-OCH$_2$C*H*CH$_2$), 5.32-5.21 (m, 2H, allyl-OCH$_2$CHC*H*$_2$), 4.60 (d, $^3J_{HH}$ = 5.7 Hz, 2H, allyl-OC*H*$_2$CHCH$_2$), 3.77 (dd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 5.7 Hz, 1H, NC*H*CO$_2$allyl), 3.09-3.03 (m, 1H, CHNC*H*H), 2.92-2.86 (m, 1H, CHNCH*H*), 2.26 (s, 1H, N*H*), 2.17-2.08 (m, 1H, NCHC*H*HCH$_2$), 1.89-1.67 (m, 3H, NCHCH*H*C*H*$_2$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 175.3 (s, *C*O$_2$allyl), 132.1 (s, allyl-OCH$_2$*C*HCH$_2$), 118.6 (s, allyl-OCH$_2$CH*C*H$_2$), 65.6 (s, allyl-O*C*H$_2$CHCH$_2$), 59.9 (s, N*C*HCO$_2$allyl), 47.1 (s, CHN*C*H$_2$), 30.4 (s, NCH*C*H$_2$CH$_2$), 26.6 (s, NCHCH$_2$*C*H$_2$) ppm.



(*S*)-*iso*-Propyl indoline-2-carboxylate (97a)

In a flame-dried two-neck flask (*S*)-indoline-2-carboxylic acid (**101**) (500 mg, 3.07 mmol, 1.00 eq.) was dissolved in *i*-PrOH (25 mL) and the solution was cooled to −30 °C. To this, $SOCl_2$ (1.12 mL, 15.4 mmol, 5.00 eq.) was added drop wise and the reaction mixture was warmed to reflux and stirred for 2 h. After cooling to room temperature the mixture was concentrated under high vacuum and aqueous NH_3-solution was added until a pH of 9 was reached. After extraction with Et_2O (3 × 30 mL) the organic phase was washed with brine (1 × 40 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford a red oil. Purification by column chromatography (SiO_2, 3 × 20 cm, cyclohexane/EtOAc = 2:1) yielded the title compound **97a** as a colorless oil (569 mg, 90%). The analytical data match the literature values.[148]

$C_{12}H_{15}NO_2$ (205.25 g mol^{-1})

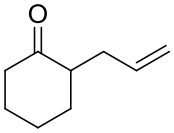
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.09-7.07 (m, 2H, Ar-C*H*), 6.76-6.71 (m, 2H, Ar-C*H*), 5.06 (sept, $^3J_{HH}$ = 6.3 Hz, 1H, OC*H*$(CH_3)_2$), 4.45 (s br, 1H, N*H*), 4.33 (dd, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 5.5 Hz, 1H, NC*H*CO_2CH), 3.39 (dd, $^2J_{HH}$ = 16.1 Hz, $^3J_{HH}$ = 10.4 Hz, 1H, NC*H*CO_2CH), 3.29 (dd, $^2J_{HH}$ = 16.1 Hz, $^3J_{HH}$ = 5.5 Hz, 1H, NC*H*CO_2CH), 1.27 (d, $^3J_{HH}$ = 6.3 Hz, 3H, OCH(C*H*$_3$)(CH_3)) 1.26 (d, $^3J_{HH}$ = 6.2 Hz, 3H, OCH(CH_3)(C*H*$_3$)) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 173.8 (s, *C*O_2CH), 150.3 (s, Ar-N*C*CH), 127.8 (s, Ar-*C*H), 126.9 (s, Ar-NC*C*CH), 124.5 (s, Ar-*C*H), 119.5 (Ar-*C*H), 110.2 (s, Ar-*C*H), 69.1 (s, O*C*H$(CH_3)_2$), 60.0 (s, N*C*HCO_2CH), 33.9 (s, NCH*C*H_2), 21.9 (s, OCH(*C*H_3)(CH_3)), 21.9 (s, OCH(CH_3)(*C*H_3)) ppm.

ESI-MS: *m/z* = 206 [M+H$^+$].

7.8.2 α-Allylation of Carbonyl Compounds

General procedure 7: In a flame-dried Young-Tube the Pd-precursor (25 µmol, 2.5 mol%) and the corresponding ligand (50 µmol, 5 mol%) were dissolved in DMSO (2 mL) and stirred at room temperature for 1 h. To this a solution of the allyl-source (1.00 mmol, 1.00 eq.), the carbonyl compound (3.00 mmol, 3.00 eq.) and the organocatalyst (300 µmol, 30 mol%) in DMSO (2 mL) was added. If the organocatalyst was bearing a carboxylic acid-function additional *p*-TsOH (50 µmol, 5 mol%) was added. After stirring at room temperature overnight, the mixture was diluted with Et_2O, washed with brine, dried over $MgSO_4$, the solvent was removed under reduced pressure and the residue was dried under high vacuum. Purification by column chromatography (SiO_2, 2 × 20 cm, eluent as listed for the R_f -value) yielded the desired α-allylated carbonyl compound.



2-Allylcyclohexanone (106a)

According to the general procedure 7, the title compound **106a** was obtained upon reaction of cyclohexanone (**104**) and allyl acetate (**105a**). The analytical data match the literature values.[122d]

$C_9H_{14}O$ (138.21 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.82-5.72 (m, 1H, allyl-CHCH_2C*H*CH_2), 5.04-4.98 (m, 2H, allyl-CHCH_2CHC*H*$_2$), 2.57-2.50 (m, 1H, alk-C*H*$_n$), 2.42-2.26 (m, 3H, alk-C*H*$_n$), 2.16-1.94 (m,

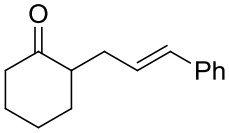
3H, alk-CH_n), 1.93-1.82 (m, 1H, alk-CH_n), 1.75-1.59 (m, 2H, alk-CH_n), 1.41-1.31 (m, 1H, alk-CH_n) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 212.7 (s, *C*(O)), 136.6 (s, allyl-CHCH$_2$*C*HCH$_2$), 116.4 (s, allyl-CHCH$_2$CH*C*H$_2$), 50.4 (s, C(O)*C*H), 42.2 (s, alk-*C*H$_2$), 33.9 (s, alk-*C*H$_2$), 33.5 (s, alk-*C*H$_2$), 28.1 (s, alk-*C*H$_2$), 25.1 (s, alk-*C*H$_2$) ppm.

MS (EI, 70 eV): *m/z* (%) = 138 (100), 137 (12), 123 (31), 110 (24), 109 (58), 95 (27), 94 (44), 40 (26).

R$_f$ = 0.38 (SiO_2, hexanes/EtOAc = 5:1).

HPLC (Daicel Chiracel OD-H, Hept/*i*-PrOH = 100:0, 0.5 mL/min, 25 °C): t_R = 19.5 min ((–)-**106a**), 10.5 min ((+)-**106a**).



2-Cinnamylcyclohexanone (106b)

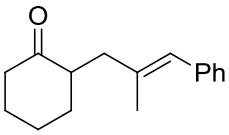
According to the general procedure 7, the title compound **106b** was obtained upon reaction of cyclohexanone (**104**) and 3-phenyl-allyl acetate or 1-phenyl-allyl acetate (**105b** or **105c**). The analytical data match the literature values.[122d]

$C_{15}H_{18}O$ (214.30 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34-7.26 (m, 4H, Ar-C*H*), 7.21-7.17 (m, 1H, Ar-C*H*), 6.39 (d, $^3J_{HH}$ = 15.8 Hz, 1H, PhC*H*CH), 6.24-6.16 (m, 1H, PhCHC*H*), 2.71-2.64 (m, 1H, alk-CH_n), 2.46-1.36 (m, 10H, alk-CH_n) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 212.6 (s, *C*(O)), 137.6 (s, Ar-*C*), 131.7 (s, Ph*C*HCH), 128.6 (s, Ar-*C*H), 128.5 (s, Ar-*C*H), 127.1 (s, PhCH*C*H), 126.1 (s, Ar-*C*H), 50.8 (s, C(O)*C*HCH$_2$), 42.2 (s, alk-*C*H$_2$), 33.7 (s, alk-*C*H$_2$), 33.1 (s, alk-*C*H$_2$), 28.1 (s, alk-*C*H$_2$), 25.2 (s, alk-*C*H$_2$) ppm.

R$_f$ = 0.27 (SiO_2, hexanes/EtOAc = 4:1).



(*E*)-2-(2-Methyl-3-phenylallyl)cyclohexanone (106c)

According to the general procedure 7, the title compound **106c** was obtained upon reaction of cyclohexanone (**104**) and 2-methyl-3-phenyl-allyl acetate (**105d**).

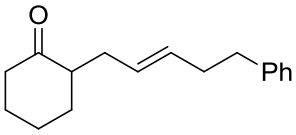
$C_{16}H_{20}O$ (228.33 g mol^{-1})

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.31 (t, $^3J_{HH}$ = 7.4 Hz, 2H, Ar-C*H*), 7.22 (d, $^3J_{HH}$ = 7.7 Hz, 2H, Ar-C*H*), 7.18 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar-C*H*), 6.26 (s, 1H, PhC*H*C), 2.74 (dd, J_{HH} = 13.9 Hz, J_{HH} = 4.2 Hz, 1H, alk-CH_n), 2.57-1.62 (m, 13H, alk-CH_n) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 212.9 (s, *C*O), 138.4 (s, Ar-*C*), 136.5 (s, PhCH*C*CH_3), 128.9 (s, Ar-*C*H), 128.1 (s, Ar-*C*H), 127.1 (s, Ar-*C*H), 126.1 (s, Ph*C*HC), 48.7 (s, C(O)*C*HCH_2), 42.1 (s, alk-*C*H_2), 40.4 (s, alk-*C*H_2), 33.2 (s, alk-*C*H_2), 28.1 (s, alk-*C*H_2), 27.1 (s, alk-*C*H_2), 24.9 (s, PhCHC*C*H_3) ppm.

R_f = 0.37 (SiO_2, hexanes/EtOAc = 5:1).

HPLC (Daicel Chiracel IC, Hept/*i*-PrOH = 99:1, 0.5 mL/min, 20 °C): t_R = 26.8 min ((–)-**106c**), 29.9 min ((+)-**106c**).



(*E*)-2-(5-Phenylpent-2-en-1-yl)cyclohexanone (106d)

According to the general procedure 7, the title compound **106d** was obtained upon reaction of cyclohexanone (**104**) and 5-phenylpent-1-en-3-yl acetate (**105e**).

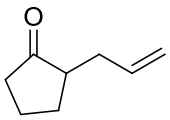
$C_{17}H_{22}O$ (242.36 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28-7.15 (m, 5H, Ar-C*H*), 5.52-5.31 (m, 2H, DB-C*H*C*H*), 2.68-1.24 (m, 15H, alk-CH_n) ppm.

MS (EI, 70 eV): *m/z* (%) = 242 (11), 151 (23), 133 (18), 106 (11), 105 (10), 98 (21), 91 (100), 85 (20), 81 (23), 79 (24), 67 (43), 65 (28), 56 (29), 43 (14), 41 (51).

R_f = 0.43 (SiO_2, hexanes/EtOAc = 3:1).

HPLC (Daicel Chiracel IC, Hept/*i*-PrOH = 99:1, 0.5 mL/min, 25 °C): t_R = 26.4 min ((–)-**106d**), 27.8 min ((+)-**106d**).



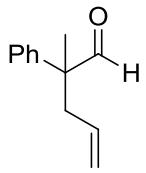
2-Allylcyclopentanone (120)

According to the general procedure 7, the title compound **120** was obtained upon reaction of cyclopentanone (**119**) and allyl acetate (**105a**). The analytical data match the literature values.[149]

$C_8H_{12}O$ (124.18 g mol^{-1})

MS (*m/z* (%)): 124 (21), 96 (41), 95 (26), 81 (25), 80 (18), 79 (20), 68 (61), 67 (100), 56 (10), 55 (59), 54 (4), 53 (42), 51 (10), 42 (20), 41 (62).

$\mathbf{R}_f$ = 0.43 (SiO_2, hexanes/EtOAc = 5:1).



2-Methyl-2-phenylpent-4-enal (133)

According to the general procedure 7, the title compound **133** was obtained upon reaction of 2-phenylpropanal (**132**) and allyl acetate (**105a**). The analytical data match the literature values.[120c]

$C_{12}H_{14}O$ (174.24 g mol^{-1})

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.52 (s, 1H, C(O)*H*), 7.40-7.36 (m, 2H, Ar-C*H*), 7.31-7.24 (m, 3H, Ar-C*H*), 5.54 (ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 7.3 Hz, 1H, DB-C*H*CH_2), 5.08-5.02 (m, 2H, DB-CHC*H*$_2$), 2.72-2.60 (m, 2H, PhCC*H*$_2$CHCH_2), 1.44 (s, 3H, C*H*$_3$) ppm.

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 202.1 (s, *C*(O)H), 139.6 (s, Ar-*C*), 133.3 (s, PhCCH$_2$*C*HCH_2), 129.0 (s, Ar-*C*H), 127.5 (s, Ar-*C*H), 127.3 (s, Ar-*C*H), 118.7 (s, PhCCH$_2$CHCH_2), 53.7 (s, Ph*C*C(O)H), 40.7 (s, PhC*C*H$_2$), 19.0 (s, PhC*C*H$_3$) ppm.

$\mathbf{R}_f$ = 0.37 (SiO_2, cyclohexane/EtOAc = 20:1).

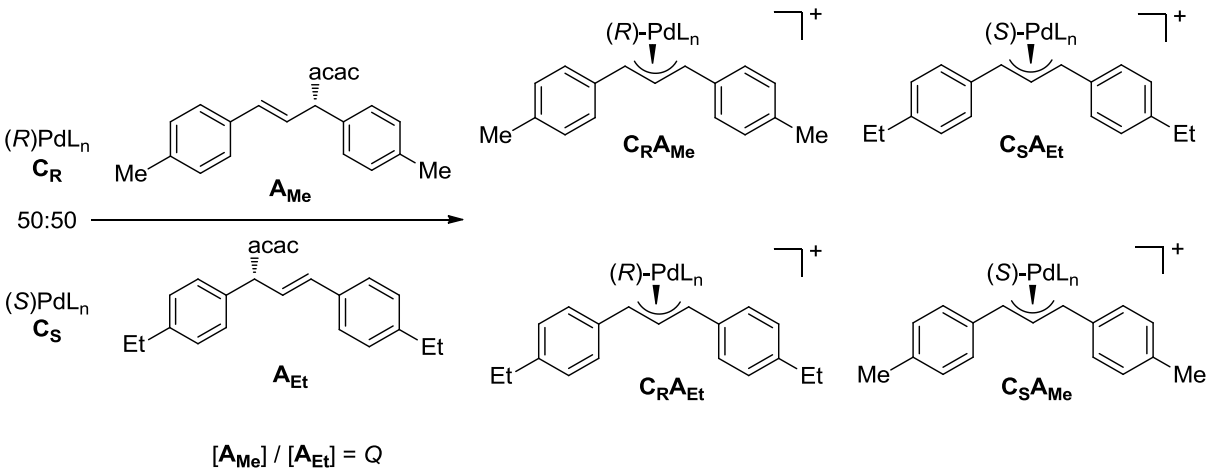
HPLC (Daicel Chiracel AD-H, Hept/*i*-PrOH = 99:1, 0.5 mL/min, 20 °C): t_R = 10.9 min ((–)-**133**), 12.0 min ((+)-**133**).

Chapter 8

Appendix

8.1 Derivation of the Formula for Selectivity Calculation for the ESI-MS Screening of Racemic Catalyst Mixtures

When catalysts $\mathbf{C_R}$ and $\mathbf{C_S}$ react with $\mathbf{A_{Me}}$ and $\mathbf{A_{Et}}$, $\mathbf{C_RA_{Me}}$, $\mathbf{C_RA_{Et}}$, $\mathbf{C_SA_{Me}}$ and $\mathbf{C_SA_{Et}}$ can be formed (see scheme below).



If $\mathbf{C_R}$ and $\mathbf{C_S}$ react with perfect selectivity, only the intermediates $\mathbf{C_RA_{Me}}$ and $\mathbf{C_SA_{Et}}$ are formed. A real catalyst will form $\mathbf{C_RA_{Et}}$ and $\mathbf{C_SA_{Me}}$ as well. In an ESI-MS screening, $\mathbf{C_RA_{Me}}$ and $\mathbf{C_SA_{Me}}$ show one signal as they have the same molecular mass. The same holds for $\mathbf{C_SA_{Et}}$ and $\mathbf{C_RA_{Et}}$. The quasienantiomeric substrates are present as a scalemic mixture with the ratio Q.

The rate of formation of the intermediates $\mathbf{C_RA_{Me}}$ and $\mathbf{C_RA_{Et}}$ is:

$$v_{R,Me} = \frac{d[C_R A_{Me}]}{dt} = [A_{Me}] \cdot [C_R] \cdot k_{R,Me} \qquad (\boldsymbol{1}) \qquad \text{and}$$

$$v_{R,Et} = \frac{d[C_R A_{Et}]}{dt} = [A_{Et}] \cdot [C_R] \cdot k_{R,Et} \qquad (\boldsymbol{2})$$

$k_{R,Me}$ and $k_{R,Et}$: rate constant for the reaction of $\mathbf{C_R}$ with $\mathbf{A_{Me}}$ and $\mathbf{A_{Et}}$. As $\mathbf{A_{Me}}$ and $\mathbf{A_{Et}}$ are quasienantiomers: $k_{R,Me} = k_{S,Et}$, $k_{R,Et} = k_{S,Me}$.

Under pseudo zero-order conditions (saturation conditions; large excess of substrate), $[\mathbf{A_{Me}}]$ and $[\mathbf{A_{Et}}]$ remain virtually constant during the first few turnovers and the ratio Q does not change. As the rates of nucleophilic addition to the four allyl intermediates are identical, their ratios only depend on the relative rates of formation. Thus:

$$\frac{[C_R A_{Me}]}{[C_R A_{Et}]} = \frac{v_{R,Me}}{v_{R,Et}} = \frac{k_{R,Me} \cdot [A_{Me}]}{k_{R,Et} \cdot [A_{Et}]} \qquad (\boldsymbol{3})$$

From $\frac{k_{R,Me}}{k_{R,Et}} = s$ (***4***) and $\frac{[A_{Me}]}{[A_{Et}]} = Q$ (***5***) follows:

$$\frac{[C_R A_{Me}]}{[C_R A_{Et}]} = s \cdot Q \qquad (\boldsymbol{6})$$

In the same way eq. (7) is derived:

$$\frac{[C_S A_{Me}]}{[C_S A_{Et}]} = \frac{k_{S,Me} \cdot [A_{Me}]}{k_{S,Et} \cdot [A_{Et}]} = \frac{1}{s} \cdot Q \qquad (\boldsymbol{7})$$

Since the catalyst is racemic ($[\mathbf{C_R}]_{tot} = [\mathbf{C_S}]_{tot}$) eq. (8) holds under saturation conditions (the four allyl intermediates are the resting state and represent the total amounts of $\mathbf{C_R}$ and $\mathbf{C_S}$).

$$[C_R]_{tot} = [C_R A_{Me}] + [C_R A_{Et}] = [C_S A_{Me}] + [C_S A_{Et}] = [C_S]_{tot} \qquad (\boldsymbol{8})$$

From equations (6), (7) and (8) the concentration of the four allyl intermediates can be calculated.

$$[C_R A_{Me}] + [C_R A_{Et}] = [C_R A_{Me}] + \frac{1}{sQ} \cdot [C_R A_{Me}] = [C_R]_{tot} \qquad (\boldsymbol{9})$$

$$[C_R A_{Me}] \cdot \left(1 + \frac{1}{s \cdot Q}\right) = [C_R]_{tot} \qquad (\boldsymbol{10})$$

$$[C_R A_{Me}] = [C_R]_{tot} \cdot \frac{s \cdot Q}{s \cdot Q + 1} \qquad (\mathbf{11})$$

$$[C_R A_{Et}] = [C_R]_{tot} \cdot \frac{1}{s \cdot Q + 1} \qquad (\mathbf{12})$$

In the same way [$\mathbf{C_S A_{Me}}$] and [$\mathbf{C_S A_{Et}}$] are calculated:

$$[C_S A_{Me}] = [C_S]_{tot} \cdot \frac{Q}{Q+s} \qquad \textbf{(13)} \qquad \text{and} \qquad [C_S A_{Et}] = [C_S]_{tot} \cdot \frac{s}{Q+s} \qquad \textbf{(14)}$$

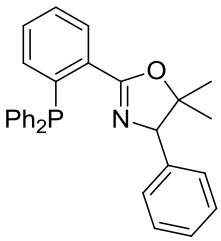
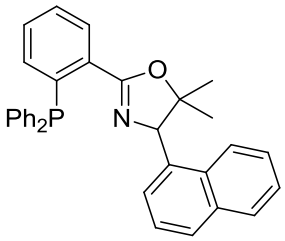
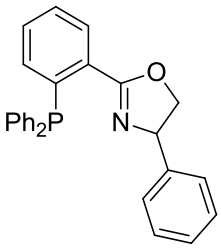
From eq. (11)-(14) the signal ratio I_{Me}/I_{Et} can be calculated:

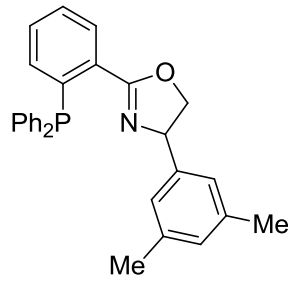
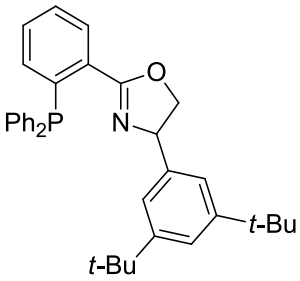
$$\frac{I_{Me}}{I_{Et}} = R = \left(\frac{s \cdot Q}{s \cdot Q+1} + \frac{Q}{Q+s}\right) : \left(\frac{1}{s \cdot Q+1} + \frac{s}{Q+s}\right) \qquad \textbf{(15)}$$

From the signal ratio the selectivity factor s can be calculated as follows:

$$s = \frac{Q^2 - R + \sqrt{(R-Q^2)^2 - (R \cdot Q - Q)^2}}{R \cdot Q - Q} \qquad \textbf{(16)}$$

8.2 Summary of Screening Results Obtained from the ESI-MS Racemate Screening

entry	Ligand	solvent	substrate ratio 8a:8b	intermediate ratio 36:37	*ee* [%]
1	 **9a**	DCM	3.30	3.18	20
2		DCM	3.30	3.17	20
3		DCM	3.02	2.92	17
4		DCM	3.02	2.83	26
5		DCM	3.00	2.85	23
				average:	21
6	 **9b**	DCM	3.30	3.28	9
7		DCM	3.25	3.24	5
8		DCM	3.42	3.42	0
9		DCM	3.06	3.05	6
				average:	5
10	 **27a**	DCM	3.15	2.27	56
11		DCM	3.16	2.27	56
				average:	56
12		Toluene	3.04	1.81	72
13		Toluene	3.09	1.72	72
				average:	72

entry	Ligand	solvent	substrate ratio 2a:2b	intermediate ratio 3a:3b	*ee* [%]
14	 **27c**	DCM	3.04	2.22	56
15	 **27d**	DCM	3.04	2.09	60.6
16		DCM	3.08	2.05	62.4
17		DCM	2.99	2.04	61.4
18		DCM	3.04	2.09	60.6
				average:	61.3

8.3 Crystallographic Data

The X-ray were measured by Dr. Markus Neuberger and Dr. Sylvia Schaffner (Department of Chemistry, university of Basel) on a Nonius KappaCCD diffractometer, solved using direct methods (SIR92[150]) and refined with Crystals.[151] Unless otherwise specified hydrogen atoms were added geometrically.

Compound	**57a**
molecular formula	$C_{30}H_{27}F_6N_2O_4P_3Pd$
molecular weight [g mol^{-1}]	792
shape	plate
color	colorless
temperature [K]	173
radiation	Mo K_α
wavelength [Å]	0.71073
crystal system	monoclinic
space group	P 2_1
crystal size [mm^3]	0.04 x 0.15 x 0.27
a [Å]	13.1637(3)
b [Å]	20.5355(5)
c [Å]	14.3590(3)
α [°]	90
β [°]	114.1870(10)
γ [°]	90
unit cell volume [Å^3]	3540.82(14)
Z	4
F(000)	1824
θ-range for data collection [°]	1.965-43.533
calculated density [g cm^{-3}]	1.711
adsorption coefficient μ [mm^{-1}]	0.958
measured reflections	62134
independent reflections	14824 (R_{int} = 0.047)
used reflections	9082
parameters refined	482
R[a]	0.0408 ($I > 3\ \sigma(I)$)
R_w[b]	0.0599
goodness-of-fit	1.1105
Flack parameter	0.003

[a]: $R = \Sigma||F_0|-|F_C||/\Sigma|F_0|$; [b]: $R_w = \{\Sigma[w(F_0-F_C)^2]/\Sigma[w(F_0)^2]\}^{1/2}$.

8.4 List of Abbreviations

Å	Ångström
Ac	acetyl
acac	acetyl acetone
anth	anthracenyl
aq	aqueous
Ar	aryl
BAr_F	tetrakis[3,5-bis(trifluoro-methyl)phenyl]borate
bipy	2,2'-bipyridine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
BSA	*N*,*O*-bis(trimethylsilyl)-acetamide
Bu	butyl
Bz	benzoyl
calc	calculated
cat	catalytic
COD	cycloocta-1,5-diene
conc.	concentrated
config	configuration
conv.	conversion
COSY	correlation spectroscopy
d	day(s)
d	doublet (NMR)
δ	chemical shift
d.r.	diastereomeric ratio
dba	dibenzylideneacetone
DCE	dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DIC	di-*iso*-propylcarbodiimide
diop	4,5-Bis(diphenylphosphanyl-methyl)-2,2-dimethyl-1,3-dioxolan
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPPF	1,1'-bis(diphenyl-phosphino)ferrocene
ee	enantiomeric excess
EI	electron-impact ionization
ent	enantiomeric
eq.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bomardement
GC	gas chromatography
gem	geminal
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
HOMO	highest occupied molecular orbital

HPLC	high performance liquid chromatography
Hz	Hertz
I	intensity
i-Pr	*iso*-propyl
J	coupling constant
k	rate constant
LUMO	lowest unoccupied molecular orbital
M	molar [$mol \cdot L^{-1}$]
M	metal
m	multiplet (NMR)
m	medium (IR)
m.p.	melting point
m/*z*	mass-to-charge ratio
MALDI	matrix assisted laser desorption ionization
MCPBA	*meta*-chlorobenzoic acid
Me	methyl
min	minute(s)
mL	milliliter
MS	mass spectrometry
MS	mole-sieves
Ms	mesyl
n.d.	not determined
naph	naphthyl
nba	norbornadiene
n-Bu	1-butyl
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
obs	observed
p	para
Pent	penatne
Ph	phenyl
PHOX	phosphino-oxazoline
ppm	parts per million
n-Pr	1-propyl
p-TsOH	*para*-toluenesulfonic acid
q	quartet
quint	quintet
rac	racemic
R_f	retention factor
ROMP	ring-opening metathesis polymerization
RT	room temperature
s	selectivity factor
s	second(s)
s	singlet (NMR)
s	strong (IR)
S/C	substrate-to-catalyst ratio
sat.	saturated
s-Bu	*sec*-butyl
sec	secondary

sept	septet
sext	sextet
SM	starting material
SOMO	single occupied molecular orbital
SPO	secondary phosphine oxide
T	temperature
t	time
t	triplet (NMR)
TBME	*tert*-butyl methyl ether
t-Bu	*tert*-butyl
TCA	trichloroacetic acid
tert	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TLC	thin layer chromatography
TMEDA	*N,N,N,N*-tetramethyl ethylenediamine
Tol	tolyl
t_R	retention time
Trt	triphenylmethyl
Ts	tosyl
w	weak

Chapter 9

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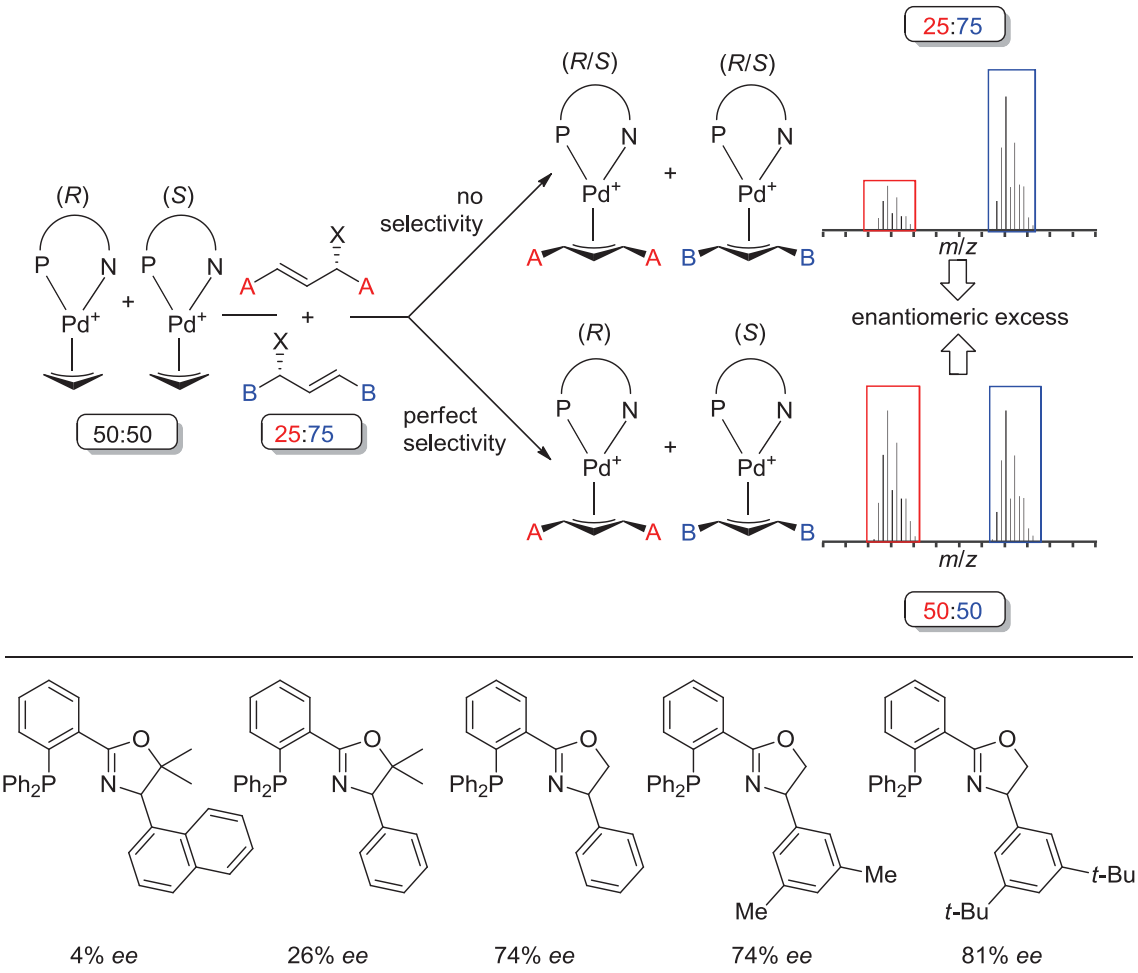
Chapter 10

Summary

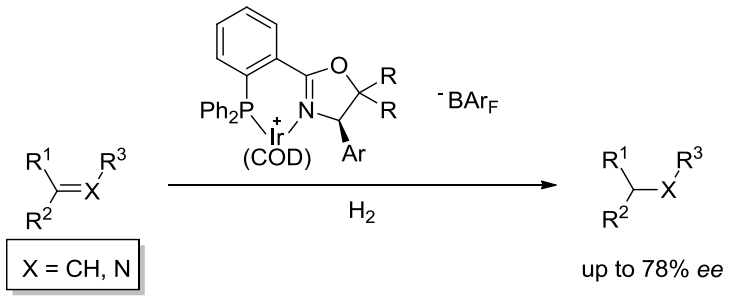
This work was dedicated to the development and evaluation of new chiral catalysts for asymmetric C-C and C-H bond forming reactions. In this context ESI-MS was used as a powerful tool for reactivity- and selectivity-studies.

In the first part an ESI-MS screening method is described, which allows the determination of the selectivity of a chiral catalyst in the palladium catalyzed asymmetric allylic alkylation by testing its racemic form. It was shown that, by reacting a racemic mixture of the with a scalemic mixture of quasi-enantiomeric mass-labeled substrates, the selectivity of the chiral catalyst can be calculated from the ratio of the formed mass-labeled reaction intermediates. The value of this new method was demonstrated when different new aryl-PHOX-type ligands, which are not easily accessible in enantiopure form, were synthesized and evaluated in the allylic alkylation reaction. In this way a more selective member of this class was found compared to the previously reported phenyl-PHOX ligand.

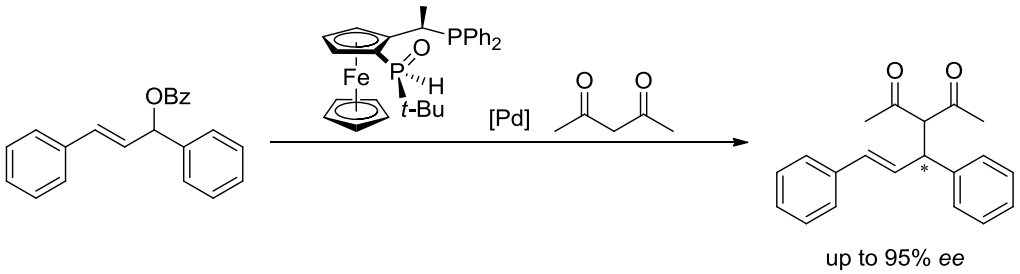


Since PHOX ligands are suitable ligands in the iridium-catalyzed asymmetric hydrogenation of C-C and C-N double bonds, the new PHOX ligands were then tested as well in the iridium-catalyzed asymmetric hydrogenation of different unsaturated compounds. Although low

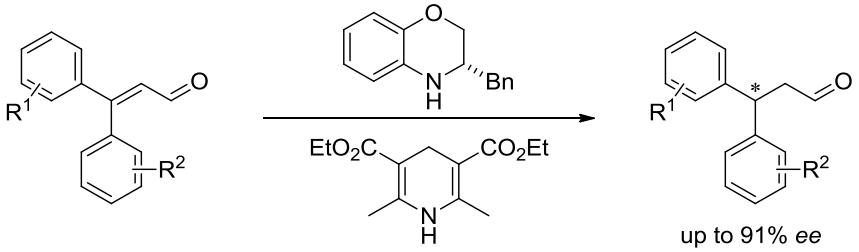
activities and selectivities were found in most cases, one ligand showed some promising results in the hydrogenation of allylic alcohols and imines.



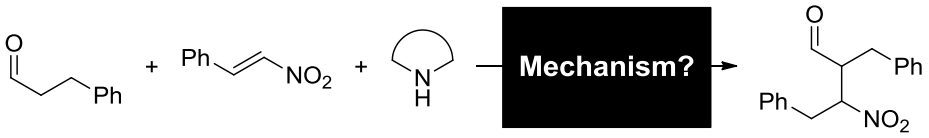
Furthermore air- and moisture-stable secondary phosphine oxide (SPO) containing bidentate ligands were tested in the palladium-catalyzed asymmetric allylic alkylation reaction. SPO,N-ligands bearing a PHOX type backbone were inactive in this transformation as they tend to form inactive palladium-bis-ligand complexes stabilized by hydrogen-bonding between the two ligands. SPO,P ligands however, were able to promote the desired reaction in a highly selective fashion although only low activities were found.



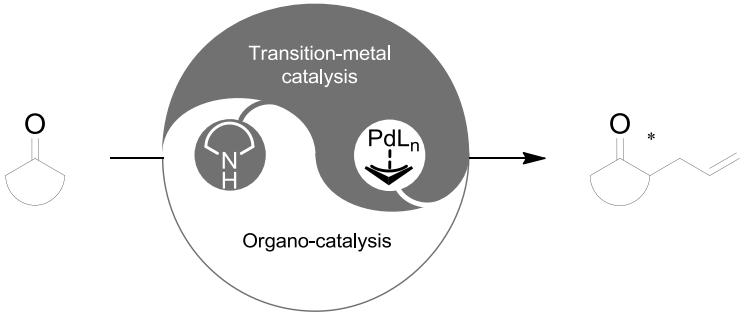
During this work as well a new organo-catalyst, based on the structure of 2,3-dihydrobenzo[1,4]oxazine, was developed which allows for the asymmetric transfer-hydrogenation of α,β-unsaturated aldehydes. Especially in the reduction of β,β-diaryl acrylaldehydes very good activities and high enantioselectivities were achieved. It was shown that for this particular substrate this catalyst outperformed the previously described ones. Thus it proved to be a useful extension to the limited known catalysts for this reaction and especially for this interesting class of products, which can act as precursors for many natural products or drugs.



Another organo-catalyzed reaction which was studied in this work was the conjugate addition reaction catalyzed by a tripeptidic organo-catalyst. As in the literature two different mechanistically pathways were hypothesized, via an enamine- or via an enol-intermediate, ESI-MS studies were carried out to clarify the actual mechanism for this transformation. All reaction intermediates which are postulated for the enamine-pathway could be found in both the forward- and the back-reaction. Furthermore the enantioselectivity of enamine-attack onto a nitroolefin was determined by an ESI-MS screening and it was shown that this enantioselectivity equals the selectivity of the preparative reaction. All of these findings strongly support the suggestion of an enamine-catalysis mechanism to be true in this reaction.



The last part of this work aimed for the asymmetric α-allylation of carbonyl compounds by a tandem-catalysis approach. An intensive screening of both the organo-catalyst and the palladium-ligand led to reaction conditions which allowed for the selective mono-allylation of ketones in high yields. The formation of a quaternary center by α-allylation of α-branched aldehydes was also achieved. However, only low enantiomeric excesses were obtained in this transformation for the different catalyst systems tested.



Curriculum Vitae

Christian Ebner

Date of Birth:	February 1, 1984
Place of Birth:	Mönchengladbach, Germany
Nationality:	German

Education

University

5/2008-4/2012	PhD work "*Development and Evaluation of Chiral Catalysts for Asymmetric C-C and C-H Bond Forming Reactions*" under the supervision of Prof. Dr. Andreas Pfaltz at the University of Basel
3/2008	Master of Science in chemistry
9/2007-3/2008	Master thesis "*Synthese und Screening racemischer Katalysatoren für die asymmetrische allylische sSubstitution*" under the supervision of Prof. Dr. Andreas Pfaltz at the University of Basel
9/2006	Bachelor of Science in chemistry
10/2003-3/2008	Studies in chemistry at the University of Basel, Switzerland

School

6/2003	Abitur, Scheffelgymnasium Bad Säckingen, Germany

Awards

1. *Swiss Chemical Society / Metrohm prize* for best oral presentation in the section "Organic Chemistry / Techniques, Properties and Mechanisms", Fall Meeting of the Swiss Chemical Society, ETH Zürich (CH), September 2010.

2. *SCS DSM prize* for the best poster in the Organic Chemistry section, Fall Meeting of the Swiss Chemical Society, EPFL Lausanne (CH), September 2011.

3. Awardee of the *Camille and Henry Dreyfus* research-grant of the University of Basel, 2012.

Presentations

Oral communications

1. *Selectivity Determination by ESI-MS Screening of Racemic Catalyst Mixtures*, Fall Meeting of the Swiss Chemical Society, ETH Zürich (CH), September 2010.

2. *Determining the Enantioselectivity of Chiral Catalysts by Mass Spectrometric Screening of Their Racemic Forms*, 5th Annual Workshop of the International Research Training Group CCROS (Catalysts and Catalytic Reactions for Organic Synthesis), University of Freiburg (D), April 2011.

Poster presentations

1. *Evaluation of SPO,N-Ligands in the Pd-Catalyzed Allylic Substitution by ESI-MS Studies*, Fall Meeting of the Swiss Chemical Society, EPFL Lausanne (CH), September 2009.

2. Selectivity Determination by ESI-MS Screening of Racemic Catalyst Mixtures, 3rd EuCheMS Chemistry Congress, Nürnberg (D), August 2010.

3. *Selectivity Determination by ESI-MS Screening of Racemic Catalyst Mixtures*, 30th Regio Symposium of the Cross-Border University Study Programs of the Universities of Basel (CH), Freiburg i.Br. (D) and Mulhouse (F), Mittelwihr (F), September 2010.

4. *Organo-Catalyzed Asymmetric Transfer-Hydrogenation of α,β-Unsaturated Aldehydes*, 17th European Symposium on Organic Chemistry, Crete (GR), July 2011.

5. *Organo-Catalyzed Asymmetric Transfer-Hydrogenation of α,β-Unsaturated Aldehydes*, Heidelberg Forum of Molecular Catalysis, Heidelberg (D), July 2011.

6. *Organo-Catalyzed Asymmetric Transfer-Hydrogenation of α,β-Unsaturated Aldehydes,* Fall Meeting of the Swiss Chemical Society, EPFL Lausanne (CH), September 2011.

Teaching Experience

9/2009-12/2010	Laboratory teaching assistant, Department of Chemistry, University of Basel, supervision of pharmacy students in basic organic chemistry and chemistry students in basic and in advanced organic chemistry

During my education at the University of Basel I attended lectures given by:

E. C. Constable, K. M. Fromm, B. Giese, P. C. Hauser, C. E. Housecroft, J. P. Maier, W. P. Maier, M. Mayor, M. Meuwly, M. Oehme, A. Pfaltz, U. Séquin, H. Wegner, H. Wennemers, H.-J. Wirz, W.-D. Woggon.