Mass Spectrometric Screening of Chiral Catalysts by Monitoring the Back Reaction: Palladium-Catalysed Allylic Substitution

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für Axel und meine Eltern

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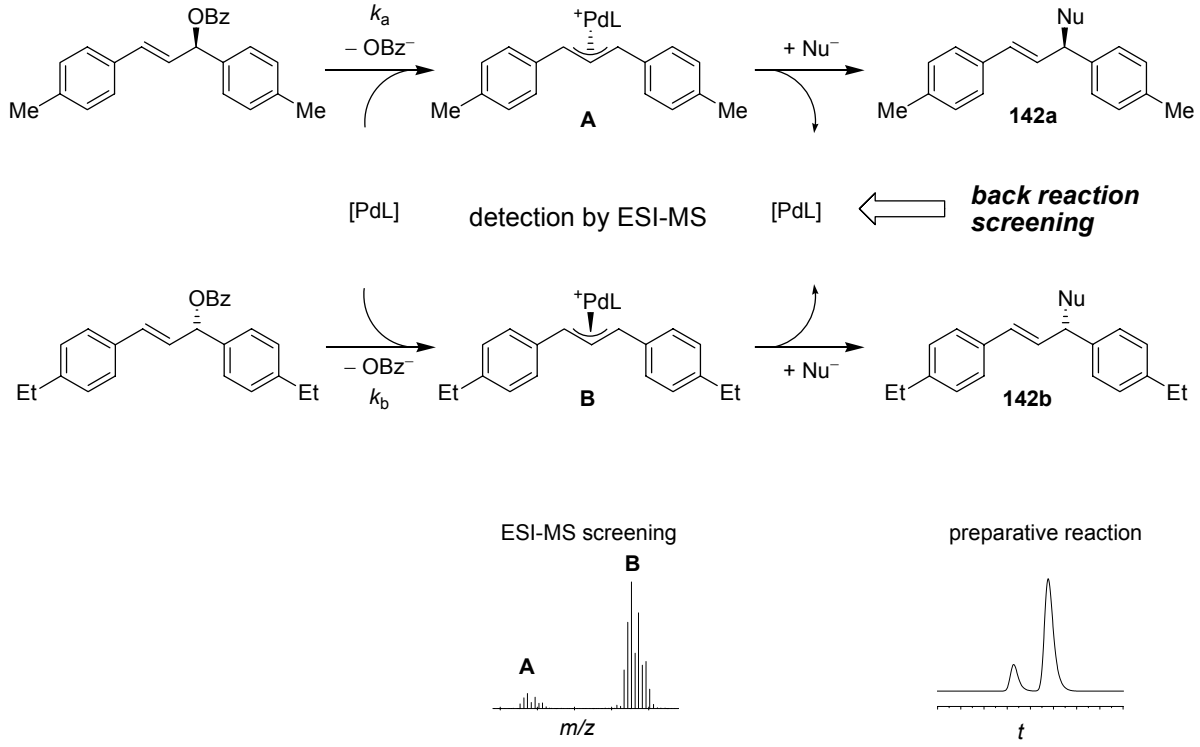
Summary

The principle of microscopic reversibility serves as the basis of a novel screening method for the evaluation of chiral catalysts within asymmetric allylic substitution reactions. Monitoring the back reaction of quasienantiomeric products **142a** and **142b** by electrospray ionisation mass spectrometry (ESI-MS) reveals the intrinsic enantioselectivity of palladium catalysts in the nucleophilic addition step and thus in the overall substitution process.

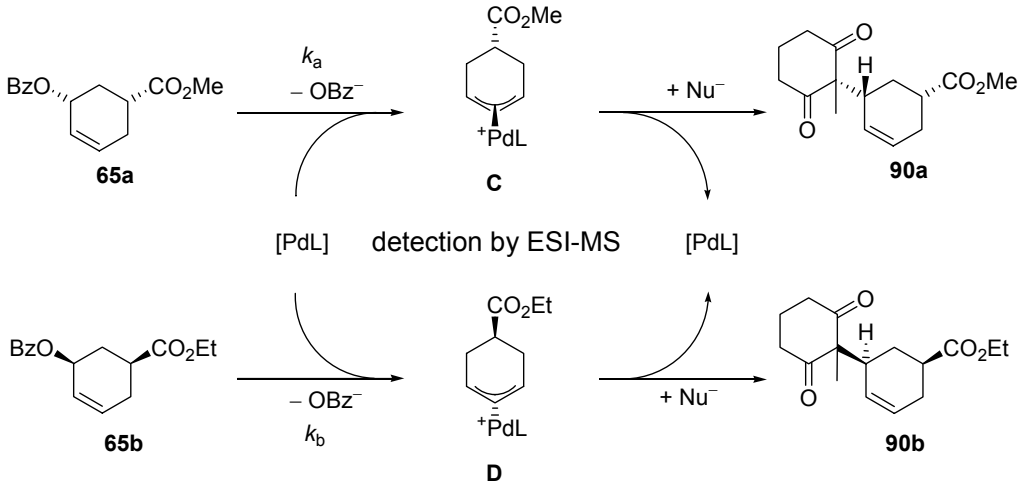


In this manner, an equimolar mixture of mass-labelled quasienantiomers **142a** and **142b** was subjected to typical reaction conditions and the ratio of the resulting cationic allyl-palladium complexes **A** and **B**, which are the only species visible in the mass spectrum, was determined with high accuracy.

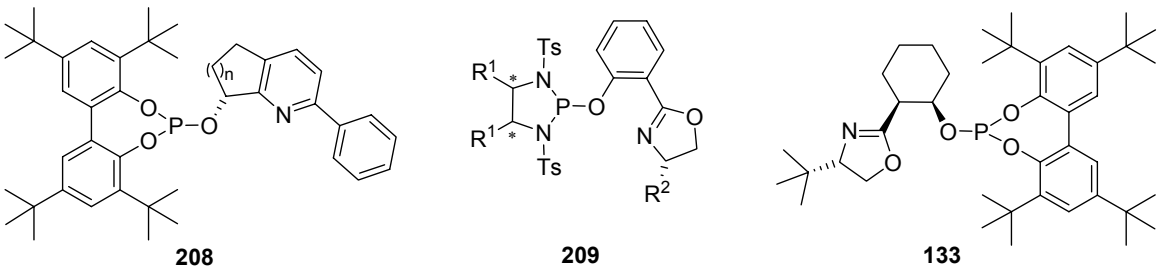
A series of linear diaryl allylation products with commonly used nucleophiles as leaving groups were initially analysed with respect to their leaving group ability, which correlates well with the pK_a values of the respective nucleophiles. Based on these results, screening procedures for allylic alkylations and aminations using substrates derived from acetyl acetone and phthalimide were developed. In both cases, the ratios of allyl intermediates **A**/**B** closely match with the enantiomeric product ratios of corresponding preparative reactions as determined by HPLC analysis of the products. The methodology is fast, reliable, and enables the simultaneous screening of catalyst mixtures, as long as the catalysts possess different

molecular masses. Three palladium complexes were tested in a single reaction vessel and the most powerful derivative was readily identified.

After having established a protocol for the evaluation of chiral palladium catalysts in allylic substitutions of linear diaryl substrates, the methodology was extended to the more demanding carbocyclic substrates. An efficient screening for the kinetic resolution of cyclohexenyl benzoate was developed by the use of cyclic allyl esters **65a** and **65b**. Moreover, analysis of the back reaction starting from the allylation products **90a** and **90b** allowed for determining the efficiency of the catalysts in the overall substitution process. The observed data were in good agreement with the corresponding preparative reactions.

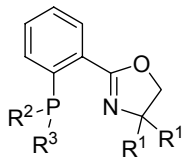


In an additional project, new pyridyl-phosphite **208**, bis(*N*-sulfonylamino)phosphine **209**, and phosphinooxazoline ligands **133** were successfully synthesised and evaluated by the ESI-MS procedures and conventional preparative catalytic reactions.



The back reaction screening method was further extended to the mass spectrometric evaluation of racemic catalysts. Using a scalemic mixture of quasienantiomers **142a** and **142b** enabled to determine the enantioselectivities of chiral catalysts by testing their racemates. This approach was used to study phosphinooxazoline ligands **143**, which possess a

stereogenic phosphorus atom as the only source of chirality, because the synthesis of the enantiomerically pure compounds is not straightforward.



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A series of derivatives was synthesised and evaluated by ESI-MS. Conventional preparative reactions of the separated enantiomers were performed as well. Ligands derived from dialkyl, alkylaryl, and diaryl phosphines induced only low to moderate selectivities in allylic substitutions and the results are not competitive with the established phox ligands derived from chiral aminoalcohols. The screening methodology was successfully used to determine these selectivities without the time-consuming preparation of the enantiomerically pure compounds.

Finally, the ESI-MS analysis of iridium-catalysed allylic substitution reactions proved the actual existence of a previously postulated allyl-iridium intermediate. Preliminary results are promising and provide information which is in accordance with the suggested reaction mechanism.

CHAPTER 1

INTRODUCTION

1 Introduction

Asymmetric catalysis is one of the most important methods for the synthesis of enantiomerically enriched compounds.[1-3] The development and fine-tuning of chiral catalysts, which provide efficient asymmetric induction for a specific transformation, is often a labour-intensive, costly, and time-consuming process. Therefore, screening methods that accelerate the identification and optimisation of new ligands are of considerable importance and increasing amount of research has been devoted to the development of high-throughput techniques in the last few years.[4, 5]

The enantioselectivity of a chiral catalyst is usually determined by measuring the enantiomeric excess of the reaction product it produces. However, the value obtained in this fashion does not necessarily reflect the intrinsic enantioselectivity of the respective catalyst. A competing unselective background reaction, catalytically active impurities, or the dissociation of a chiral ligand from the metal centre might lead to low enantiomeric purity of the product, despite the high selectivity of the catalyst itself.

In our group, a method based on quasienantiomeric substrates and electrospray ionisation mass spectrometry (ESI-MS) was developed, allowing for the determination of a catalyst´s intrinsic enantioselectivity.[6] This approach relies on the quantification of charged reaction intermediates and does not require product analysis. As a first application, the kinetic resolution of racemic allyl esters by palladium-catalysed allylic substitution was studied.

1.1 Electrospray Ionisation Mass Spectrometry

Electrospray ionisation (ESI), which originated in the paint and coatings industry, was first applied to mass spectrometry in the late 1960's. Dole realised that electrospraying of a polymer solution into an evaporation chamber resulted in the formation of intact macroions in the gas phase.[7] The method was considerably improved by Fenn, who coupled an electrospray source to a quadrupole mass analyser, thus enabling the mass spectrometric analysis of thermally fragile polar molecules such as proteins and peptides.[8-10] For this contribution Fenn was awarded the Nobel Prize for Chemistry in 2002, along with Tanaka, who introduced matrix assisted laser desorption (MALDI) in mass spectrometry.[11, 12]

Electrospay ionisation (ESI) is a mild technique that allows for transfer of intact molecular ions from a dilute solution directly into the gas phase.[13-15] The charged compounds being analysed can either be transient species, or protonated/deprotonated forms or ion adducts of neutral species.

The spraying process can be described with relative simplicity.[16] The solution containing the analyte is pumped through a charged capillary. The high voltage generates a mist of charged droplets (nebulisation), which pass through a potential and pressure gradient towards the analyser of the mass spectrometer.[17] The solvent in these droplets is evaporated by a warm flow of drying gas, usually nitrogen. As a consequence, the charge density increases to a point at which electrostatic repulsion becomes of the same order of magnitude as the surface tension.[18] At this point the droplet fragments in what is termed a 'Coulomb explosion', producing many daughter droplets, which in turn undergo the same process.[19] Whether or not this iterative process finally produces the bare analyte ions is still a subject of debate. Alternatively ions can 'evaporate' from the droplet's surface.[20] Whatever the exact mechanism might be, electrospray ionisation is a very 'soft' means of ionisation, that causes little or no fragmentation of the analyte. Proteins can be ionised without denaturation and noncovalent receptor-ligand complexes remain intact. The method can even be used for the examination of charged non-covalent and non-volatile organometallic complexes, which are usually not compatible with most ionisation techniques.[21]

1.2 Mass Spectrometric Detection of Reaction Intermediates

Electrospray ionisation as a tool for the analysis of ionic transition metal complexes was first described by Chait for bipyridyl (bpy) and 1,10-phenanthroline complexes of ruthenium in 1990.[22] A dilute solution of $[Ru(II)(bpy)_3]^{2+}$ in acetonitrile was analysed and the signal for the intact cation detected. The collision energy was found to be an adjustable parameter, which controls the extent of desolvation and fragmentation. Under mild conditions, the mass spectrum exhibited additional peaks resulting from the attachment of one to four acetonitrile molecules to the ruthenium centre, whereas at higher energies the doubly charged ion dissociated and signals for the fragments $[Ru(II)(bpy)_2]^{2+}$and $[Ru(II)(bpy)]^{2+}$ were observed. Fragmentation of the complex by collisional activation is a characteristic feature for mass spectra of coordination compounds.[23] Typically, the loss of an intact ligand occurs rather than its fragmentation. This is particularly helpful for the identification and structural assignment of signals in the mass spectra and can be used for the characterisation of organometallic complexes.[21]

During the last two decades there has been considerable growth in the applications of electrospray ionisation mass spectrometry as a tool for mechanistic investigations, especially for homogeneous transition metal-catalysed reactions.[24-26] The great utility of ESI-MS can be

ascribed to its ability to transfer ions of many different types, charges, and broad mass ranges from the reaction solution directly to the gas phase and to characterise these ions quickly, sensitively, and selectively. The gentle ion transfer ensures a close relation between the detected gas-phase ion and the actual species in solution.[24] The opportunity to directly analyse dilute solutions is a major advantage, as catalytically active species often exist only under these conditions and can not be isolated as pure compounds. The optimal concentration range (0.001-10 mM) for ESI-MS corresponds to typical catalyst concentrations of many reactions. The ability of ESI-MS to selectively 'fish' for ionic species[27] allows to analyse the course of various transformations by interception, characterisation, and reactivity investigations of charged intermediates.

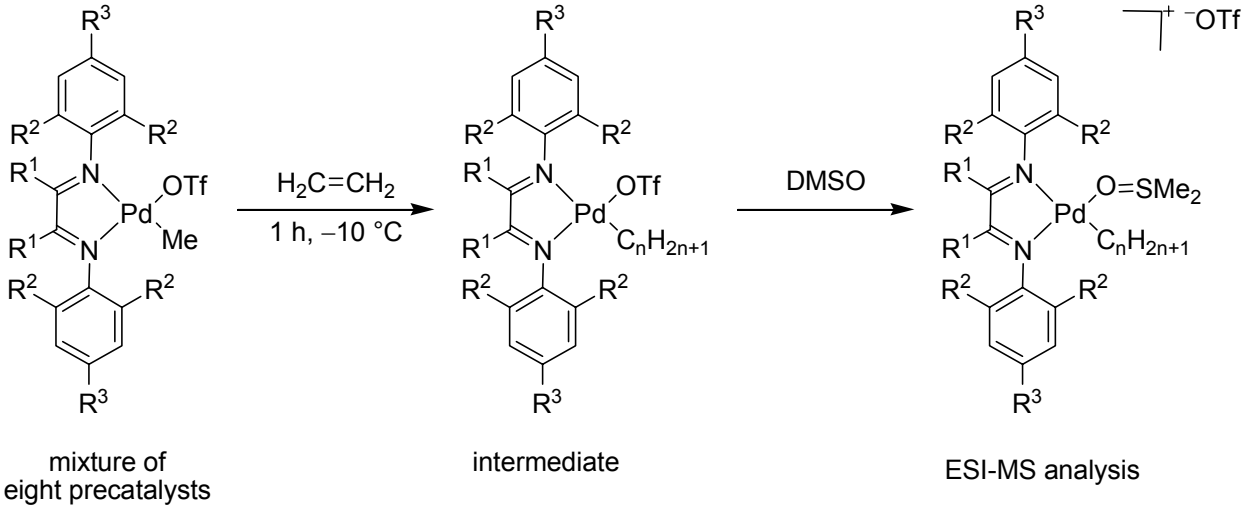
Pioneering work in this field was accomplished by Chen, who also advanced ESI-MS as a tool for the mechanistic investigation of transition metal-catalysed reactions by the development of more sophisticated instruments. The interests of Chen's group have included catalytic hydrogenations with rhodium,[28] iridium,[29] and ruthenium complexes,[30, 31] C-H activation reactions with iridium(III),[32, 33] and platinum(II),[34-36] olefin metatheses,[37-41] Ziegler-Natta polymerisations using zirconocene catalysts,[42, 43] the olefination of aldehydes with high-valent rhenium compounds,[44] and the palladium-catalysed polymerisation of ethene.[45, 46]

Furthermore, ESI-MS has been applied by other groups to study additional palladium-catalysed transformations such as Heck,[47] Suzuki,[48, 49] and Stille reactions,[50] the oxidative homocoupling of arylboronic acids,[51] and allylic substitution reactions.[52, 53] Its usefulness for studying reactions involving other metal ions has been demonstrated for nickel-catalysed C-C couplings,[54] catalytic epoxidations with oxomanganese(V) complexes,[55, 56] iridium-catalysed hydrosilylations of terminal alkynes,[57] and cobalt-mediated Pauson-Khand reactions.[58]

Along with a variety of transition metal-catalysed reactions, ESI-MS has become a major tool for the detection of reaction intermediates in organocatalytic transformations. These species are mostly either charged (e.g. iminium ions) or can be easily protonated by protic solvents. The first study in this field was reported by Eberlin, who investigated the Baylis-Hillman reaction catalysed by 1,4-diazabicyclo[2,2,2]octane (DABCO).[59] More recently, the analysis of direct Mannich-type α-methylenation of ketoesters was described.[60] Metzger used ESI-MS as an analytical tool to study the respective reaction mechanisms for electron transfer-initiated Diels-Alder reactions,[61] proline-catalysed aldol reactions,[62] and the direct organocatalytic α-halogenation of aldehydes.[63]

The variety of transformations analysed by ESI-MS to date demonstrates the enormous potential of this method for mechanistic studies. Beyond this, several applications in reactivity screenings for the discovery and development of catalysts were described.[24]

An elegant evaluation of different Brookhard-type catalysts was reported by Chen.[45] The polymerisation of ethene was carried out in the presence of a simultaneously synthesised mixture of eight different precatalysts.



Scheme 1. Polymerisation of ethene using eight different Brookhard-type catalysts in one pot.

The ESI-MS analysis of the reaction mixture after the addition of dimethylsulfoxide provided a complex spectrum. Several overlapping series of oligo- and polymeric ions corresponded to each catalyst with zero to hundred attached ethylene units. The most efficient catalyst, carrying the longest polymer chain, was identified by a collision induced dissociation (CID) experiment. A series of intermediates with $m/z > 2200$ was filtered out and fragmented by xenon collision. The β-hydride elimination of the hydrocarbon chain, induced in this manner, generated a palladium hydride, which allowed for identification of the most effective catalyst.

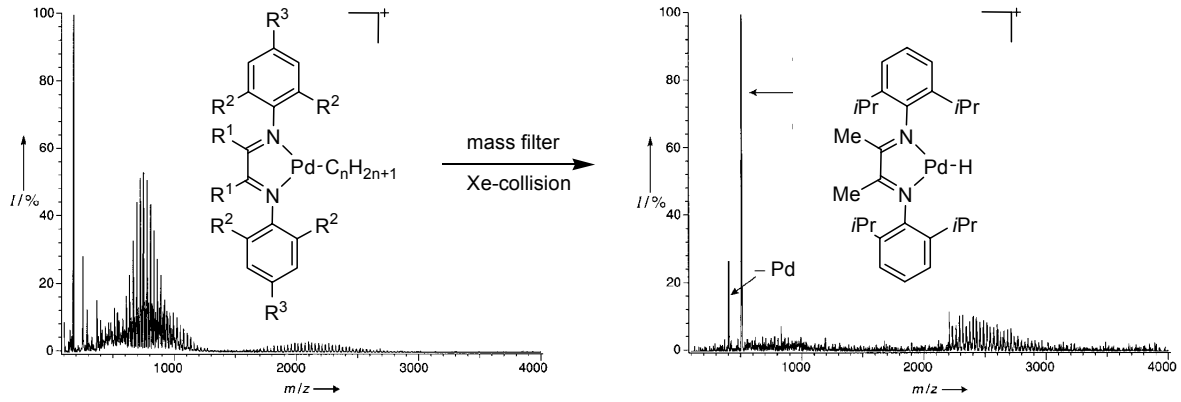


Figure 1. Mass spectrometric screening for reactivity.

1.3 Quasienantiomers in Mass Spectrometry

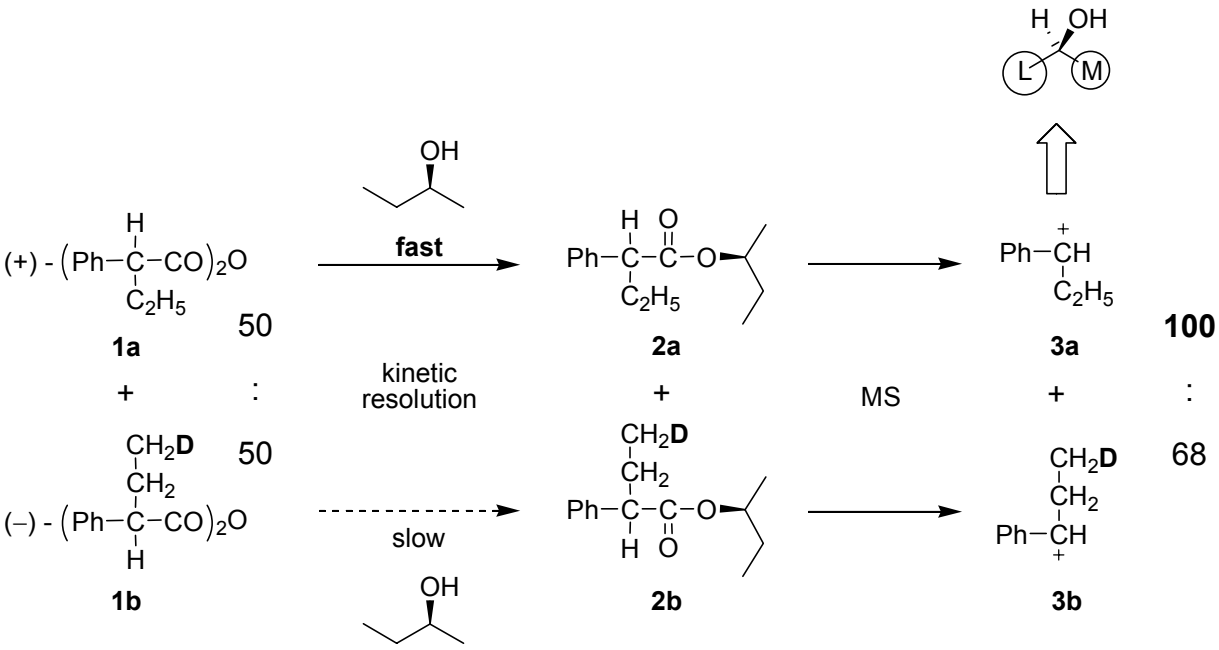
Mass spectrometry is an attractive analytical method for high-throughput applications due to its wide scope (many types of molecules can be detected), sensitivity, tolerance of impurities (peaks other than the masses of interest can be ignored), and speed. However no stereo information is provided by this technique, because enantio- or diastereomeric compounds can not be distinguished as they have the same mass.

In the last two decades several methods for distinction of stereoisomers by mass spectrometry have been developed,[64] including the kinetic method based on the dissociation of cluster ions,[65-67] the formation of diastereomeric host guest adducts, [68-71] and the collision-induced dissociation (CID) of diastereomeric adducts of the analyte and a chiral reference in a MS/MS experiment.[72]

An elegant method, introduced by Horeau in 1990, is based on the use of mass labels to determine the absolute configuration of secondary alcohols by mass spectrometry.[73]

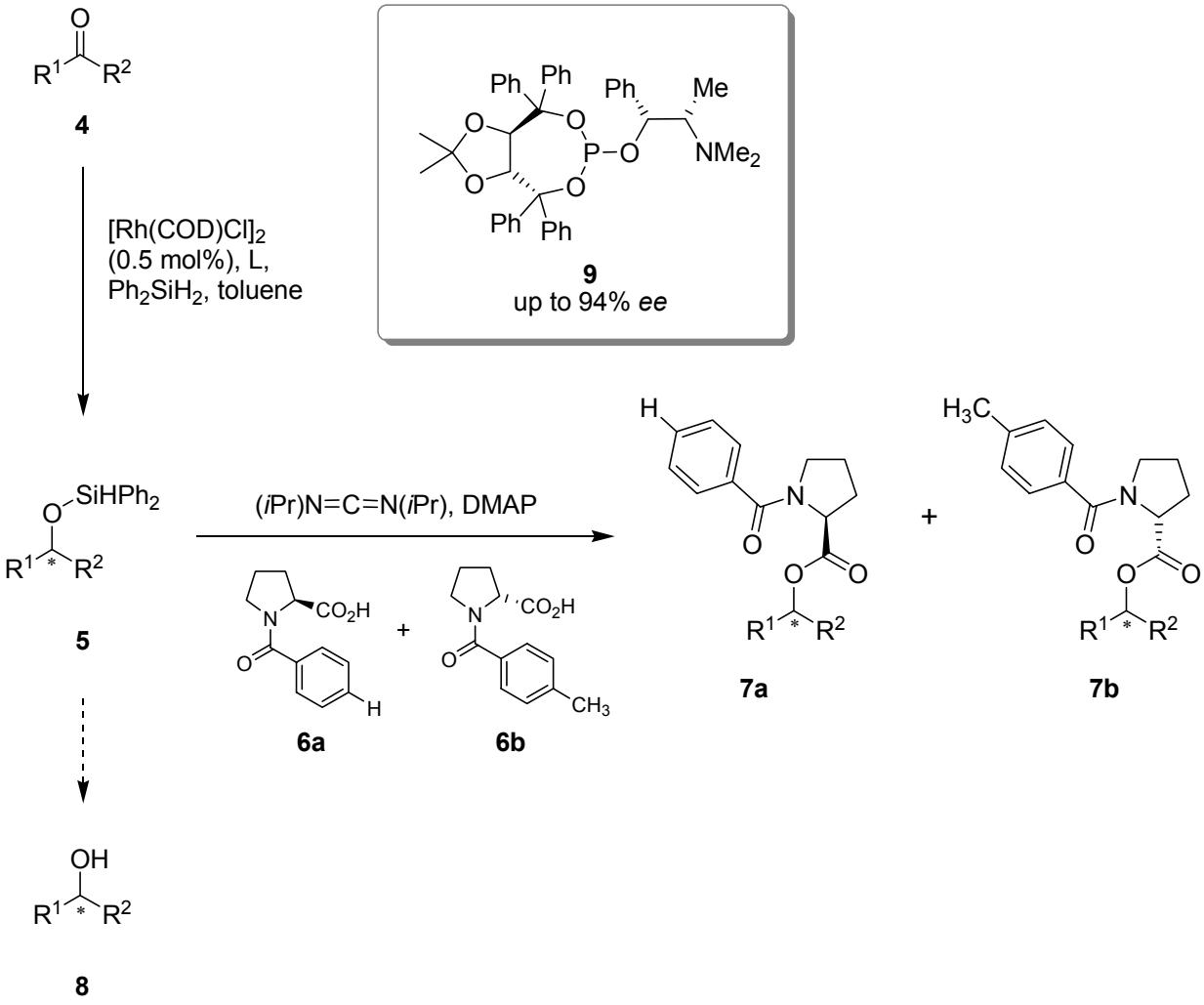
An equimolar mixture of chiral anhydrides **1a** and **1b** was used for the acylation of an enantiomerically pure secondary alcohol of unknown configuration (Scheme 2). The transformation proceeds by kinetic resolution to give the diastereoisomeric esters **2a** and **2b**. The anhydrides **1a** and **1b** differed not only in their absolute configuration but also in mass. By the introduction of a deuterium label, the resulting esters **2a** and **2b** could be distinguished through mass spectrometry. After the reaction mixture had been subjected to electron impact ionisation spectrometry, the relative peak intensities of species **3a** and **3b**, formed by

fragmentation, were compared. Based on the more abundant species, the absolute configuration could be unambiguously assigned.



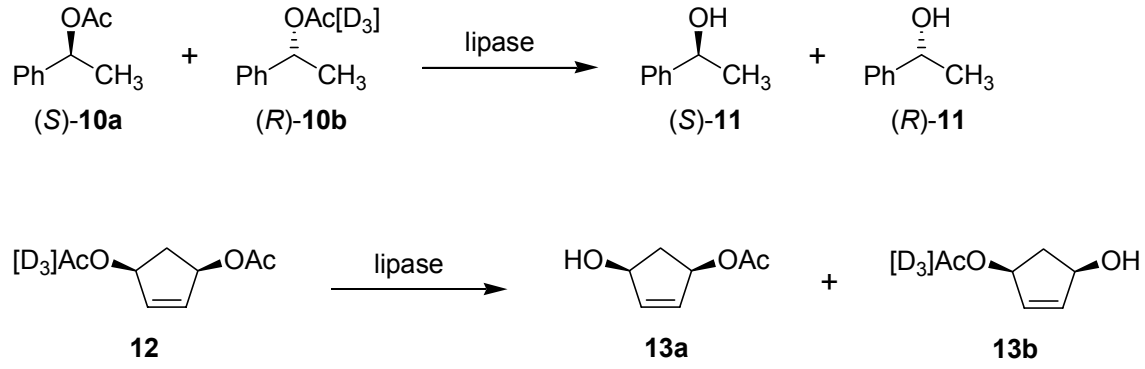
Scheme 2. Assignment of the absolute configuration of secondary alcohols according to Horeau.

An extension of this methodology to determine the enantiomeric excess of secondary alcohols was described by Finn.[74] The approach uses chiral mass-labelled *N*-acylprolines as the acylating agents, which differ in a substituent remote to the stereogenic centre. The validation of this so-called 'mass spectrometry enantiomeric excess determination' (MSEED) analytical method was performed by screening a family of chiral phosphite P,N-ligands for the rhodium-catalysed asymmetric hydrosilylations of ketones.[75] The catalysts were tested in the reduction of several substrates (Scheme 3). The obtained silyl ethers **5** were reacted with mass-labelled acylprolines **6a** and **6b** to give a mixture of diastereomeric esters **7a** and **7b**, which could then be distinguished by mass spectrometry. Based on the ratio of these derivatives the enantiomeric excesses of the hydrosilylation products were estimated. For comparison aliquots of the silyl ethers **5** were hydrolysed to the corresponding alcohols **8**, which were then analysed by HPLC on a chiral column. The values obtained from both methods were quite similar (within ± 10% *ee* for all examples). Phosphite **9** was identified as the most selective ligand in this screening with enantioselectivities of up to 94%.



Scheme 3. Method for examining the enantiomeric excesses of hydrosilylation products **8**.

Another approach based on mass-labelled enantiomers for the determination of enantiomeric excesses was developed by Reetz (Scheme 4) .[76]



Scheme 4. Mass spectrometric investigations of kinetic resolutions and desymmetrisations.

The lipase-catalysed kinetic resolution of 1-phenylethyl acetate **10a** was studied. Through deuterium labelling, the sodium adducts of both substrate enantiomers (*S*)-**10a** and (*R*)-**10b** appeared at different *m/z* values in the mass spectrum and the enantiomeric excess of the remaining substrate could be calculated by simple integration of these two signals. In addition, the desymmetrisation of prochiral substrates, such as *cis*-1,4-diacetoxycyclopentene **12** was analysed in a similar manner by mass spectrometric monitoring of products **13a** and **13b**.

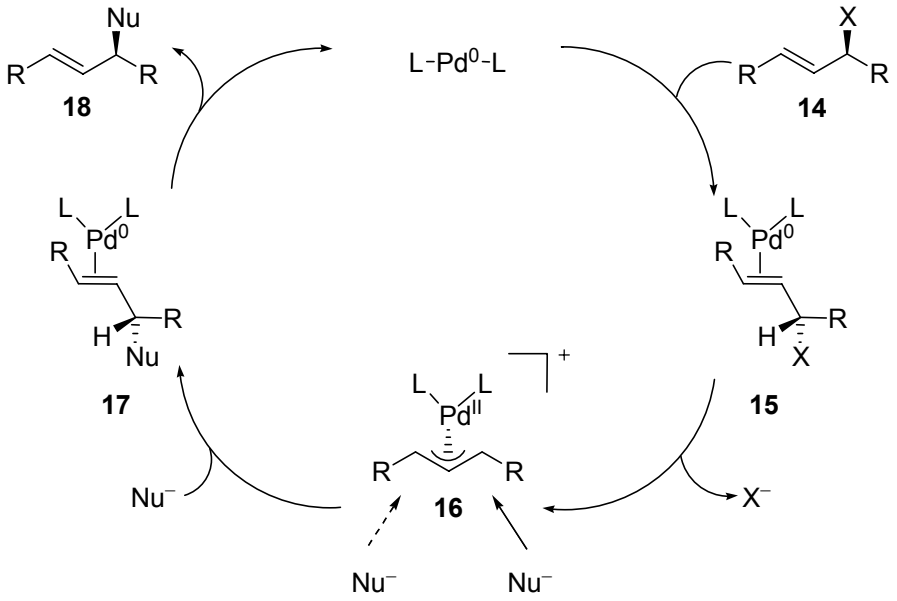
Mass-labelled enantiomers, which were introduced by Horeau, are known as quasienantiomers. The terms 'pseudoenantiomers' and 'pseudoracemate', often used instead, should be avoided, since the latter has a well-established different meaning in crystallography.[77, 78] It refers to one of the three possible crystalline forms of true racemates and therefore should be reserved for this purpose. Several applications of mass-labelled quasienantiomers have been described recently in a review by Curran.[77]

Quasienantiomeric substrates were also used in our group for measuring the intrinsic selectivities of chiral catalysts by mass spectrometric monitoring of the respective reaction intermediates. This methododology was successfully applied to the kinetic resolution of racemic allyl esters by palladium-catalysed allylic substitution (Section 1.4.2) and the enantioselective Diels-Alder reaction.[6, 79]

1.4 Palladium-Catalysed Allylic Substitutions

1.4.1 Reaction Mechanism

Asymmetric palladium-catalysed allylic substitution is a powerful method for the construction of carbon-carbon and carbon-heteroatom bonds.[80, 81] The most important of these transformations involve reactions with 'soft' nucleophiles such as stabilised carbanions or amines. The reaction mechanism has been intensely investigated and elucidated in detail (Scheme 5). An allylic substrate **14**, typically an acetate, reacts with the catalyst, which enters the catalytic cycle on the palladium(0) oxidation level. The transformation is initiated by the formation of a π-complex **15**, which eliminates the leaving group X^- to generate a cationic η^3-allyl-palladium(II) complex **16** by oxidative addition. The resulting anion X^- can then coordinate to the palladium centre in an equilibrium resulting in a neutral species depending on the structure of the ligand, the solvent, and the anion. With bidentate ligands the cationic complex **16** usually predominates.



Scheme 5. Mechanism of palladium-catalysed allylic substitutions.

The electrophilic palladium(II) centre activates the allylic system for nucleophilic attack, which can occur at either terminus of the fragment. Various chiral ligands can control this addition through steric or electronic effects. A rather unstable palladium(0) olefin complex **17** is formed, which rapidly releases the product **18** and the catalyst. Both the oxidative addition and the subsequent nucleophilic attack proceed with inversion of the configuration at the reacting allyl carbon atom, which results in an overall retention of stereochemistry.

The formation of allyl intermediate **16** is fast, while the nucleophilic addition to the allyl system is slower and the rate-limiting step. The cationic intermediate **16**, the only charged species of the catalytic cycle represents the resting state of the reaction. In the absence of a suitable nucleophile it is stable and can be isolated. It exists in a sufficiently high concentration in the reaction mixture to be detectable by ESI-MS under typical conditions. This attractive feature allowed for the development of a mass spectrometric screening protocol for the evaluation of chiral ligands in the kinetic resolution of allylic esters by palladium-catalysed allylic substitution.[6]

1.4.2 Screening of Chiral Catalysts in the Kinetic Resolution of Allyl Esters

In 2004, Markert and Pfaltz developed a protocol for determining the intrinsic enantioselectivities of chiral catalysts based on quasienantiomeric substrates and electrospray ionisation mass spectrometry (ESI-MS) as an analytical tool.[6] In contrast to previously developed screening methods for asymmetric reactions, which also make use of quasienantiomeric substrates (Section 1.3), this method relies on the quantification of catalytic intermediates rather than product analysis.

As a first application the kinetic resolution of racemic allyl esters by palladium-catalysed allylic substitution was studied using an equimolar mixture of quasienantiomeric substrates (*S*)-**19a** and (*R*)-**19b** (Figure 2). The benzoates bear mass labels at the *para*-position of one aryl group, allowing for the mass spectrometric differentiation of allyl intermediates **20a** and **20b**. A rapid screening method was developed and the selectivity factors $s = k_a/k_b$ for several catalysts were deduced from the ratios of the corresponding allyl intermediates **20a** and **20b**.

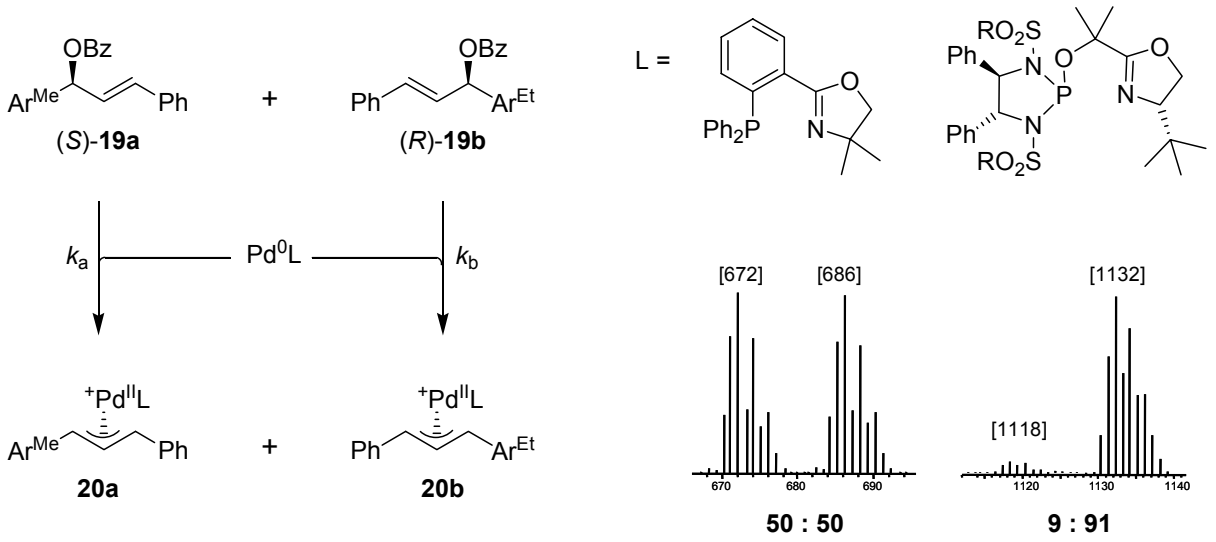
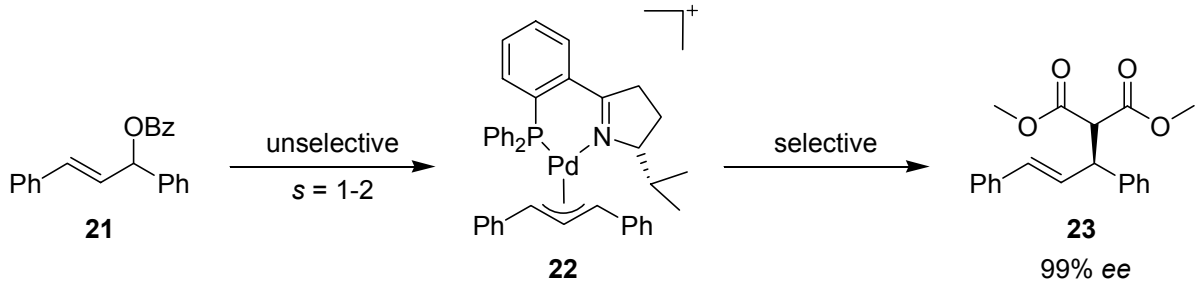


Figure 2. Mass spectrometric screening of chiral catalysts in the kinetic resolution of allylic esters.

The method is fast and reliable, does not require workup of the reaction mixture, and in contrast to methods based on product analysis, allows for the simultaneous screening of several catalysts in one pot, as long as the catalysts have different molecular masses. The most selective ligand for this kinetic resolution to date ($s > 100$) was identified in this fashion, illustrating the potential of the approach. It was also demonstrated that mass spectrometric screening of quasienantiomeric substrates can considerably simplify the structural optimisation of chiral catalysts. Starting from a mixture of suitable building blocks libraries of modular ligands were prepared in a single batch and simultaneously evaluated by ESI-MS.[82]

Furthermore, a dinuclear allyl-bridged palladium(I) complex was discovered during the screening process, which is reversibly formed in substantial amounts in the course of the catalytic reaction.[53]

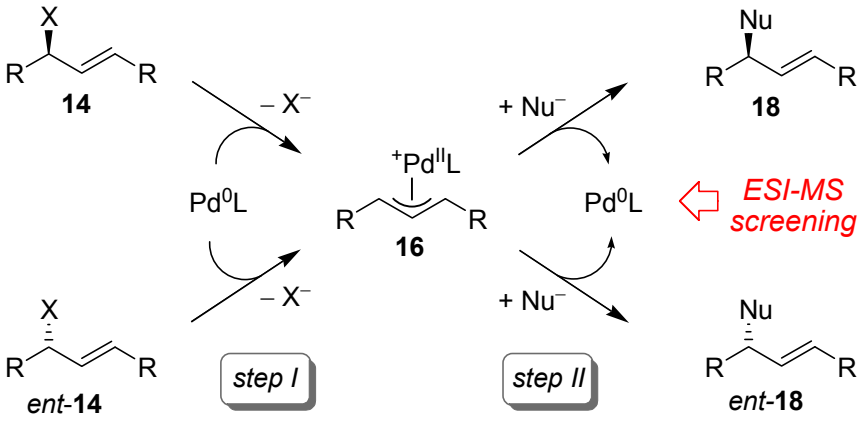
However, screening a large number of catalysts revealed that the selectivity of a catalyst in the kinetic resolution step does not necessarily correlate with the enantioselectivity of the nucleophilic addition to the allyl intermediate **22**, which determines the enantioselectivity of the overall reaction leading from racemic allyl ester **21** to the optically active substitution product **23** (Scheme 6). A range of palladium complexes that gave high enantioselectivities in the overall reaction were found to be inefficient in the kinetic resolution of allyl esters.



Scheme 6. Allylic alkylation using a phox ligand.

1.5 Objectives of this Work

The main objective of this work was to develop an ESI-MS screening technique to evaluate the intrinsic enantioselectivity of chiral catalysts within asymmetric allylic substitution reactions. As described in the preceding Section 1.4.2, analysis of the kinetic resolution step (step II, Scheme 7) provides no information on the efficiency of the overall allylic substitution process leading from racemic allyl ester **14**/*ent*-**14** to the optically active substitution product **18**/*ent*-**18**. In order to determine the enantioselectivity of product formation, the nucleophilic addition (step II, Scheme 7) must be studied and thus we decided to monitor the back reaction leading from product **18**/*ent*-**18** to the corresponding allyl-palladium complex **16**. According to the principle of microscopic reversibility, the transition states of the forward and the back reactions are identical and the enantioselectivity determined in this way is the same as the enantioselectivity of the forward reaction.



Scheme 7. General mechanism of the palladium-catalysed allylic substitution of racemic substrate **14**/*ent*-**14**.

Monitoring the palladium-bound allyl intermediates **16** should directly provide the intrinsic selectivity of the catalyst when quasienantiomeric mass-labelled substrates are used. We decided to study substrates with leaving groups, which are normally applied as nucleophiles in the forward reaction. Linear diarylallyl derivatives, which are most often used in asymmetric allylic substitutions for the evaluation of new ligands, were chosen for the development of this screening method.

After having proved the viability of this approach, it was planned to extend the methodology to more demanding carbocyclic substrates, including the mass spectrometric analysis of both the kinetic resolution step and the nucleophilic addition.

A further goal of this thesis was to use the ESI-MS technique as an analytical tool for the evaluation of new ligands, such as bis(*N*-sulfonylamino)phosphine-oxazoline and pyridyl-phosphite derivatives.

In principle the method should also be applicable to the mass spectrometric evaluation of racemic catalysts. According to Lloyd-Jones[83] the use of a scalemic mixture of quasienantiomeric substrates allows to determine the enantioselectivity of a chiral complex by testing its racemate. In order to demonstrate the feasability of this approach, it was intended to synthesise racemic phosphinooxazoline ligands with stereogenic phosphorus atoms and to study them in asymmetric allylic substitutions.

CHAPTER 2

ESI-MS SCREENING OF LINEAR DIARYLALLYL SUBSTRATES

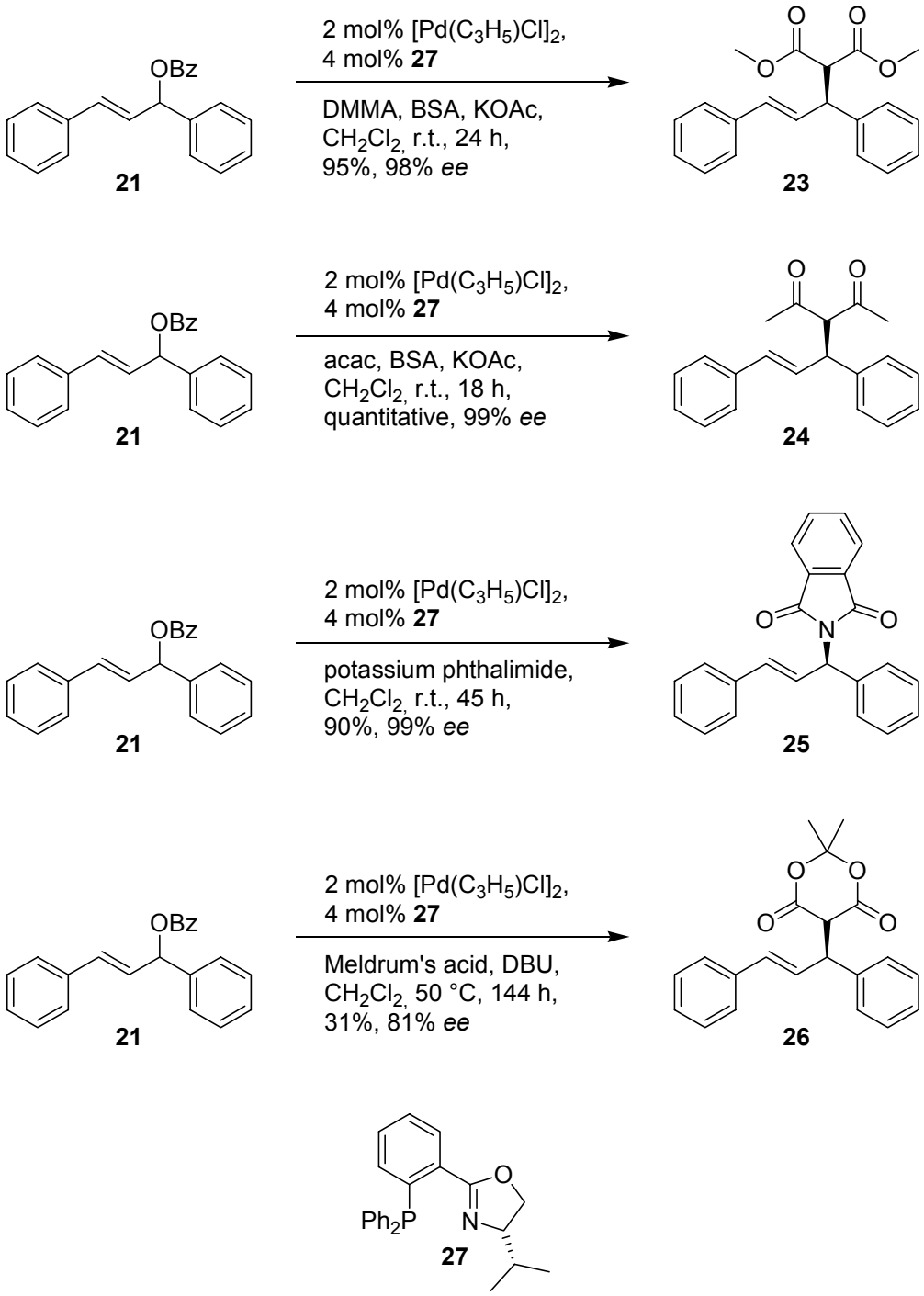
2 ESI-MS Screening of Linear Diarylallyl Substrates

We were interested in developing an ESI-MS screening technique to evaluate the intrinsic enantioselectivity of chiral catalysts within asymmetric allylic substitution reactions. In order to determine the enantioselectivity of the product formation, nucleophilic addition must be studied. This was accomplished by monitoring the back reaction based on the principle of microscopic reversibility.

2.1 Leaving Group Ability of Selected Substrates

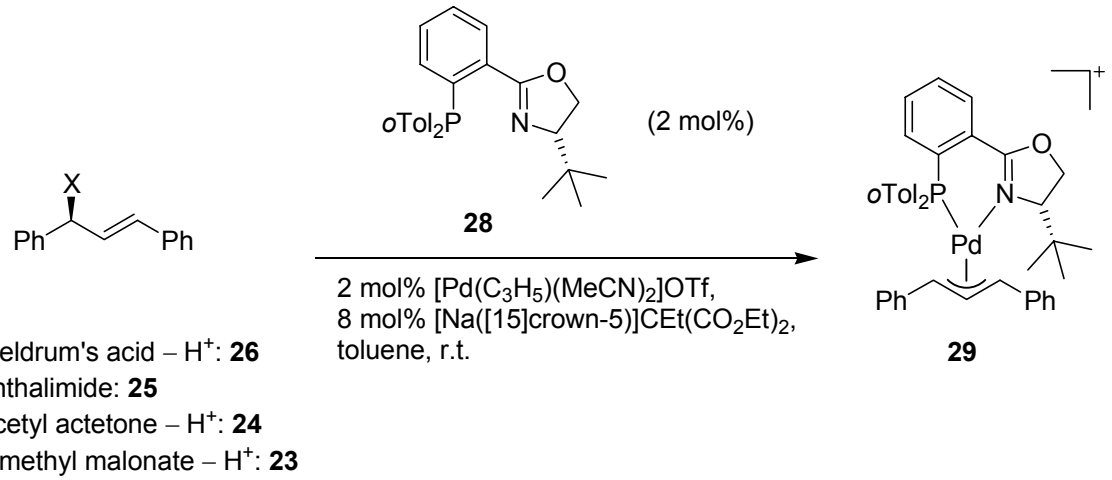
In order to find a nucleophile with sufficient reactivity as leaving group, a range of allylation products **18** (R = Ph) derived from Meldrum's acid, phthalimide, acetyl acetone and dimethyl malonate was initially screened. Substrates **23**-**26** were prepared by palladium-catalysed allylic alkylation (Scheme 8).[84]

Benzoate **21** did not react with Meldrum's acid under standard conditions to give the desired product **26**. With 2 mol% of catalyst, prepared *in situ* from $[Pd(C_3H_5)Cl]_2$ and chiral ligand **27**, *N*,*O*-bis(trimethylsilyl)acetamide and potassium acetate in both dichloromethane and tetrahydrofuran no product formation was observed. A NMR experiment showed that silyl transfer between *N*,*O*-bis(trimethylsilyl)acetamide and Meldrum's acid takes place within a few minutes. This was overcome by variation of the base. Using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane at 50 °C was found to give the best result. However, product **26** was only obtained in 31% yield with an enantiomeric excess of 81% under these optimised conditions.



Scheme 8. Synthesis of substrates with different leaving groups.

The leaving group ability was determined by screening the back reaction of these substitution products using ESI-MS (Scheme 9). In all cases allyl-palladium complexes, from the elimination of the nucleophile, were detected under the standard conditions usually applied in preparative allylic substitutions (2 mol% catalyst, toluene, r.t.).



A) X = Meldrum's acid – H^+: **26**
B) X = phthalimide: **25**
C) X = acetyl actetone – H^+: **24**
D) X = dimethyl malonate – H^+: **23**

Scheme 9. Back reaction screening of different substrates.

From the relative intensities of the signals corresponding to the precatalyst $[Pd(C_3H_5)L]^+$ and the substituted allyl complex **29** a qualitative order of leaving group ability was established for the four allylation products (Figure 3). As expected the reactivities correlate with the respective pK_a values of the conjugated acids in the order Meldrum's acid (pK_a = 4.97)[85] > phthalimide (pK_a = 8.3)[86] > acetyl acetone (pK_a = 8.95)[87] > dimethyl malonate (pK_a = 13.3).[87]

The Meldrum's acid-derived compound showed the highest reactivity, evident from a high consumption of the catalyst precursor. The dimethyl malonate derivative showed the lowest leaving group ability as demonstrated by an intense signal of the catalyst precursor.

Based on these results a screening protocol for the reaction of quasienantiomeric allylation products derived from acetyl acetone was developed, which both is a sufficiently reactive leaving group and has similar properties as other widely used *C*-nucleophiles such as malonates.

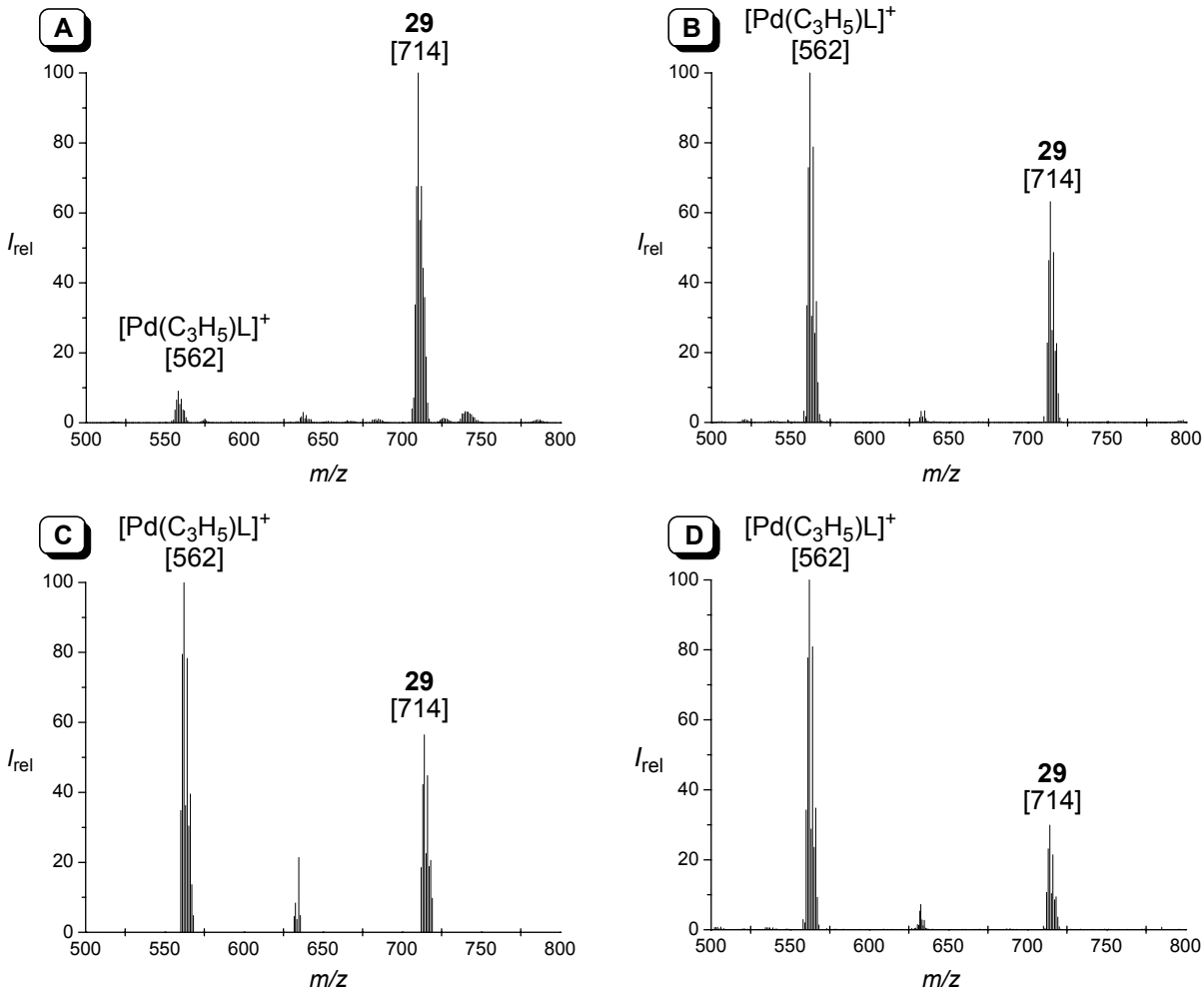


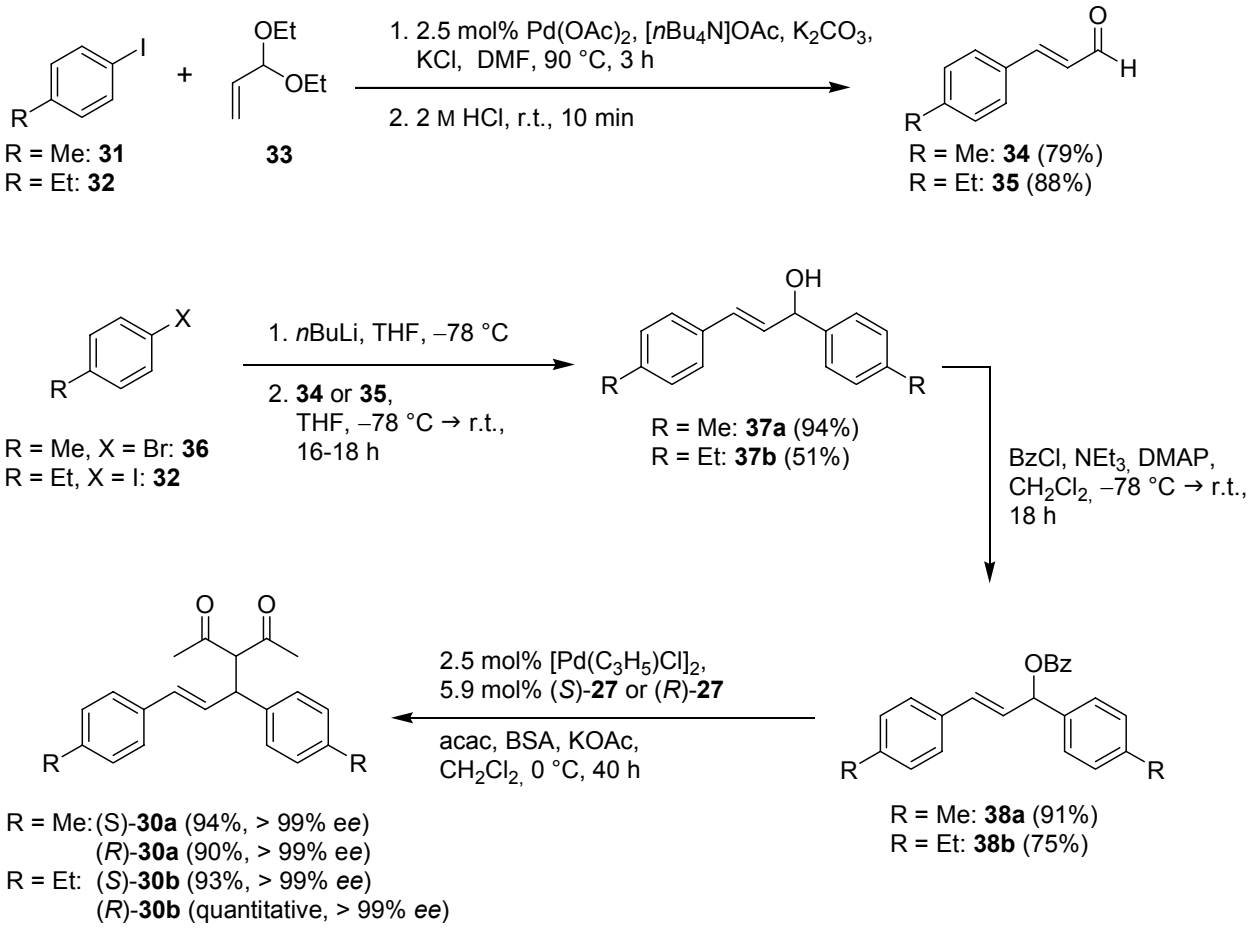
Figure 3. Reactivity screening (Scheme 9) using substrates derived from Meldrum's acid **26** (A), phthalimide **25** (B), acetyl acetone **24** (C) and dimethyl malonate **23** (D).

2.2 Asymmetric Allylic Alkylations

2.2.1 Synthesis of New Quasienantiomeric Substrates

Enantiomerically pure quasienantiomers **30a** and **30b** derived from acetyl acetone were prepared by palladium-catalysed allylic alkylation as key step (Scheme 10). In contrast to previous studies they bear mass labels at the *para*-positions of both aryl substituents.[6] A double mass labelling strategy not only eases substrate synthesis, but also offers the advantage of providing symmetric allyl-palladium intermediates during the ESI-MS screening reaction.

According to a literature procedure, aryl iodides **31** and **32** were reacted with acrolein diethyl acetal **33** in presence of $Pd(OAc)_2$, followed by acidic workup to give products **34** and **35** (Scheme 10).[88]



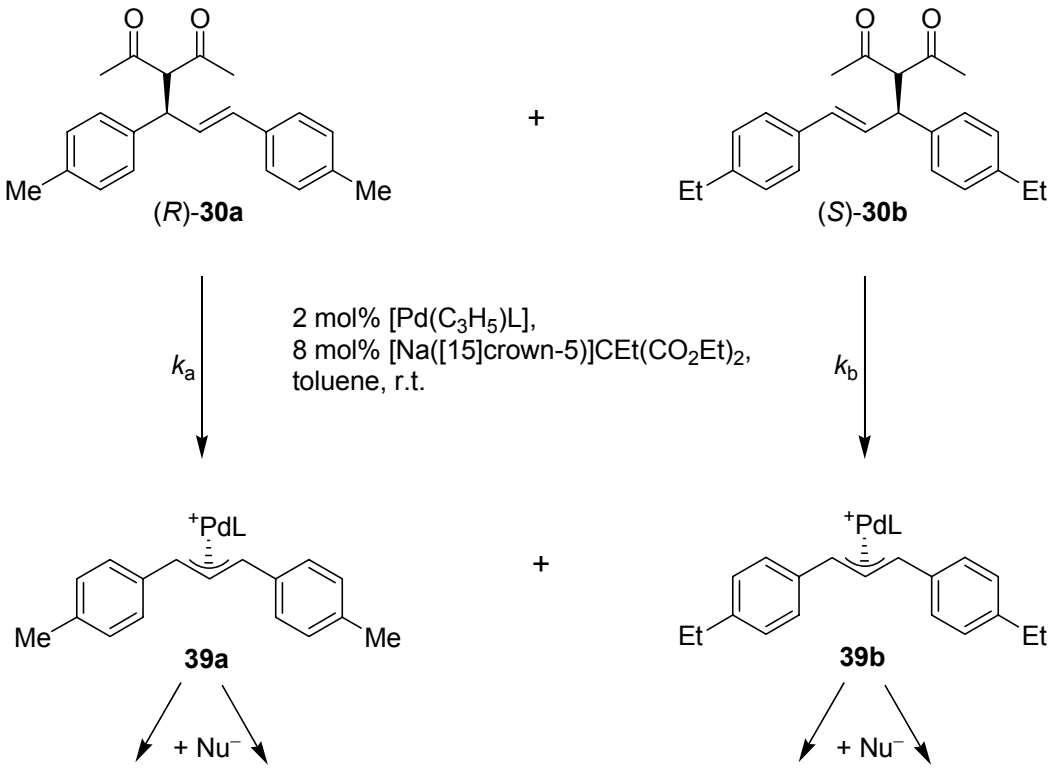
Scheme 10. Synthesis of quasienantiomeric substrates **30a** and **30b**.

Cinnamaldehydes **34** and **35** were then converted to allylic alcohols **37a** and **37b** and after subsequent esterification, with benzoylchloride, 4-(dimethylamino)pyridine and triethylamine benzoates **38a** and **38b**, were produced in good yields.[89]

Allylic alkylation with acetyl acetone in the presence of 2.5 mol% of the catalyst, prepared *in situ* from $[Pd(C_3H_5)Cl]_2$ and phox ligand **27**, a mixture of *N*,*O*-bis(trimethylsilyl)acetamide and catalytic amounts of potassium acetate as base smoothly afforded substitution products **30a** and **30b**.[84] However, the reactions had to be carried out at 0 °C to obtain high enantioselectivities. Transformations using ligand (*S*)-**27** provided the methyl-labelled quasienantiomer (*S*)-**30a** and the ethyl-substituted compound (*S*)-**30b** with an enantiomeric excess of > 99% in both cases. In the same way the (*R*)-alkylation products were obtained with ligand (*R*)-**27** in high enantiomeric purity.

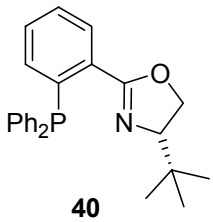
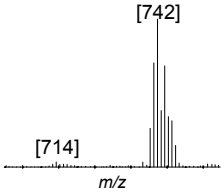
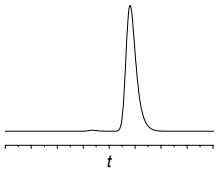
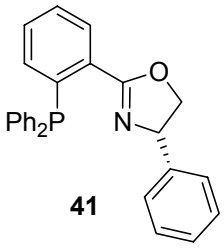
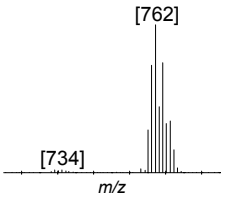
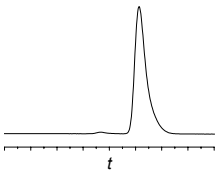
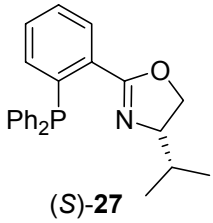
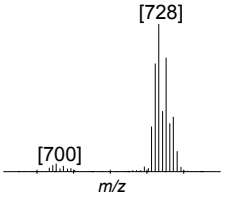
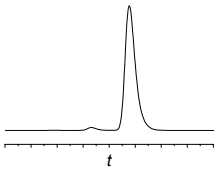
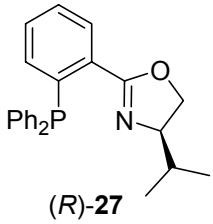
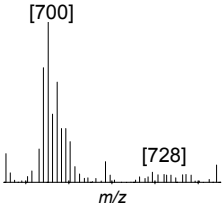
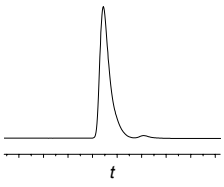
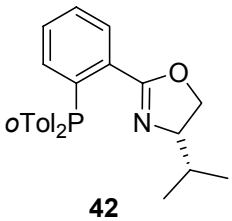
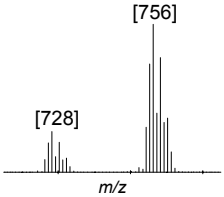
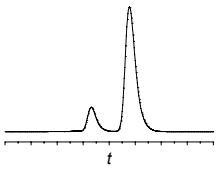
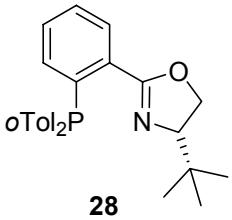
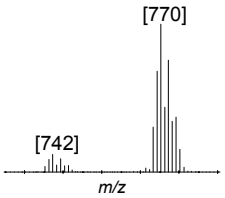
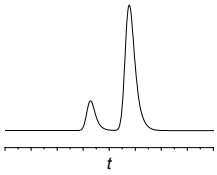
2.2.2 Mass Spectrometric Screening of Phosphinooxazoline Ligands

Having prepared quasienantiomers **30a** and **30b** screening conditions for the back reaction were investigated to determine the selectivity of the nucleophilic addition step within these allylic substitutions. The influence of reaction temperature, solvent and the amount of nucleophile was studied to obtain the optimum conditions (Scheme 11). The catalysts were prepared *in situ* from $[Pd(C_3H_5)(MeCN)_2]OTf$ and stoichiometric amounts of the corresponding chiral ligands in toluene. An equimolar mixture of (*R*)-**30a** and (*S*)-**30b** (25 equivalents based on Pd each) was added and the reaction started by activation of the precatalyst with the crown ether sodium salt of diethyl ethylmalonate (4 equivalents based on Pd). A limited amount of nucleophile was required to ensure a defined conversion and obtain reproducible mass spectra. After 30 seconds at room temperature, a sample was taken, diluted with dichloromethane and directly injected into the mass spectrometer.



Scheme 11. Back reaction screening of the nucleophilic addition step of allylic substitutions with acetyl acetone.

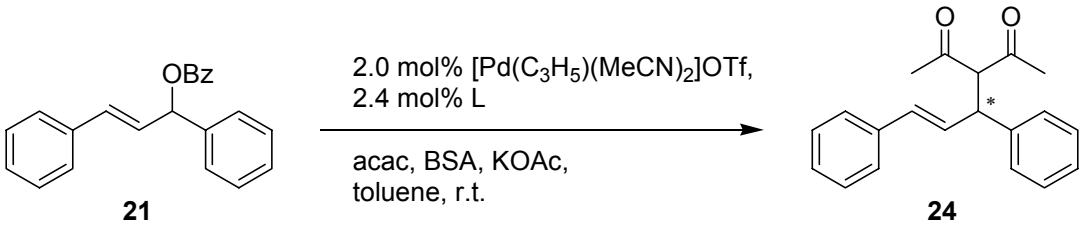
Table 1. ESI-MS screening of allylic alkylations using quasienantiomers (*R*)-**30a** and (*S*)-**30b** according to Scheme 11.

Entry	Ligand	Screening **39a** : **39b**	Preparative Reaction[a] (*R*)-**24** : (*S*)-**24**
1	 **40**	3 : 97 	1 : 99 
2	 **41**	2 : 98 	1 : 99 
3	 (*S*)-**27**	4 : 96 	2 : 98 
4	 (*R*)-**27**	96 : 4 	98 : 2 
5	 **42**	20 : 80 	14 : 86 
6	 **28**	17 : 83 	17 : 83 

[a] HPLC analysis (Daicel Chiracel AD-H, heptane/isopropanol 97:3, 0.9 mL*min^{-1}, 20 °C, 254 nm): t_R = 16.3 (*R*), 17.9 (*S*) min.

Under these conditions the signals of the allyl complexes **39a** and **39b**, formed by elimination of acetyl acetonate, are clearly visible and show the characteristic isotope pattern of palladium.

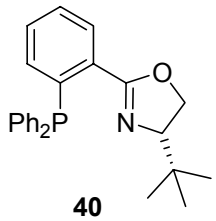
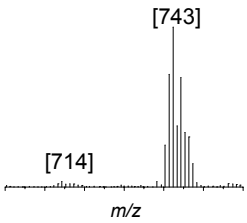
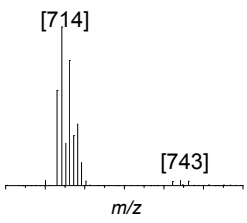
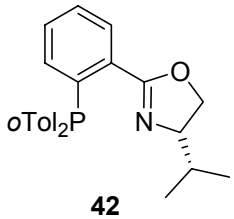
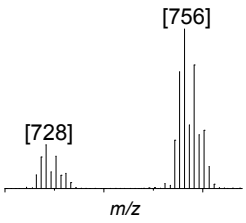
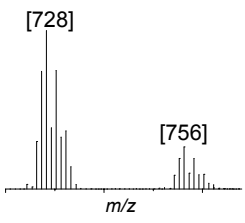
Screening results with a selection of phox ligands **27**, **28** and **40**-**42** are depicted in Table 1. The selectivities, calculated from the ratios of the peak heights of the two signal clusters, correlate very well with the enantiomeric ratios of the products from the corresponding preparative reactions of racemic 1,3-diphenyl-2-propenyl benzoate with acetyl acetone, as measured by HPLC analysis (Scheme 12).



Scheme 12. Preparative allylic alkylation reaction with acetyl acetone as nucleophile.

Phox derivatives **40**, **41** and **27** are clearly the most effective ligands whereas the analogous bis(*ortho*-tolyl)-substituted phosphanes **42** and **28** induce only moderate enantioselectivities. The two enantiomeric ligands (*S*)-**27** and (*R*)-**27** gave the exactly reverse peak ratios, confirming that quasienantiomers (*R*)-**30a** and (*S*)-**30b** perfectly behave as real enantiomers. This result was verified by an additional control experiment with inversely labelled quasienantiomers (*S*)-**30a** and (*R*)-**30b** bearing interchanged methyl and ethyl groups. The screening was carried out with ligands **40** and **42** under the conditions described in Scheme 11 and in both cases a perfectly reverse peak ratio was obtained (Table 2).

Table 2. ESI-MS screening of quasiracemates (*R*)-**30a** + (*S*)-**30b** and (*S*)-**30a** + (*R*)-**30b** using ligands (*S*)-**40** and (*S*)-**42**.

Ligand	(*R*)-**30a** : (*S*)-**30b**	(*S*)-**30a** : (*R*)-**30b**
 **40**	3 : 97 	97 : 3 
 **42**	20 : 80 	80 : 20 

The results obtained with phosphinooxazoline ligands **27**, **28** and **40**-**42** prove that the ESI-MS screening of the back reaction is a fast and reliable method for evaluating libraries of chiral catalysts.

2.2.3 Reversibility of the Back Reaction

During the investigations described above it became clear that the selectivity observed within the screening is time-dependent. As shown in Figure 4 the peak ratio slowly decreases when aliquots at differing reaction times are taken.

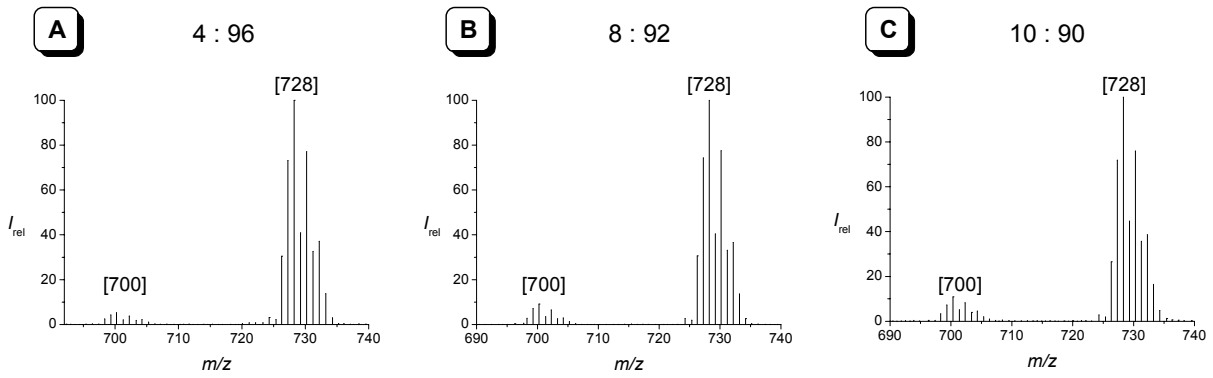
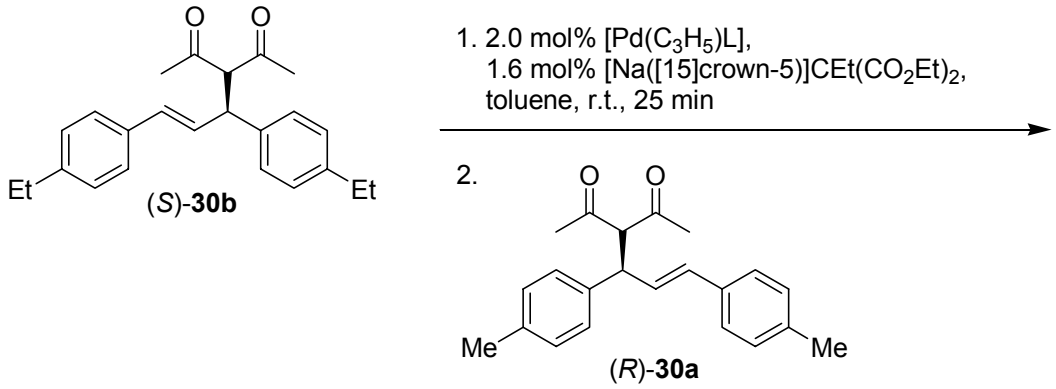


Figure 4. ESI-MS screening of ligand (*S*)-**27** using quasiracemate (*R*)-**30a** + (*S*)-**30b**. Samples were taken after 30 s (A), 15 min (B) and 45 min (C).

This is presumably caused by the reversibility of the reaction as the elimination of acetyl acetonate is an endergonic process. For clarification a substitution experiment was carried out. A precatalyst solution, prepared from $[Pd(C_3H_5)(MeCN)_2]OTf$ and an equimolar amount of ligand (*S*)-**42** was mixed with the ethyl-labelled quasienantiomer (*S*)-**30b** and the reaction was initiated by addition of the crown ether sodium salt of diethyl ethylmalonate (Scheme 13). In contrast to standard screening conditions a substoichiometric amount of nucleophile, based on the palladium-precursor, was used (0.8 equivalents). The corresponding mass spectrum showed the allyl-palladium intermediate **39b** as expected (Figure 5, A). After a reaction time of 25 minutes, when no initial nucleophile was assumed to be left, a solution of the methyl-substituted quasienantiomer (*R*)-**30a** was added. The reaction mixture was analysed by ESI-MS and allyl-palladium intermediate **39a** was visible in small quantities indicating that the screening reaction is reversible (Figure 5, B).



Scheme 13. Investigating the reversibility of the screening reaction.

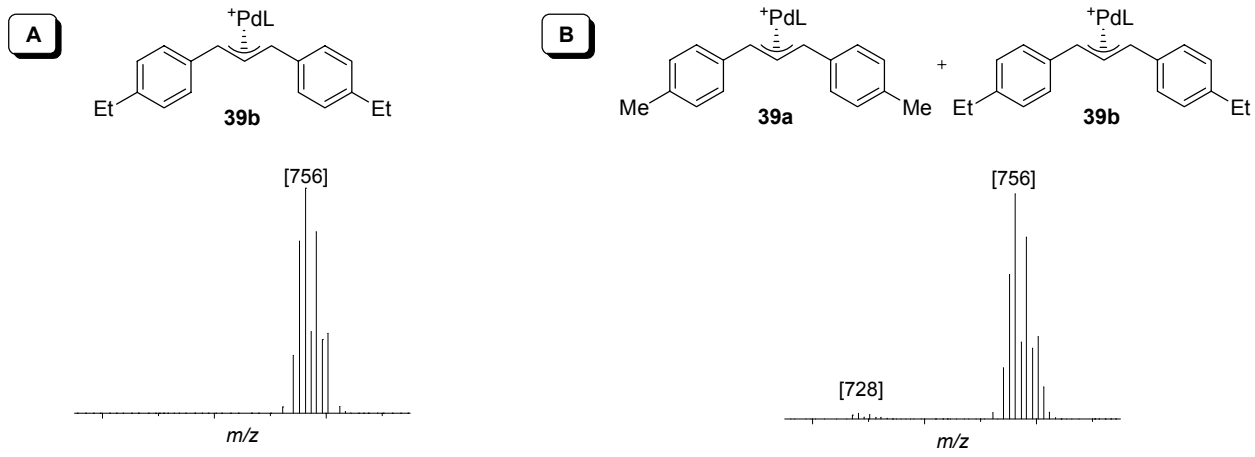


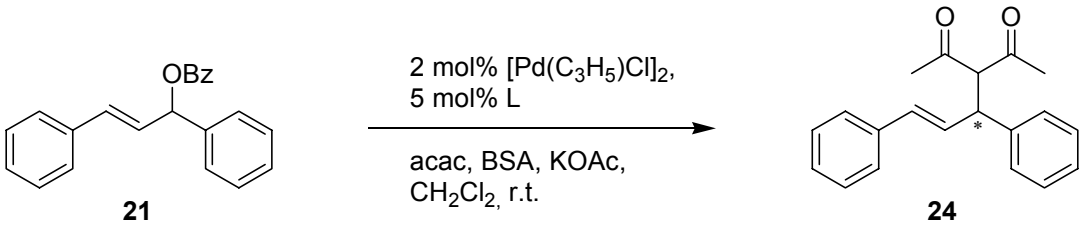
Figure 5. ESI-MS experiment investigating the reversibility of the screening reaction. Mass spectrum obtained when using (*S*)-**30b** and ligand (*S*)-**42** (A) and mass spectrum after the addition of (*R*)-**30a** (B).

These findings indicate, that the peak ratio decreases slowly due to racemisation of quasienantiomers (*R*)-**30a** and (*S*)-**30b** through the reversible elimination-readdition of acetyl acetonate. However, at the initial stage of the reaction the concentration of acetyl acetonate is much lower than that of diethyl ethylmalonate and therefore the addition of acetyl acetonate to the allyl-palladium complexes negligible. The results of the screening are not affected if the samples are taken at the very beginning of the reaction.

The equilibrium between the allylation products **30a** and **30b** and the corresponding allyl complexes **39a** and **39b** must lie almost entirely on the side of **30a** and **30b**, as these are known to be stable products. Nevertheless, due to the high sensitivity of ESI-MS both the reliable detection and the accurate quantification of the allyl intermediates is possible despite their low overall concentration.

2.2.4 Influence of Palladium-Precursor and Solvent on the Selectivity in Preparative Allylic Alkylation Reactions

The investigations also demonstrated that enantioselectivities of the preparative reactions under screening conditions ($[Pd(C_3H_5)(MeCN)_2]OTf$ in toluene, Scheme 12) are superior to those obtained under standard conditions ($[Pd(C_3H_5)Cl]_2$ in CH_2Cl_2, Scheme 14). A comparison is shown in Table 3. With the most efficient catalysts **40**, **41** and **27** only small deviations are observed, whereas the selectivity of bis(*ortho*-tolyl)-substituted phosphanes **42** and **28** was found to be more sensitive to changes in reaction conditions.



21 **24**

Scheme 14. Allylic alkylation of benzoate **21** with acetyl acetone and ($[Pd(C_3H_5)Cl]_2$ as catalyst precursor in CH_2Cl_2.

Table 3. Comparison of different reaction conditions for the allylic alkylation of benzoate **21** with acetyl acetone.

		$[Pd(C_3H_5)(MeCN)_2]OTf$ in toluene (Scheme 12)			$[Pd(C_3H_5)Cl]_2$ in CH_2Cl_2 (Scheme 14)		
Entry	Ligand	Time [h]	Yield [%]	*ee* [%][a]	Time [h]	Yield [%]	*ee* [%][a]
1	**40**	14	92	> 99	16	96	94
2	**41**	16	98	97	1	98	97
3	**27**	17	100	96	16	98	92
4	**42**	85	100	72	52	78	41
5	**28**	71	100	66	17	98	21

[a] HPLC analysis (Daicel Chiracel AD-H, heptane/isopropanol 97:3, 0.9 mL*min^{-1}, 20 °C, 254 nm): t_R = 16.3 (*R*), 17.9 (*S*) min.

2.2.5 Mass Spectrometric Screening of Other Chiral Ligands

After having established a reliable ESI-MS screening protocol a series of other ligands was tested to investigate the scope of this new approach. It was not possible to determine the efficiency of all catalysts, as with a number of ligands only unreacted precatalyst $[Pd(C_3H_5)L]^+$ was detected. With the majority of Walphos-, Mandyphos- and Taniaphos-type ligands from the Solvias ligand kit,[90] as well as the other ligands shown in Figure 6, no allyl-palladium intermediates **39a** and **39b** were observed.

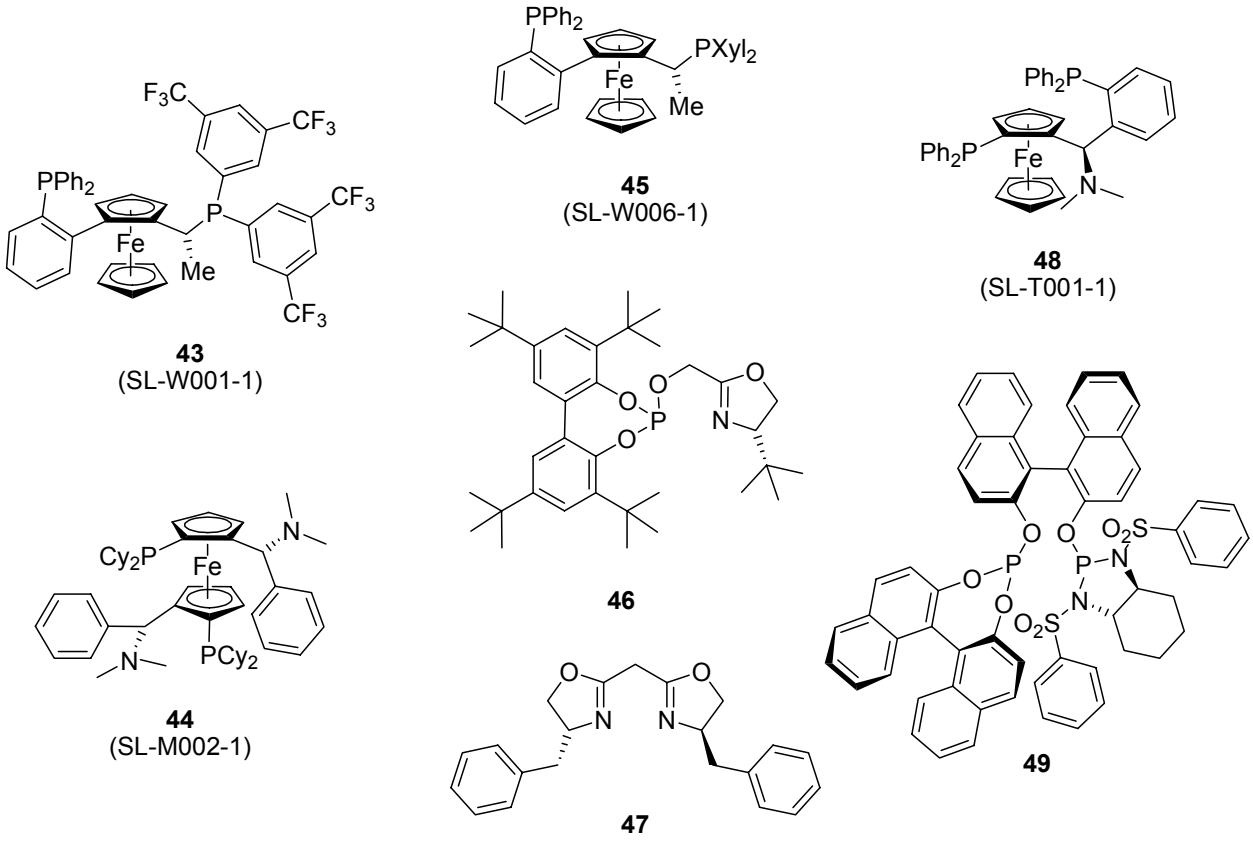
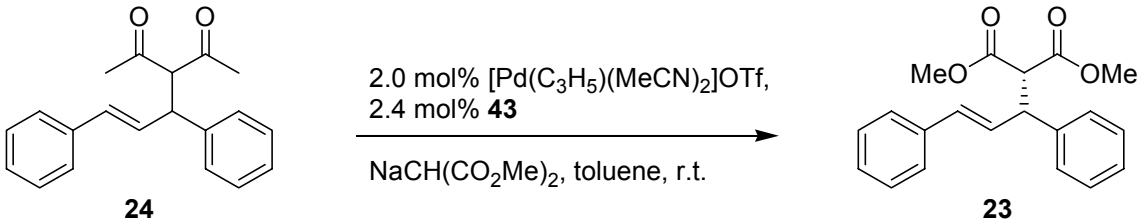


Figure 6. Selected ligands showing no allyl-palladium intermediates **39a** and **39b** in the back reaction screening according to Scheme 11.

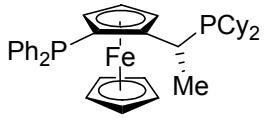
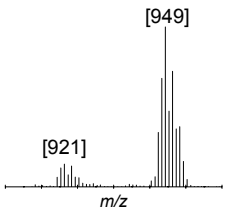
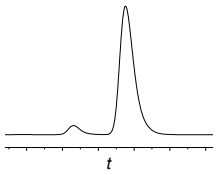
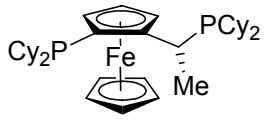
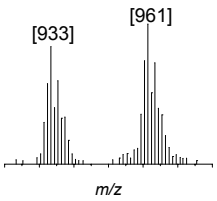
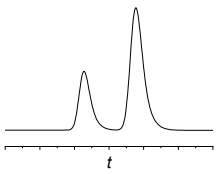
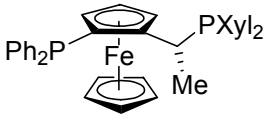
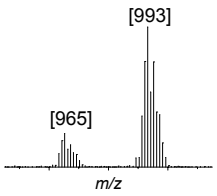
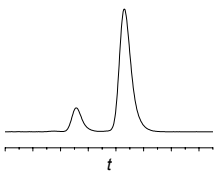
Exemplary, a preparative reaction with Walphos-type ligand **43** was carried out for comparison according to Scheme 12. After 19.5 hours the alkylation product **24** was obtained in high yield with 92% *ee* (*R*), showing that allylic alkylation proceeded smoothly. The preparative back reaction of **24** using ligand **43** was also analysed and no product formation was observed under ESI-MS screening conditions, indicating a high activation energy for the back reaction.



Scheme 15. Preparative back reaction of substrate **24** using ligand **43**.

When an analogous experiment was carried out with the sodium salt of dimethyl malonate in tetrahydrofuran product **23** was formed in small amounts according to NMR analysis (Scheme 15). However, no allyl-palladium complex **16** (R = Ph) was detected in the mass spectrum under these conditions (for further discussions see Chapter 3.3).
Results with Josiphos-type ligands **50**-**52** are depicted in Table 4.

Table 4. ESI-MS screening of allylic alkylations with Josiphos-type ligands **50**-**52** using quasienantiomers (*R*)-**30a** and (*S*)-**30b** according to Scheme 11.

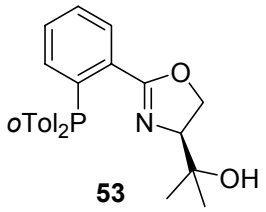
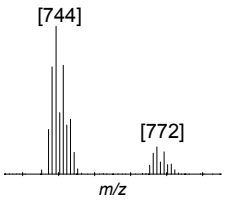
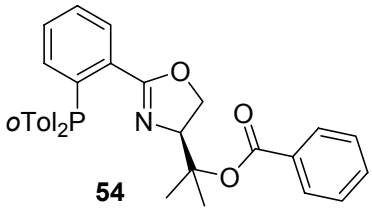
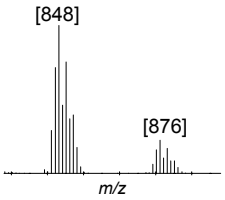
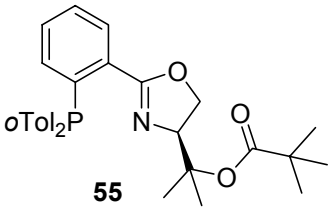
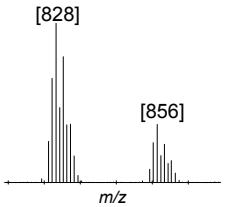
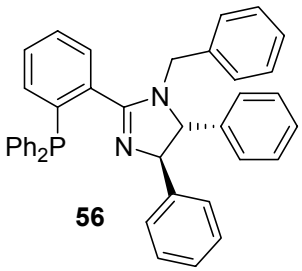
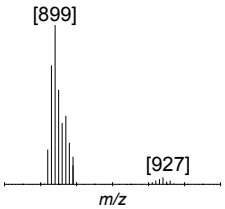
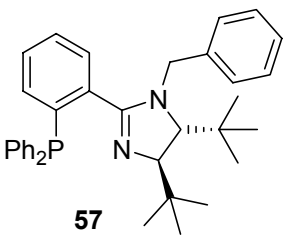
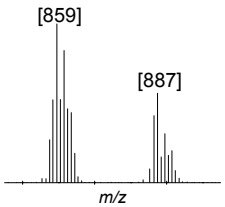
Entry	Ligand	Screening **39a** : **39b**	Preparative Reaction[a] (*R*)-**24** : (*S*)-**24**
1	 **50** (SL-J001-1)	12 : 88 	7 : 93 
2	 **51** (SL-J003-1)	44 : 56 	30 : 70 
3	 **52** (SL-J005-1)	20 : 80 	23 : 77 

[a] HPLC analysis (Daicel Chiracel AD-H, heptane/isopropanol 97:3, 0.9 mL*min^{-1}, 20 °C, 254 nm): t_R = 16.3 (*R*), 17.9 (*S*) min.

The selectivities determined by ESI-MS correlate with the data from the HPLC analysis of the preparative reactions of racemic 1,3-diphenyl-2-propenyl benzoate **21** with acetyl acetonate. With ligand **51** only mass spetra of low quality were obtained, this presumably explains the poor correlation observed. However, enantioselectivity of the most selective ligand **50** was easily determined and the order of selectivity reliably reproduced.

Phox and phim ligands **53**-**57**[91] were also analysed to evaluate their efficiency in the allylic alkylation of **21** with acetyl acetone (Table 5).

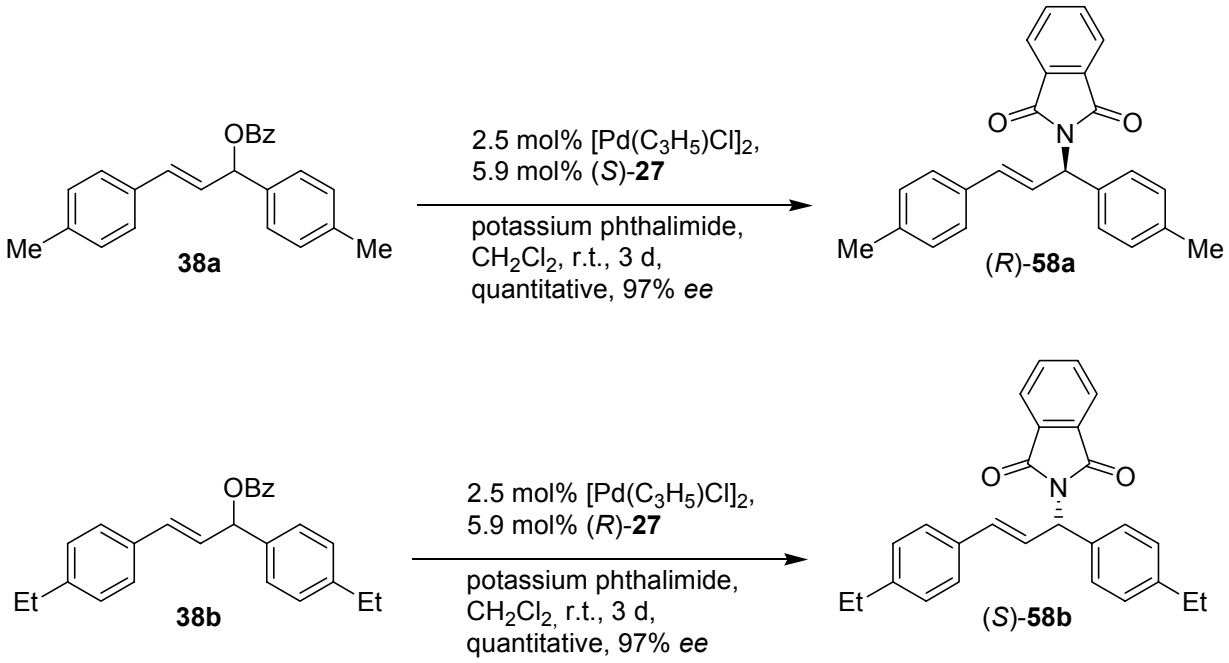
Table 5. ESI-MS screening of allylic alkylations with phox and phim ligands **53**-**57** using quasienantiomers (*R*)-**30a** and (*S*)-**30b** according to Scheme 11.

Entry	Ligand	**39a : 39b**
1	 **53**	86 : 14 
2	 **54**	82 : 18 
3	 **55**	72 : 28 
4	 **56**	97 : 3 
5	 **57**	63 : 37 

The majority of ligands exhibit only moderate selectivities, but phim **56** proved to be very efficient giving allyl-palladium intermediates **39a** and **39b** with a ratio of 97:3. This result was verified by comparison with the corresponding preparative reaction. Product **24** was thereby isolated with 96% *ee* (*R*), again validating the method.

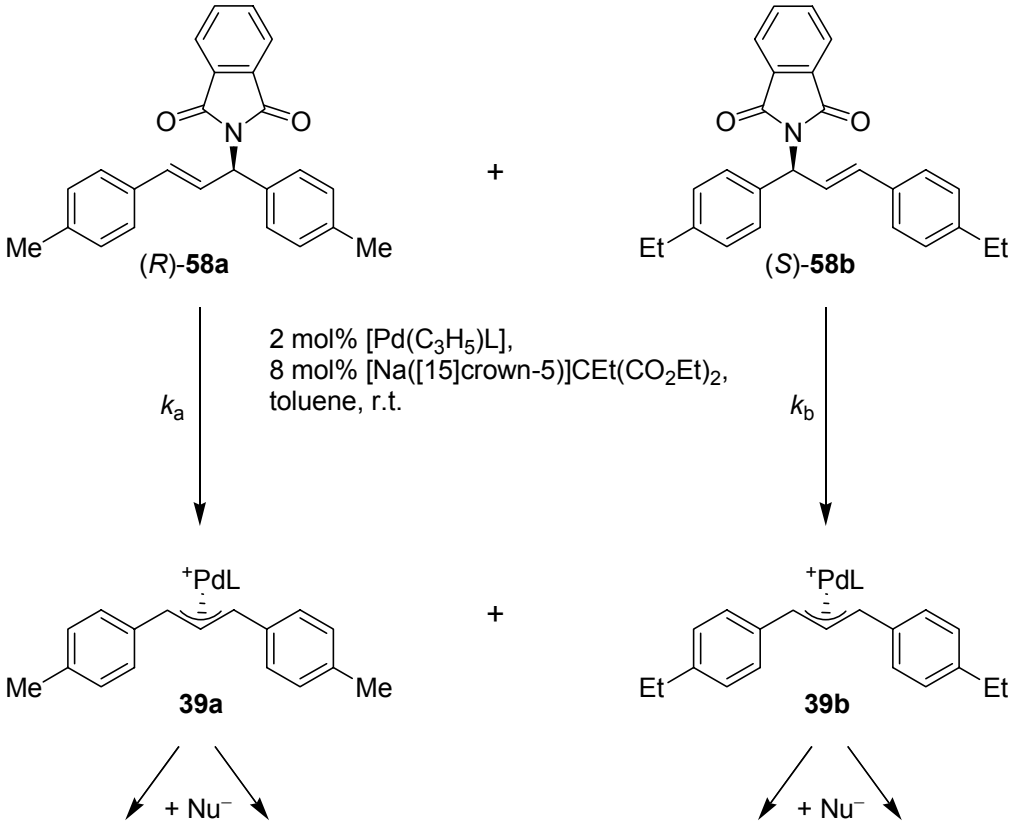
2.3 Asymmetric Allylic Aminations

After having established a reliable screening protocol for the allylic alkylation reaction, we turned our attention to allylic aminations. The back reaction screening technique was successfully applied to the allylic amination using phthalimide. Quasienantiomers (*R*)-**58a** and (*S*)-**58b** were prepared from benzoates **38a** and **38b** according to Scheme 16. The respective reactions with potassium phthalimide gave the products in excellent yields and enantioselectivities of 97% *ee* each.



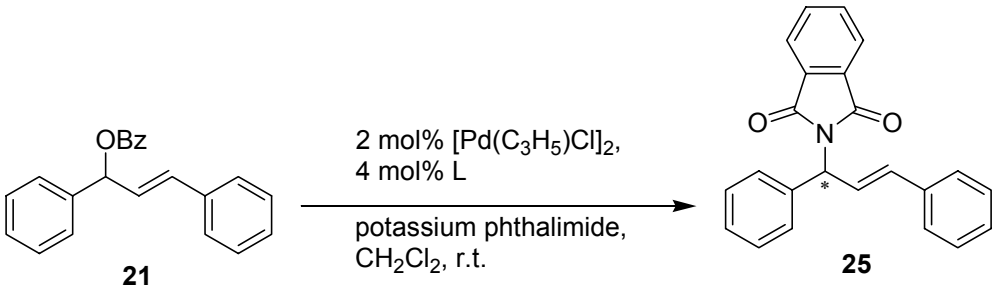
Scheme 16. Synthesis of quasienantiomers (*R*)-**58a** and (*S*)-**58b** by palladium-catalysed allylic aminations.

When quasienantiomeric *N*-allyl phthalimides (*R*)-**58a** and (*S*)-**58b** were reacted under the conditions used for screening reactions with acetyl acetonate as nucleophile, the corresponding allyl-palladium intermediates **39a** and **39b** were observed by ESI-MS and the selectivities were determined using the signal intensity ratios of the two signal clusters (Scheme 17).



Scheme 17. Back reaction screening of the nucleophilic addition step of allylic aminations with phthalimide.

For comparison, the corresponding preparative reactions of racemic 1,3-diphenyl-2-propenyl benzoate with potassium phthalimide and 2 mol% of catalyst, prepared *in situ* from $[Pd(C_3H_5)Cl]_2$ and the chiral ligand, were carried out in dichloromethane at room temperature (Scheme 18). Under the conditions used for the ESI-MS screening using toluene as the solvent no conversion was observed, presumably due to the insolubility of the potassium phthalimide in the reaction medium.



Scheme 18. Preparative allylic aminations using potassium phthalimide as nucleophile.

Table 6. ESI-MS screening of allylic aminations using quasienantiomers (*R*)-**58a** and (*S*)-**58b** according to Scheme 17.

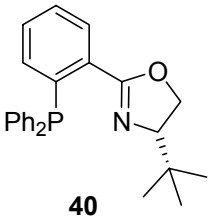
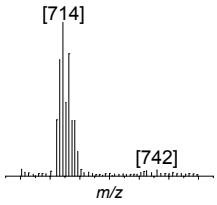
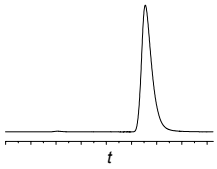
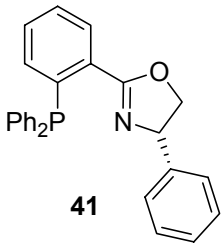
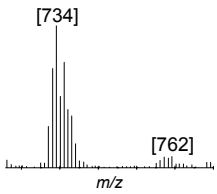
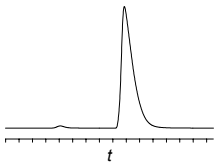
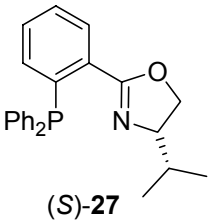
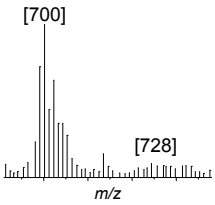
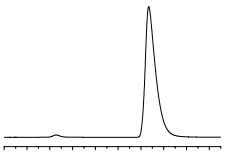
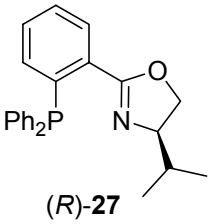
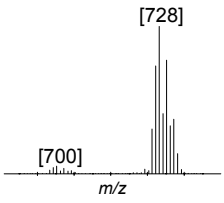
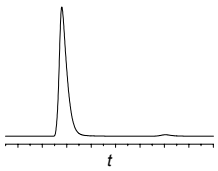
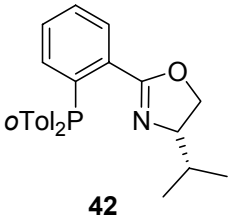
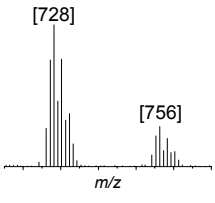
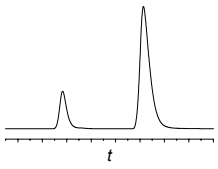
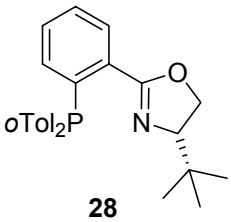
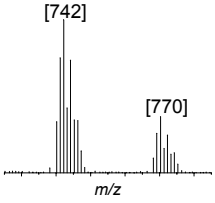
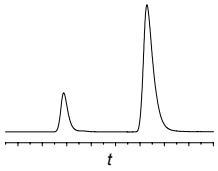
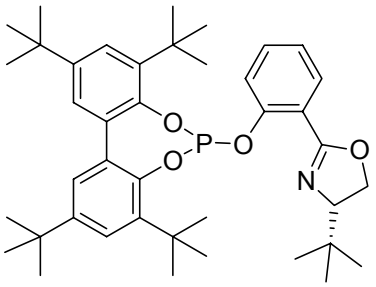
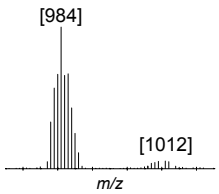
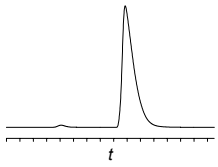
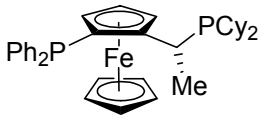
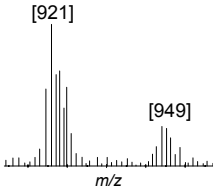
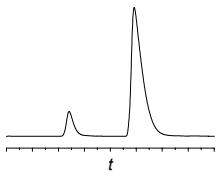
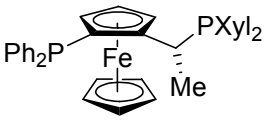
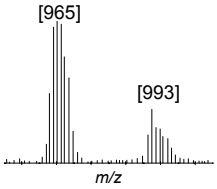
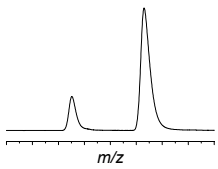
Entry	Ligand	Screening **39a** : **39b**	Preparative Reaction[a] (*S*)-**25** : (*R*)-**25**
1	 **40**	97 : 3 	< 1 : > 99 
2	 **41**	94 : 6 	1 : 99 
3	 (*S*)-**27**	96 : 4 	1 : 99 
4	 (*R*)-**27**	4 : 96 	99 :1 
5	 **42**	78 : 22 	19 : 81 
6	 **28**	78 : 22 	19 :81 

Table 6. Continued.

Entry	Ligand	Screening **39a** : **39b**	Preparative Reaction[a] (*S*)-**25** : (*R*)-**25**
7	 **59**	95 : 5 	1 : 99 
8	 **50** (SL-J001-1)	82 : 18 	18 : 82 
9	 **52** (SL-J005-1)	86 : 14 	14 : 86 

[a] HPLC analysis (Daicel Chiracel OD-H, heptane/isopropanol 99:1, 0.5 mL*min^{-1}, 20 °C, 254 nm): t_R = 37.6 (*S*), 51.8 (*R*) min.

It is evident from Table 6 that the enantioselectivities induced by ligands **27**, **28** and **40-42** are very similar to those measured for the analogous reaction with acetyl acetonates (Table 1). Peak ratios determined by ESI-MS correlate well with the results of the preparative reactions. The somewhat lower selectivities obtained in the screening may be due to the different conditions applied in the preparative reactions and/or the reversibility of phthalimide elimination (see Chapter 2.2.3). However, despite these small deviations, the ESI-MS method reveals the correct selectivity order and therefore allows reliable identification of the most selective catalyst. With the Josiphos-type ligands the data from the screening correlate also very well with the results obtained by preparative allylic amination reactions.

2.4 Screening of Catalyst Mixtures

The preceding results show that the developed ESI-MS screening technique provides data on the enantioselectivity of allylic alkylation and amination reactions with excellent agreement to the results obtained from preparative reactions.

After establishing a reliable protocol for the screening of single catalysts the method was extended to analyse mixtures of several palladium catalysts in one reaction pot. Initial studies focused on the allylic amination as a test reaction (Scheme 17) because phthalimide shows a higher leaving group ability in the back reaction when compared to acetyl acetonate. Three different precatalysts were combined with the quasiracemate (*S*)-**58a** and (*R*)-**58b** in toluene at –20 °C and the reaction was started by the addition of the crown ether sodium salt of diethyl ethylmalonate. The control spectrum before activation of the precatalyst showed the corresponding three allyl-palladium complexes as expected.

It was previously demonstrated that the screening of mixtures in the kinetic resolution of allylic esters has to be carried out at –78 °C in order to suppress ligand exchange.[6] In the back allylic amination we also experienced ligand exchange at room temperature, whereas at –78 °C unsufficient reactivity was observed. For this reason the reaction temperature had to be slightly increased. Initial results were obtained for different Phox, Josiphos-type and Claver-type ligands. It became clear that the analysis of these mixtures is hindered by the low reactivity of the back reaction in general. Possible ligand combinations are further limited due to similar molecular masses and differences in reactivity of the respective catalysts. Phox ligands, particularly with bis(*ortho*-tolyl)-substituted phosphorus atoms, were found to be much more reactive than the Josiphos or Claver-type derivatives and the signals of the latter become too small or unobservable. Provided that catalyst reactant complexes are detected in the mixture, it is possible to establish a qualitative selectivity order from the spectra. One example is shown in Figure 7, in which all precatalysts and catalyst reactant complexes are visible in the mass spectrum. Phosphinooxazoline **40**, bearing a *tert*-butyl group on the oxazoline, was found to be the most selective ligand in this mixture with a ratio of 12:88, followed by **41** with 13:87 and commercially available **52** with 30:70. The same selectivity order was obtained by comparison of each individual screening result. In these experiments phox ligands **40** and **41** show similar selectivities as well.

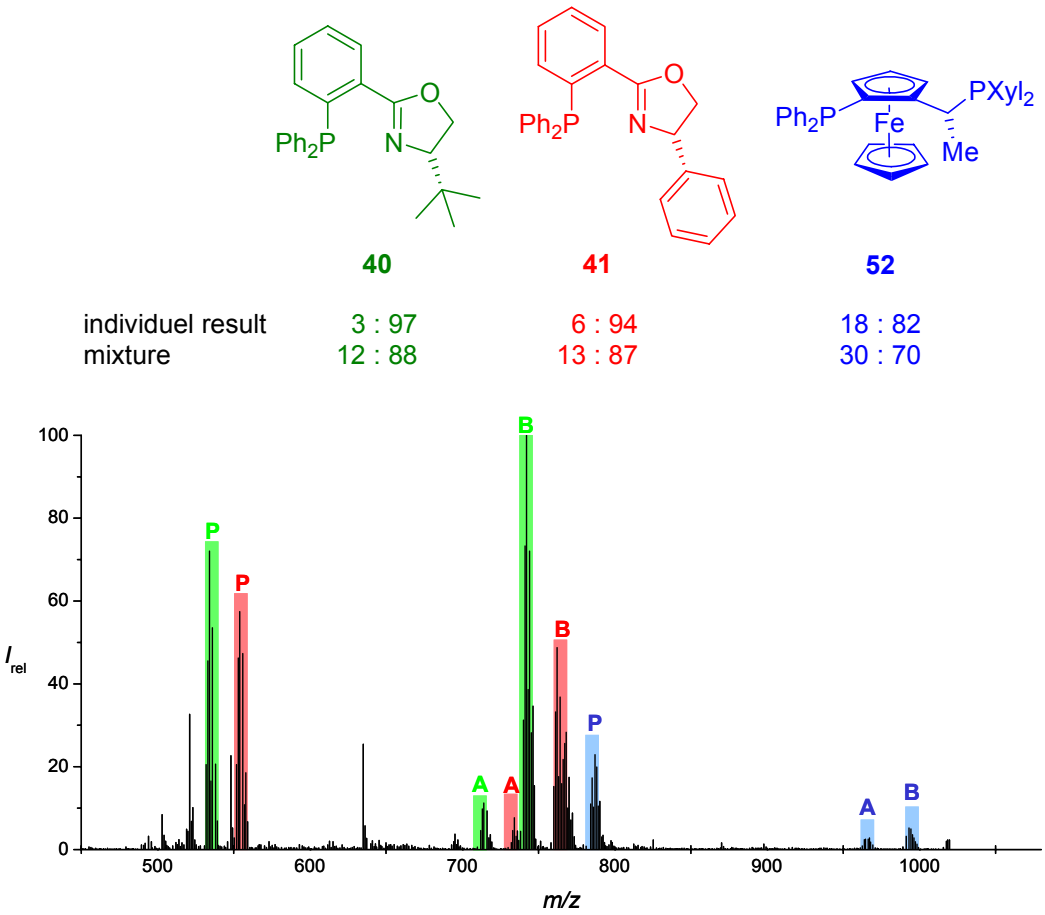


Figure 7. Back reaction screening of a catalyst mixture using quasienantiomers (*S*)-**58a** and (*R*)-**58b** with P **=** $[Pd(C_3H_5)L]^+$, A = **39a** and B = **39b**.

A mixture screening procedure was also developed for the back allylic alkylation reaction of quasienatiomeric substrates (*R*)-**30a** and (*S*)-**30b** according to Scheme 11. As expected this transformation was even more hampered by the decreased reactivity at lower temperatures. However a better correlation with results from the single catalyst screening was obtained compared to analogous allylic aminations. The analysis of the mixture shown in Figure 7, containing catalysts derived from (*S*)-**40**, (*S*)-**41** and **52** at –20 °C yielded ratios of 10:90, 8:92 and 22:78, respectively, for the corresponding allyl complexes **39a** and **39b**, whereas selectivities of 3:97, 2:98 and 20:80 were obtained by screening the isolated catalysts. Although the efficiencies are lower in multicatalyst screening for both allylic aminations and alkylations the order of selectivity remains unchanged and the most efficient catalysts can easily be determined.

2.5 Conclusions and Outlook

A fast and reliable method for the screening of chiral catalysts in palladium-catalysed asymmetric allylic substitutions of linear diarylallyl substrates, the most prominent model reaction in this field, has been developed. Based on the principle of microscopic reversibility the back reaction of the nucleophilic addition step was studied by electrospray mass spectrometry in order to evaluate the enantioselectivities of the respective catalysts. An equimolar mixture of mass-labelled quasienantiomeric allylation products was subjected to typical reaction conditions and the ratio of the resulting cationic allyl-palladium complexes, visible in the mass spectrum, determined with high accuracy.

Initially several derivatives, with commonly used nucleophiles as leaving groups, were analysed with respect to their reactivity in the back reaction. As expected the leaving group ability and hence suitability for the screening of the allylation products correlated perfectly with the pK_a values of the respective nucleophiles.

Based on these observations an ESI-MS screening procedure was developed for determining the efficiency of chiral palladium catalysts in allylic alkylations and aminations using substrates derived from acetyl acetone and phthalimide. In both cases selectivities of the back reactions observed by the ESI-MS were in excellent agreement with the corresponding data from the analogous preparative nucleophilic substitution reaction, proving the utility of this novel approach. As only the intrinsic selectivity is measured in the screening the effects of unselective background reaction, catalytically active impurities and ligand dissociation do not alter the results, in contrast to product analysis.

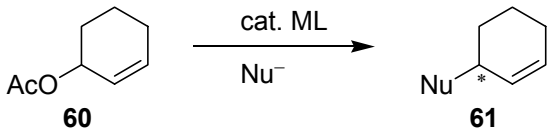
This methodology was extended to the simultaneous evaluation of several palladium complexes in a single reaction vessel. Although the selectivities obtained in this case were somewhat lower than the corresponding values measured for the single catalyst screening, the orders of selectivity remained the same. This allowed for a fast and reliable identification of the most powerful catalyst in the mixture.

CHAPTER 3

ESI-MS SCREENING OF CARBOCYCLIC SUBSTRATES

3 ESI-MS Screening of Carbocyclic Substrates

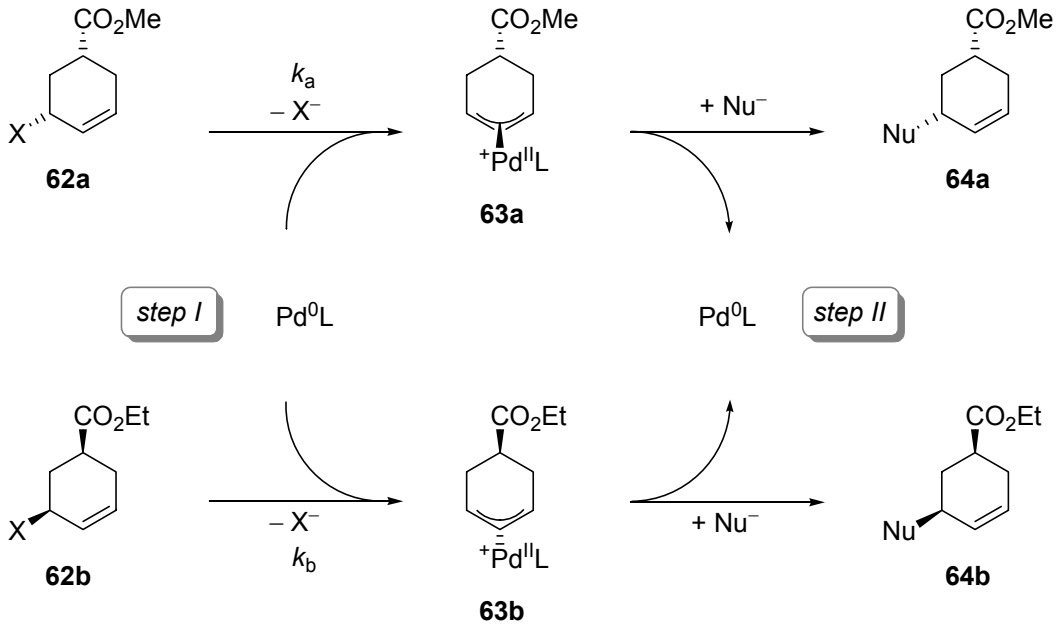
Asymmetric allylic substitution reactions of cyclic substrates remain a challenge. The enantioselectivities are usually more difficult to control due to the presence of less sterically demanding *syn* substituents.[80, 81]



Scheme 19. Allylic substitution of cyclohex-2-enyl acetate **60**.

To date only a limited number of ligands, such as diphenylphosphino benzoic acid (DPPBA) based derivatives,[92, 93] phosphite-oxazolines,[94, 95] cymantrene-based systems and β-phosphinocarboxylic acids[96] have been described to induce high selectivities in these transformations. Hence, the development of a rapid screening protocol based on ESI-MS for discovering highly selective palladium catalysts is of great interest.

The allylic alkylation of cyclohex-2-enyl acetate **60** with dimethyl malonate is commonly used as model reaction for the evaluation of new chiral ligands (Scheme 19).[80, 81, 92] Inspired by the work of Trost for the palladium-catalysed deracemisations of cyclic allyl esters,[97] ester groups were introduced as mass labels allowing for a simple differentiation of the two allyl-palladium intermediates. The catalytic cycle for the allylic substitution process using mass-labelled quasienantiomeric substrates is shown in Scheme 20. Both reaction steps can be analysed by mass spectrometry, as with previously studied allylic substitutions (Chapter 2). By using an equimolar mixture of **62a** and **62b**, the selectivity factor $s = k_a/k_b$ for the kinetic resolution (step I) can be deduced from the ratio of the corresponding allyl intermediates **63a** and **63b**. Furthermore the analysis of the back reaction of quasiracemate **64a**/**64b** to the latter allows determination of the enantioselectivity of the nucleophilic addition step and thus the selectivity of the overall allylic substitution process (step II).



Scheme 20. Mechanism of the palladium-catalysed allylic substitution of quasienantiomeric substrates **62a** and **62b**.

3.1 Kinetic Resolution of Racemic Allyl Esters

3.1.1 Initial Experiments

Initially an appropriate set of quasienantiomers **62a** and **62b** had to be identified for the screening of the kinetic resolution of cyclic allyl esters. Racemic methyl- and ethyl-labelled benzoates **65a** and **65b** were prepared (Scheme 21) and an equimolar mixture was analysed by ESI-MS. With phox ligand **28** the corresponding allyl complexes **63a** and **63b** were observed under the usual conditions applied in the back reaction screening for linear substrates (2 mol% catalyst, [Na([15]crown-5)]$CEt(CO_2Et)_2$, toluene, r.t., Chapter 2.2.2). The signals of **63a** and **63b** were detected with high intensity and a perfect 1:1 ratio, showing that quasienantiomeric substrates **65a** and **65b** behave like real enantiomers (Figure 8).

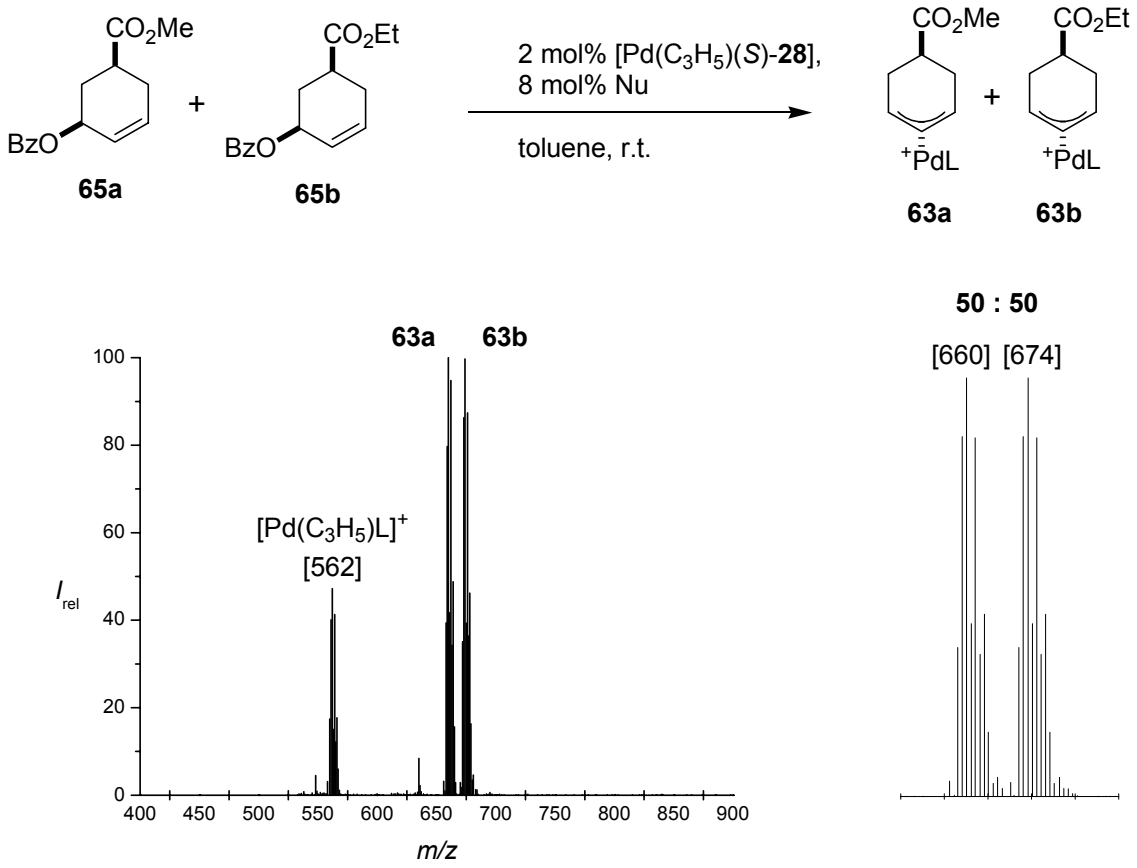
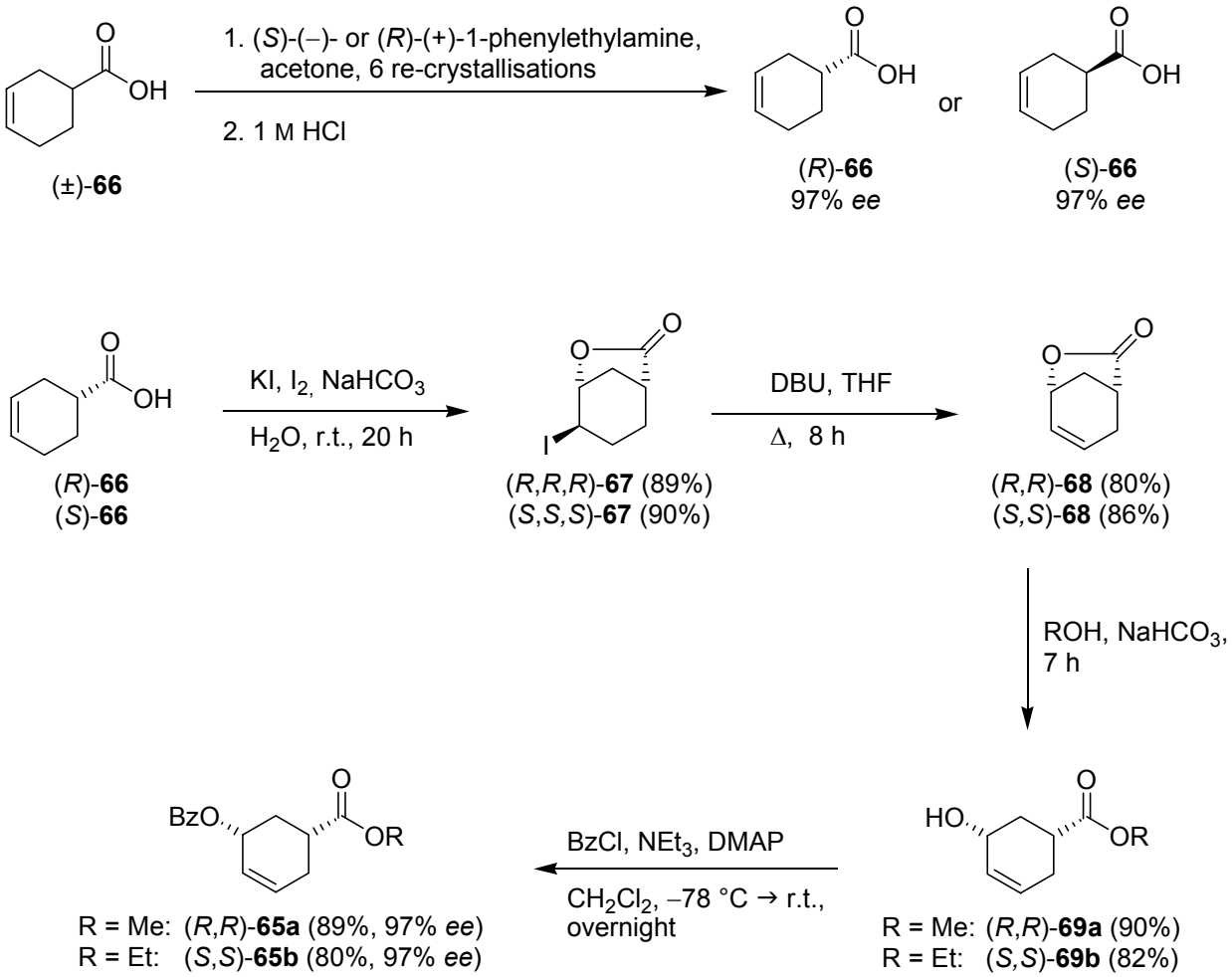


Figure 8. Control experiment with racemic quasienantiomers **65a** and **65b** (Nu = [Na([15]crown-5)]CEt(CO_2Et)$_2$).

3.1.2 Synthesis of Quasienantiomeric Benzoates

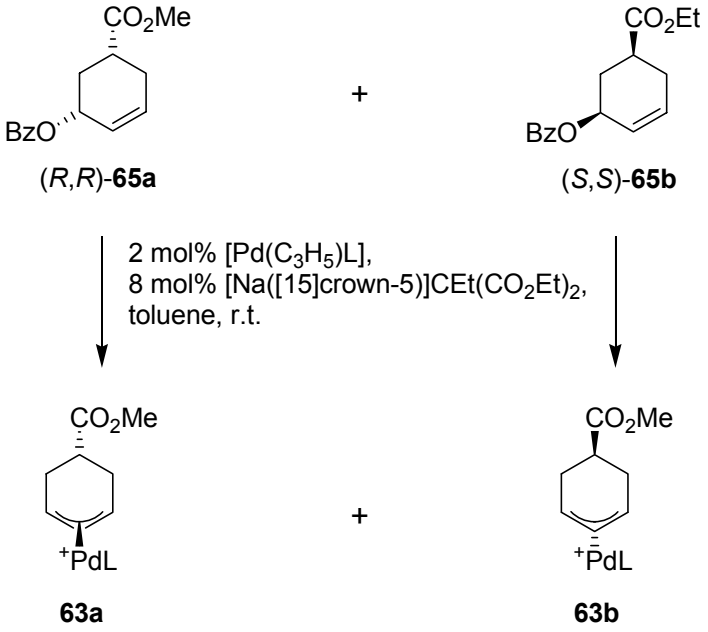
The preparation of benzoates (*R*,*R*)-**65a** and (*S*,*S*)-**65b** required enantiomerically pure cyclohex-3-enecarboxylic acid (**66**). Acid **66** was synthesised from from cyclohex-3-enecarbaldehyde by oxidation[98] and resolved by re-crystallisations of the corresponding (+)- and (–)-α-phenylethylamine salts.[99, 100] The free acid was obtained after acidic hydrolysis of the salts and both enantiomers were isolated with 97% *ee*. Iodolactonisation and DBU-induced elimination of the resulting iodides **67** gave unsaturated lactones (*R*,*R*)- and (*S*,*S*)-**68** in good yields.[101, 102] Ring opening was accomplished using sodium hydrogen carbonate in methanol and ethanol respectively.[102] The alcohols (*R*,*R*)-**69a** and (*S*,*S*)-**69b** were then converted to the corresponding benzoates. Both quasienantiomers (*R*,*R*)-**65a** and (*S*,*S*)-**65b** were isolated as single diastereomers with an enantiomeric excesses of 97% and similar results were obtained for the inversely labelled quasienantiomers (*S*,*S*)-**65a** and (*R*,*R*)-**65b**.



Scheme 21. Synthesis of quasienantiomeric substrates (*R*,*R*)-**65a** and (*S*,*S*)-**65b**.

3.1.3 Mass Spectrometric Evaluation of Chiral Ligands

Applying the established screening protocol according to Scheme 22 several palladium complexes were subjected to ESI-MS analysis (Figure 9). The catalysts were prepared *in situ* from equimolar amounts of $[Pd(C_3H_5)(MeCN)_2]OTf$ and the corresponding chiral ligands. A 1:1 mixture of (*R*,*R*)-**65a** and (*S*,*S*)-**65b** (25 equivalents based on Pd) was added and the reaction initiated by addition of the crown ether sodium salt of diethyl ethylmalonate (4 equivalents based on Pd). After 30 seconds at room temperature, an aliquot was taken and diluted with dichloromethane before direct injection into the mass spectrometer.



Scheme 22. Catalyst screening of the kinetic resolution using quasienantiomeric substrates (*R*,*R*)-**65a** and (*S*,*S*)-**65b**.

Allyl-palladium intermediates **63a** and **63b** were easily detected by ESI-MS, except for Walphos-type and phosphoramidite ligands. However, phosphinooxazolines, phosphino-imidazolines and most ligands of the Solvias ligand kit[90] were inefficient in the kinetic resolution of allylic esters (*R*,*R*)-**65a** and (*S*,*S*)-**65b**. Moderate results were obtained with **74** (63:37), **75** (37:63) and **76** (22:78), whereas good selectivity was achieved with ligand **49** (85:15).

Claver recently described a new family of phosphite-oxazolines with a bulky biphenyl phosphite moiety, which gave excellent reaction rates and enantioselectivities for a broad number of substrates in palladium-catalysed asymmetric allylic substitution reactions.[94] Ligand **59** was synthesised following the literature procedure and applied in the screening as well. The intermediates **63a** and **63b** were obtained in a ratio of 8:92, the best result in the screening to date.

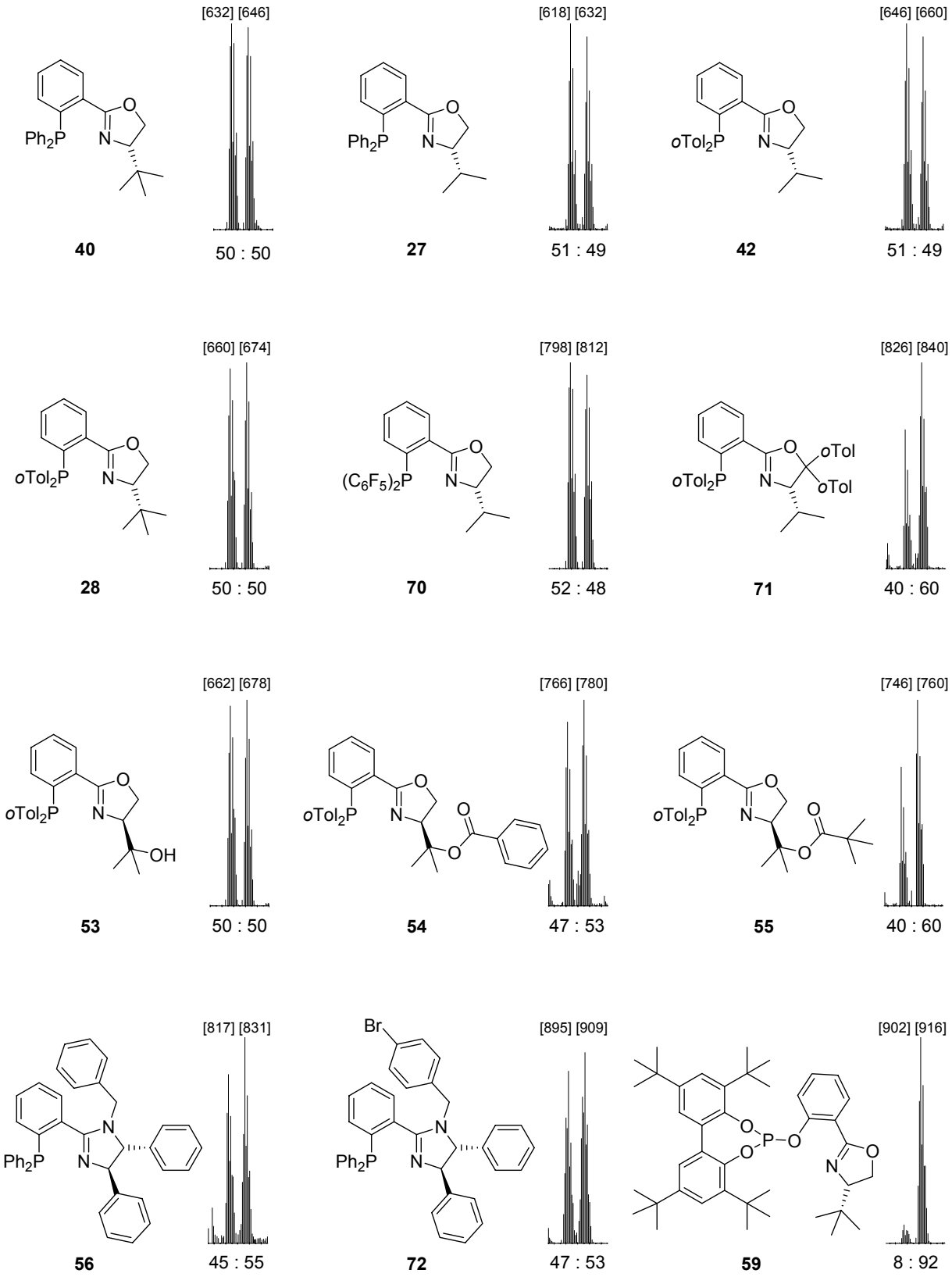


Figure 9. Screening results for the kinetic resolution of (*R*,*R*)-**65a** and (*S*,*S*)-**65b**.

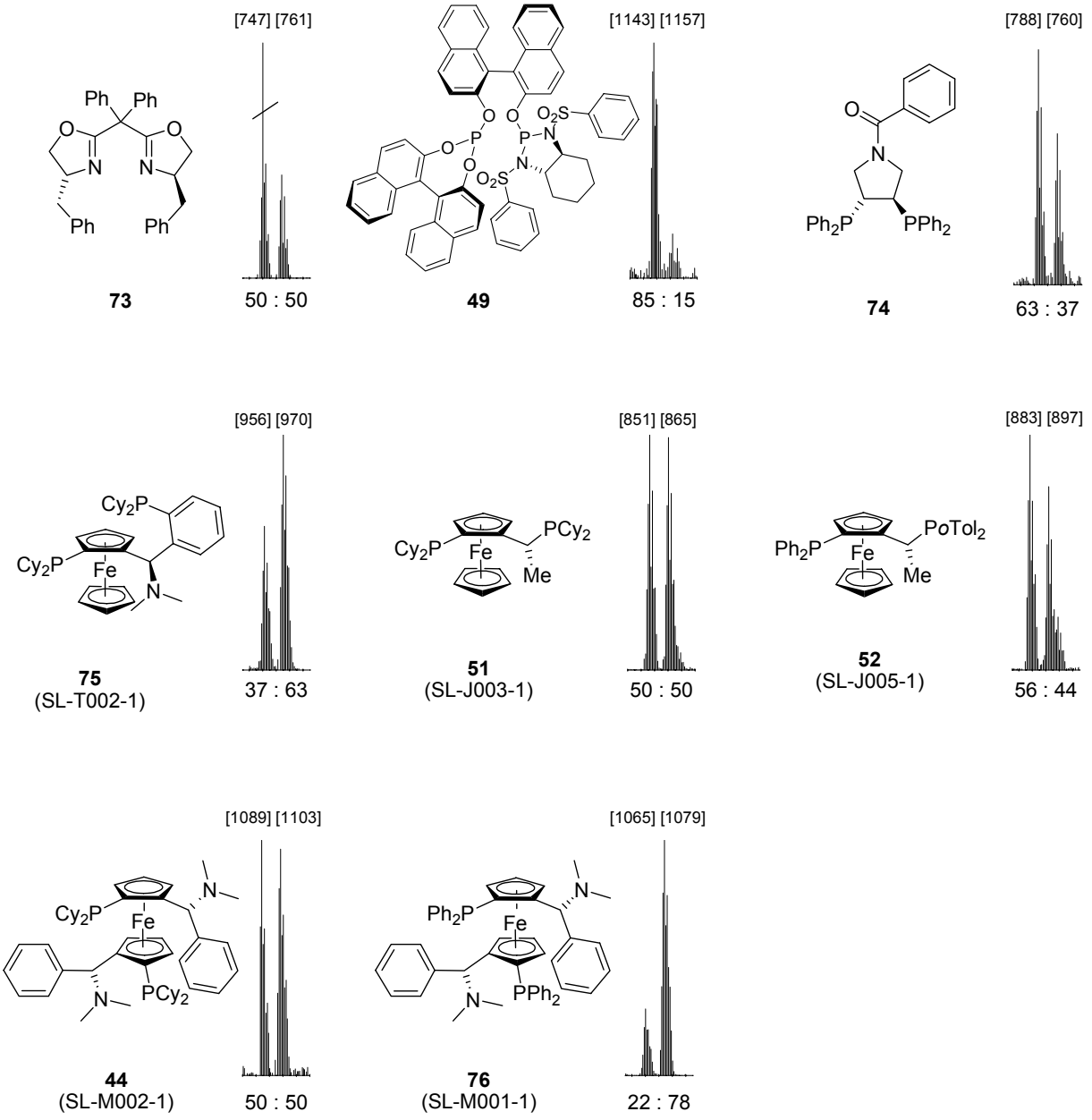


Figure 9. Continued.

3.1.4 Kinetic Analysis of Preparative Resolutions

In order to confirm the ESI-MS screening results the kinetic analysis of corresponding preparative reactions was carried out.

The kinetic resolution of benzoate **77** was initially studied using phosphite-oxazoline **59**, as this was the most selective ligand in the screening with a selectivity factor of $s = 11.5 \pm 0.29$ (Figure 10).

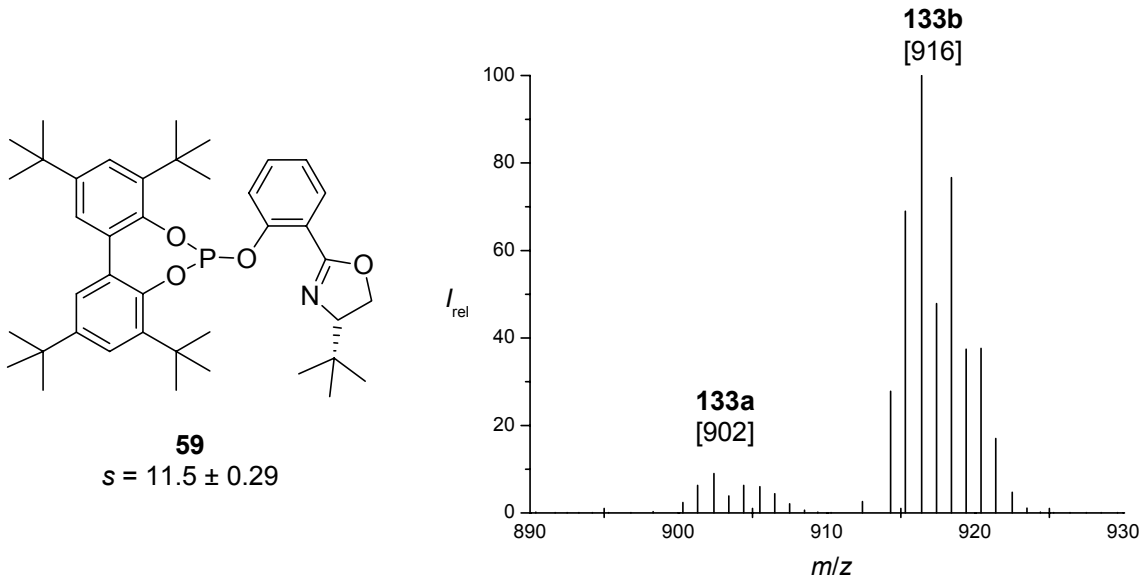
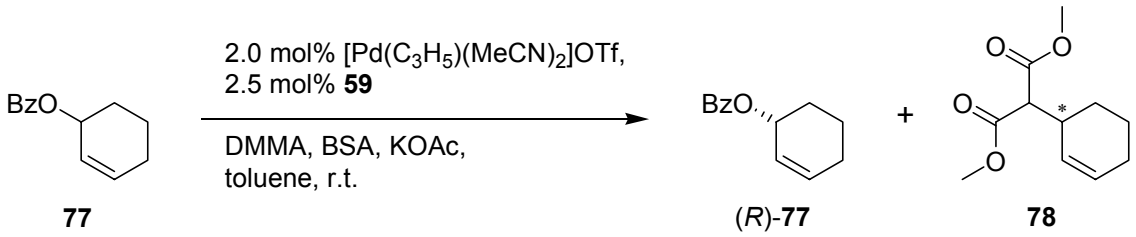


Figure 10. ESI-MS spectrum for the kinetic resolution depicted in Scheme 22 using ligand **59**.

The reaction was performed in toluene at room temperature using 2 mol% of catalyst, prepared *in situ* by stirring a solution of $[Pd(C_3H_5)(MeCN)_2]OTf$ with 1.25 equivivalents of **59** for three hours (Scheme 23). Three equivalents of both dimethyl malonate and *N*,*O*-bis(trimethylsilyl)acetamide were added, followed by a catalytic amount of potassium acetate.



Scheme 23. Preparative kinetic resolution of **77**.

In the simplest case of a kinetic resolution the substrate enantiomers interact with the chiral catalyst to generate two diastereotopic transition states. The free energies of these transition states define the rate constants for converting the fast- and slow-reacting enantiomers and therefore determine the product distribution. Assuming first order kinetics in substrate, the selectivity factor *s*, which is equal to the ratio k_{fast}/k_{slow}, can be calculated from the conversion and the enantiomeric excess of the remaining substrate (Equation **1**).[103]

$$s = \frac{\ln\left[\left(1-\frac{conversion}{100}\right)\left(1-\frac{ee_{substrate}}{100}\right)\right]}{\ln\left[\left(1-\frac{conversion}{100}\right)\left(1+\frac{ee_{substrate}}{100}\right)\right]} \qquad \textbf{[1]}$$

The *s* factor of the resolution depicted in Scheme 23 was measured by taking aliquots over the reaction course. The conversions were analysed by GC and corrected for catalyst loading. This correction is necessary, because substrate bound to the catalyst as a η^3-allyl fragment is removed during the workup.[104] The enantiomeric excesses of the remaining substrate were measured by chiral HPLC analysis. The experiment was repeated with consistent results and both sets of data points were analysed in one diagram (Figure 11).

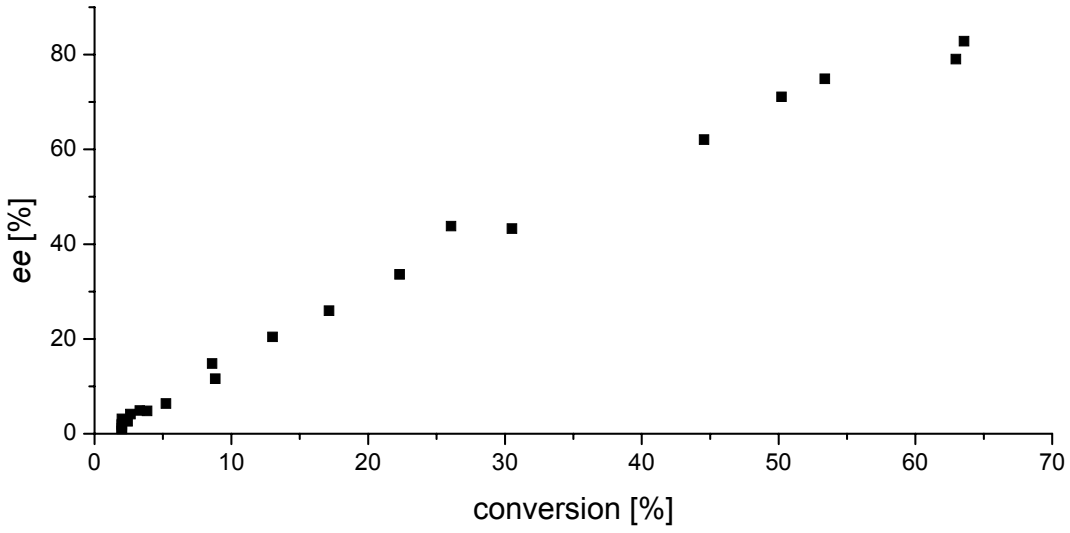


Figure 11. Kinetic resolution according to Scheme 23 using ligand **59**. Plot of the enantiomeric excess of the remaining substrate **77** against conversion.

The inverse function **2** of Equation **1** was used to calculate *s* by the least squares method.[104]

$$conversion\,[\%] = 100 \cdot \left[1-\frac{\left(1-\frac{ee_{Substrate}}{100}\right)^{1/s-1}}{\left(1+\frac{ee_{Substrate}}{100}\right)^{s/s-1}}\right] \qquad \textbf{[2]}$$

However, it was not possible to fit the data with this approach. After an initial induction period a nearly linear correlation was found. The Kagan model is not applicable in this case as

it requires the catalyst concentration to be stable.[103] The resolution catalysed by Claver-type ligand **59** seems not to fulfil this requirement. Within the first 15 minutes no conversion was observed and the reaction most likely suffers from catalyst decomposition after extended time. Even though it is more accurate to determine the *s* factor from multiple pairs of data points, it was not possible to evaluate the selectivity in this way. Therefore calculations from single point measurements were pursued. After conversions of 50% and 53% the remaining substrate was isolated with 71% and 75% *ee*, respectively. These pairs of data points correspond to *s* factors of 12.1 and 10.5. The 11.3 average of these two values matches the result from the screening very well.

A complete kinetic analysis was carried out for the resolution of **77** using Mandyphos-type ligand **76**, for which a *s* factor of 3.5 ± 0.31 was determined from the mass spectrum (Figure 12).

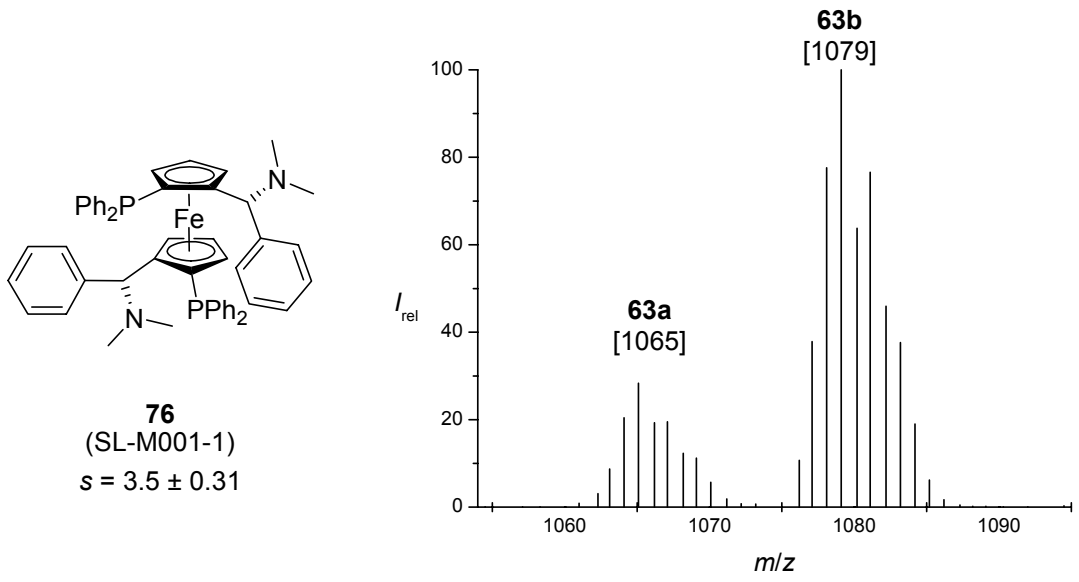


Figure 12. ESI-MS spectrum for the kinetic resolution depicted in Scheme 22 using ligand **76**.

The kinetic analysis was performed under analogous reaction conditions as described in Scheme 23. The experiment was repeated with consistent results and therefore both series of data points were plotted in one diagram (Figure 13). According to Equation **2** a value of 3.50 ± 0.08 was calculated using the least squares method, which exactly matches the *s* factor determined by ESI-MS.

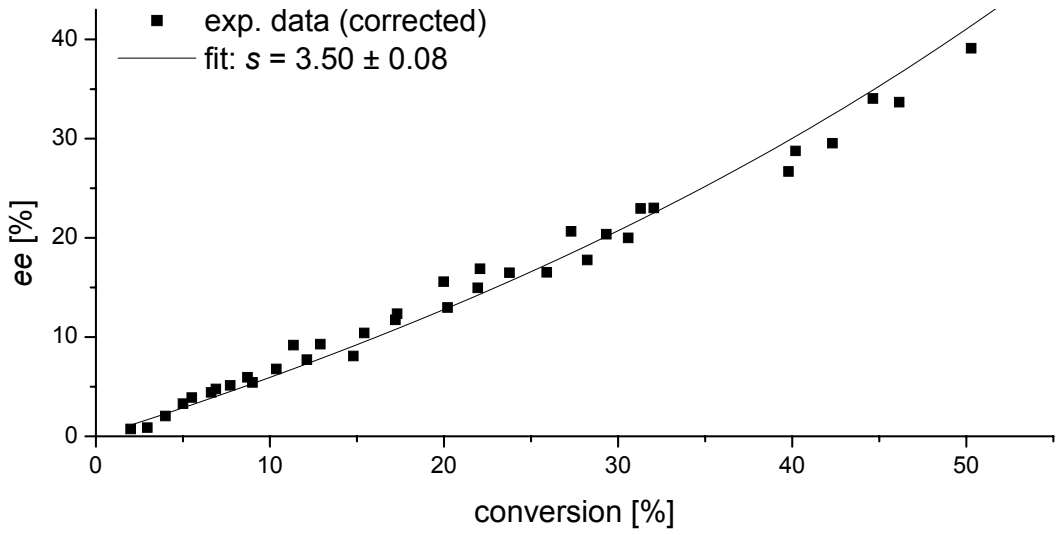


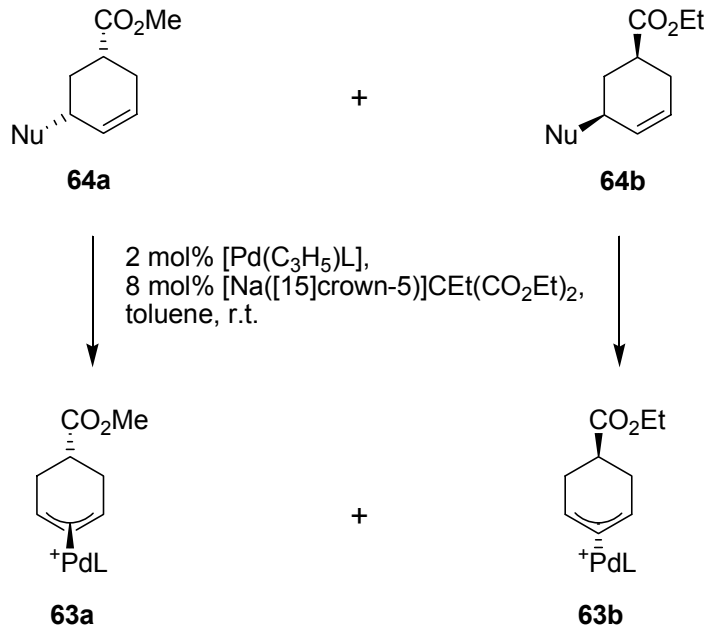
Figure 13. Kinetic resolution according to Scheme 23 using ligand **76**. Plot of the enantiomeric excess of the remaining substrate **77** against conversion.

These results prove the ESI-MS screening to be a fast and reliable method for evaluating libraries of chiral catalysts in the palladium-catalysed kinetic resolution of cyclohexenyl esters. Like this it can be used as efficient tool for the development of new ligand systems.

3.2 Back Reaction of Carbocyclic Substrates

3.2.1 Screening Method Development

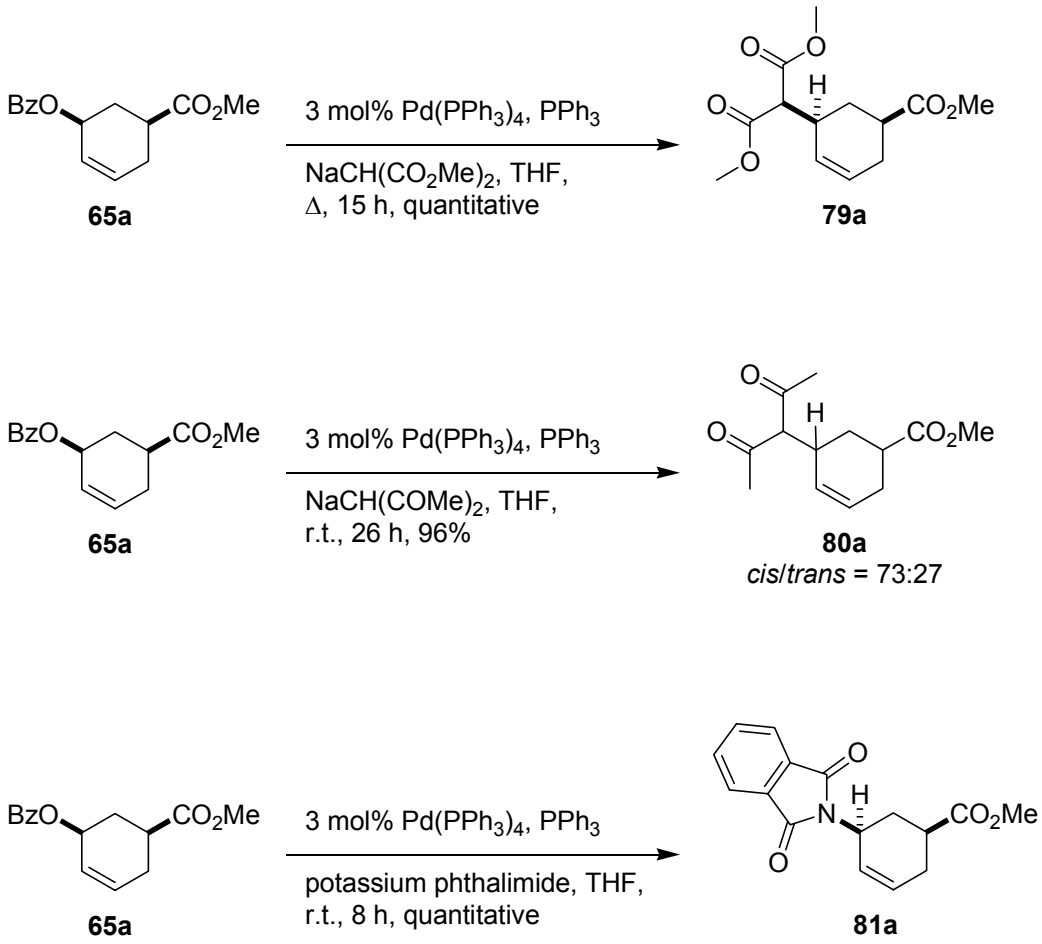
The next objective was to use the ESI-MS screening technique in palladium-catalysed asymmetric allylic substitutions of carbocyclic substrates. As already described in Chapter 2, the selectivity of product formation can be determined by monitoring the back reaction, *i.e.* formation of the corresponding allyl intermediates **63a** and **63b** from quasienantiomers **64a** and **64b** (Scheme 20). Again, we decided to use leaving groups that are usually applied as nucleophiles in the forward reaction.



Scheme 24. Back reaction screening of the nucleophilic addition step in allylic substitutions yielding products **64a** and **64b**.

A range of allylation products derived from dimethyl malonate, acetyl acetone and phthalimide were screened to find a nucleophile with sufficient reactivity as a leaving group (Scheme 25). Allyl-palladium complexes generated by elimination of these nucleophiles were successfully detected by ESI-MS for the corresponding linear substrates (Chapter 2.1). The analysis of a Meldrum's acid-based substrate was initially discarded as synthesis proved difficult.

Racemic products **79a-81a** were obtained by palladium-catalysed allylic substitutions as shown in Scheme 25.



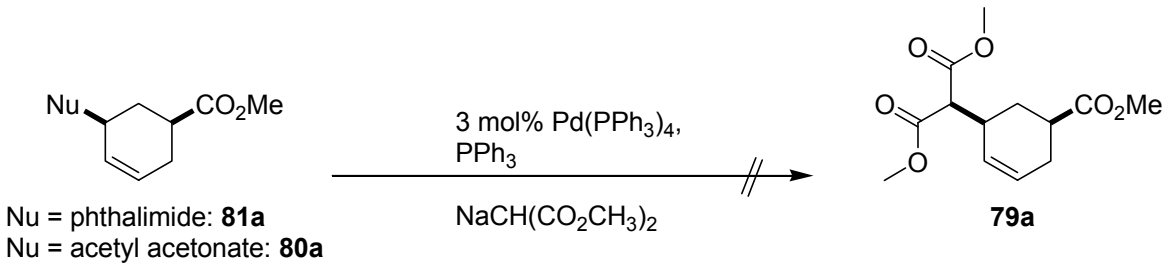
Scheme 25. Preparation of substrates **79a**-**81a** by palladium-catalysed allylic substitutions.

Alkylation of **65a** using sodium dimethyl malonate, tetrakis(triphenylphosphine)palladium and an excess of triphenylphosphine in refluxing tetrahydrofuran afforded product **79a** in quantitative yield.[105] The reaction proceeds with complete retention of configuration, whereas the corresponding transformation with acetyl acetone gives the product **80a** as a c*is*/*trans* mixture in a ratio of 73:27. Benzoate **65a** smoothly reacted with potassium phthalimide to produce the *cis*-diastereomer of **81a** exclusively.

No allyl-palladium complex **63a** was detected employing substrates **79a**-**81a** with several structurally different ligands under the standard conditions (Scheme 24). Variation of the reaction solvent, such as toluene, tetrahydrofuran, dichloromethane and dimethylformamide gave no observable back reaction. Increasing the reaction temperature had also no positive influence on the outcome of the screening.

Preparative back reactions were carried out to confirm that no product formation occurs in this reaction. Phthalimide derived substrate **81a** was treated with the sodium salt of dimethyl malonate in the presence of tetrakis(triphenylphosphine)palladium and an excess of triphenylphosphine in tetrahydrofuran (Scheme 26). The reaction mixture was analysed by

ESI-MS and no signals were detected. After two days either at room temperature or reflux no conversion was observed and aqueous workup gave a quantitative recovery of the starting material.



Scheme 26. Preparative back reactions using racemic substrates **81a** and **80a**.

The transformation was carried out under microwave conditions in tetrahydrofuran or acetonitril and no product formation observed in either case. The preparative back reaction of **80a** was also investigated using the same conditions described above (Scheme 26). After two days at either room temparature or reflux no conversion of the starting material was found and no allyl-palladium complex **63a** detected by ESI-MS analysis over the course of the reaction. Interestingly the mass spectrum did show a single signal at $m/z = 867$ corresponding to the complex **82** (Figure 14).

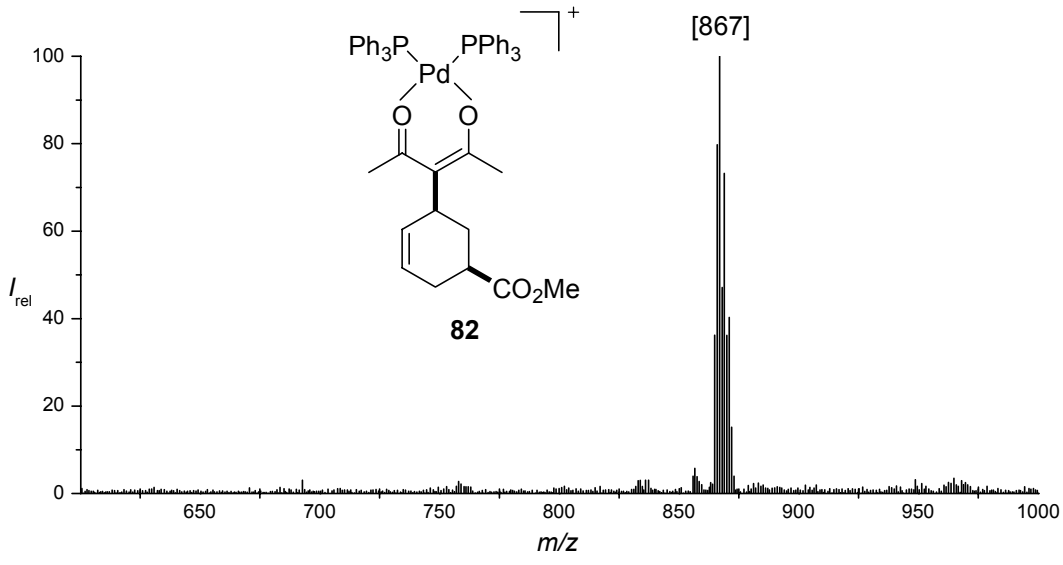
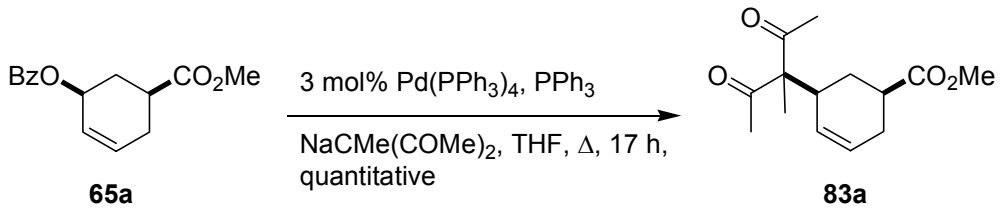


Figure 14. Detection of complex **82** by deprotonation of substrate **80a**.

This result suggests that substrate **80a** is deprotonated under the described reaction conditions and afterwards acts as a ligand for palladium. The anionic acetyl acetone moiety can not serve

as a leaving group any longer. Furthermore, the catalytically active palladium is consumed and thus no back reaction is possible. Identical results were obtained, when the reaction mixture was heated under microwave irradiation using tetrahydrofuran or acetonitril as solvent.

In order to prevent this undesired side reaction, substrate **83a**, derived from 3-methyl-2,4-pentanedione, was synthesised (Scheme 27). Under similar conditions as described earlier the product was obtained quantitatively as single *cis*-diastereomer.



65a **83a**

Scheme 27. Preparation of **83a** by palladium-catalysed allylic substitution.

The corresponding back reaction was investigated by mass spectrometry according to Scheme 24, using various reaction conditions and structurally different ligands, but no allyl-palladium intermediate **63a** was detected. A typical mass spectrum obtained when using phox ligand **40** is shown in Figure 15.

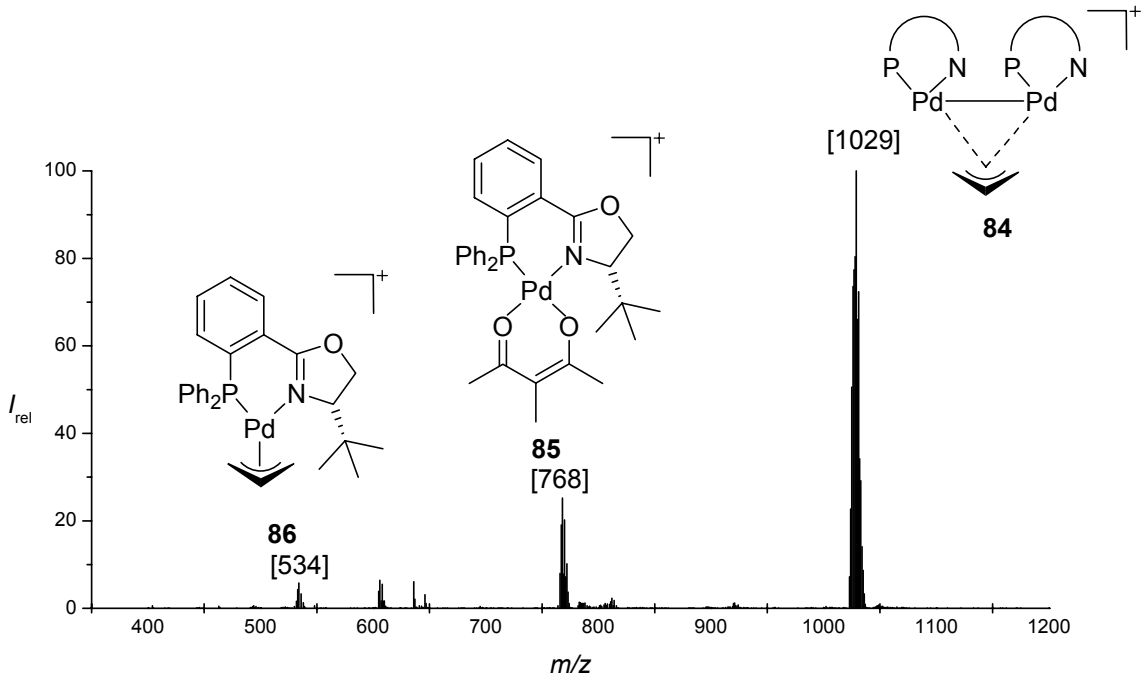


Figure 15. Mass spectrum observed for the back reaction of substrate **83a** using phox ligand **40**.

The dinuclear palladium complex **84** was observed as the main species. Presumably, this indicates a low reactivity of substrate **83a** and as a consequence the activated palladium(0) species reacts with the precatalyst to form **84**.[53]

Furthermore, all mass spectra showed significant signals at *m/z* = Pd+L+113 corresponding to complexes of the type **85**. These intermediates most likely result from a base-catalysed elimination of methyl acetyl acetonate.

For the sake of completeness preparative back reactions of substrate **83a** were analysed in analogy to Scheme 26 using various reaction conditions, but no product formation was observed in either case. ESI-MS analysis solely referred to the formation of complex **87**, as depicted in Figure 16.

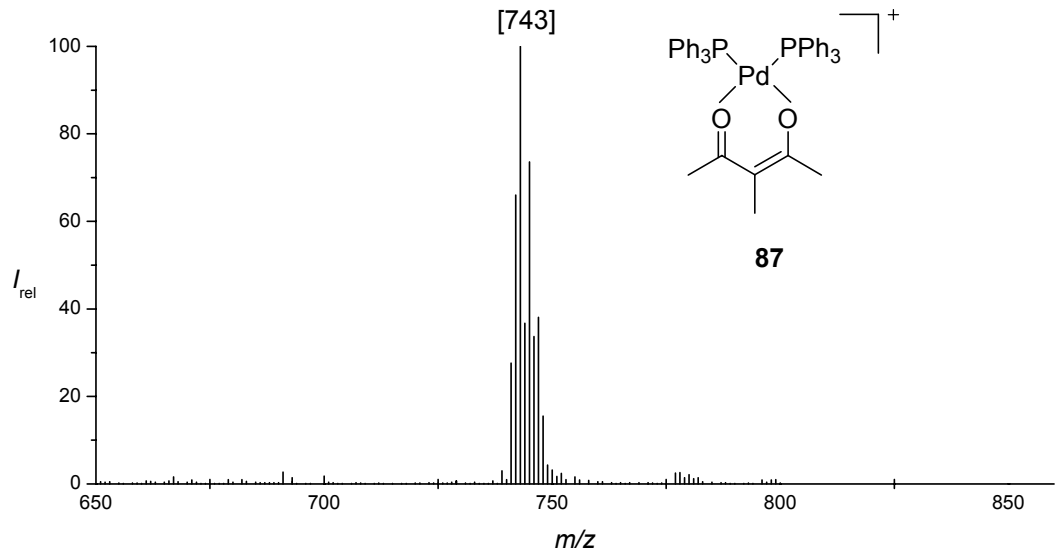
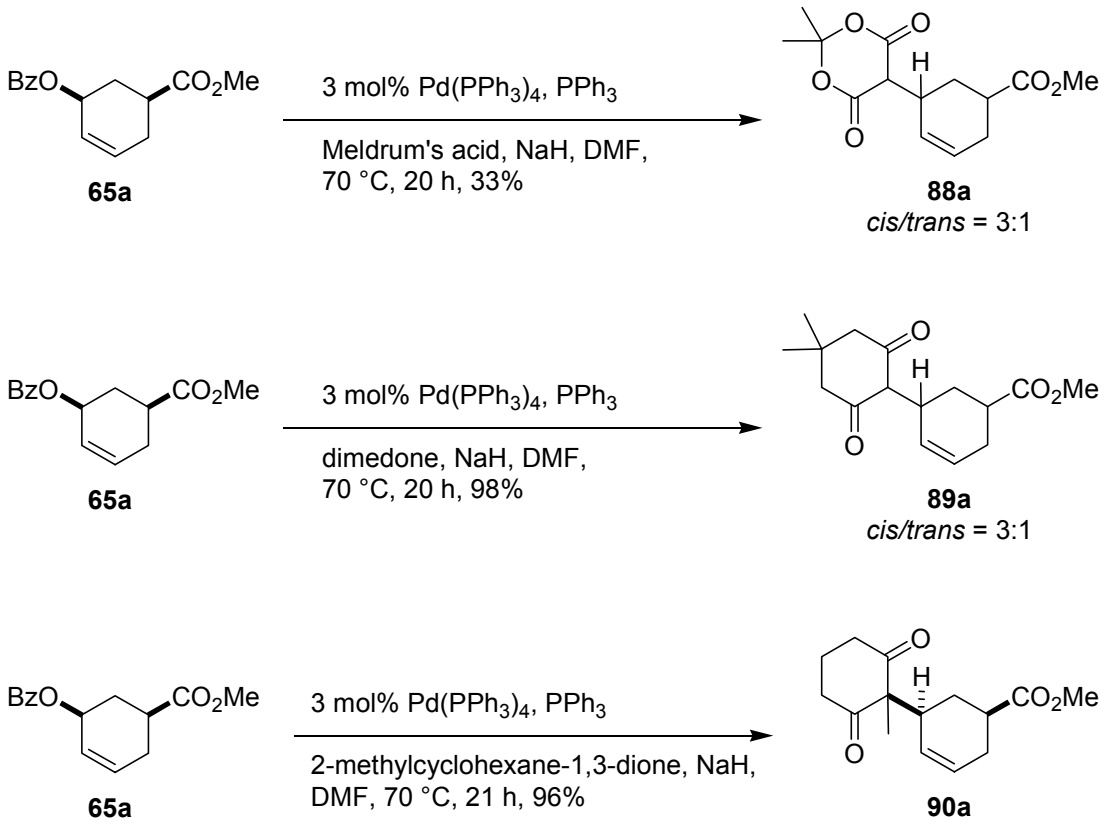


Figure 16. ESI-MS spectrum for the back reaction of substrate **83a** with tetrakis(triphenylphosphine)-palladium as catalyst.

The introduction of more reactive leaving groups was necessary for the back reaction of quasienantiomers **64a** and **64b** to proceed. Meldrum's acid was considered as a good leaving group as high reactivity was found for the corresponding diphenylallyl derivative **26** (Chapter 2.1).

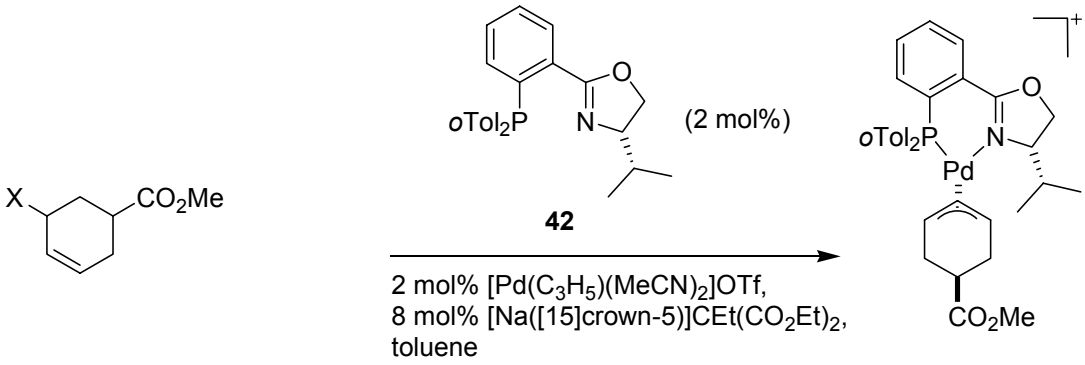
During the synthesis of substrate **88a** from benzaote **65a** with the anion of Meldrum's acid complex mixtures of aromatic compounds were produced, when weak bases, such as DBU, triethylamine and potassium acetate, were used in excess for the deprotonation. Methyl benzoate was formed as the main product presumably by oxidation of the diene, which is generated by the elimination of Meldrum's acid. Benzoate **65a** was treated with sodium hydride and Meldrum's acid in presence of tetrakis(triphenylphosphine)palladium in tetrahydrofuran accordording to Scheme 25, but no conversion of the starting material was observed. However, when the reaction was carried out in dimethylformamide at 70 °C the desired product **88a** was obtained in low yield as a mixture of the two diastereomers (Scheme 28).



Scheme 28. Preparation of substrates **88a**-**90a** by palladium-catalysed allylic substitution.

Using these reaction conditions, substrates **89a** and **90a** derived from dimedone and 2-methylcyclohexane-1,3-dione were prepared in high yields as well (Scheme 28). Thereby the latter was isolated as single *cis*-diastereomer, whereas the reaction with dimedone gave a 3:1 mixture of diastereomers.

In order to test their leaving group ability in the back reaction substrates **88a-90a** were analysed by ESI-MS (Scheme 29). Meldrum´s acid-derivative **88a** was treated with 2 mol% of the palladium catalyst and four equivalents (based on Pd) of nucleophile in toluene. The experiment was carried out at room temperature and analysed after 30 seconds, 5 and 15 minutes by ESI-MS, but no allyl-palladium intermediate **63a** was detectable in the mass spectra.



X = Meldrum's acid – H^+: **88a**
X = dimedone – H^+: **89a**
X = 2-methylcyclohexane-1,3-dione – H^+: **90a**

92

Scheme 29. Screening for reactivity using substrates **88a**-**90a**.

Therefore the reaction was repeated at 50 °C under otherwise identical conditions. After four minutes the mass spectrum was dominated by an intense signal of the catalyst precurser **91** (Figure 17, A). Along with a significant amount of dinuclear palladium complex **84**, a small quantity of allyl complex **92** was detected. During the course of the transformation the relative abundance of the dinuclear complex **84** increased considerably and the signal of intermediate **92** remained near constant. This indicates a low reactivity of substrate **88a** for this reaction in general (Figure 17, B).

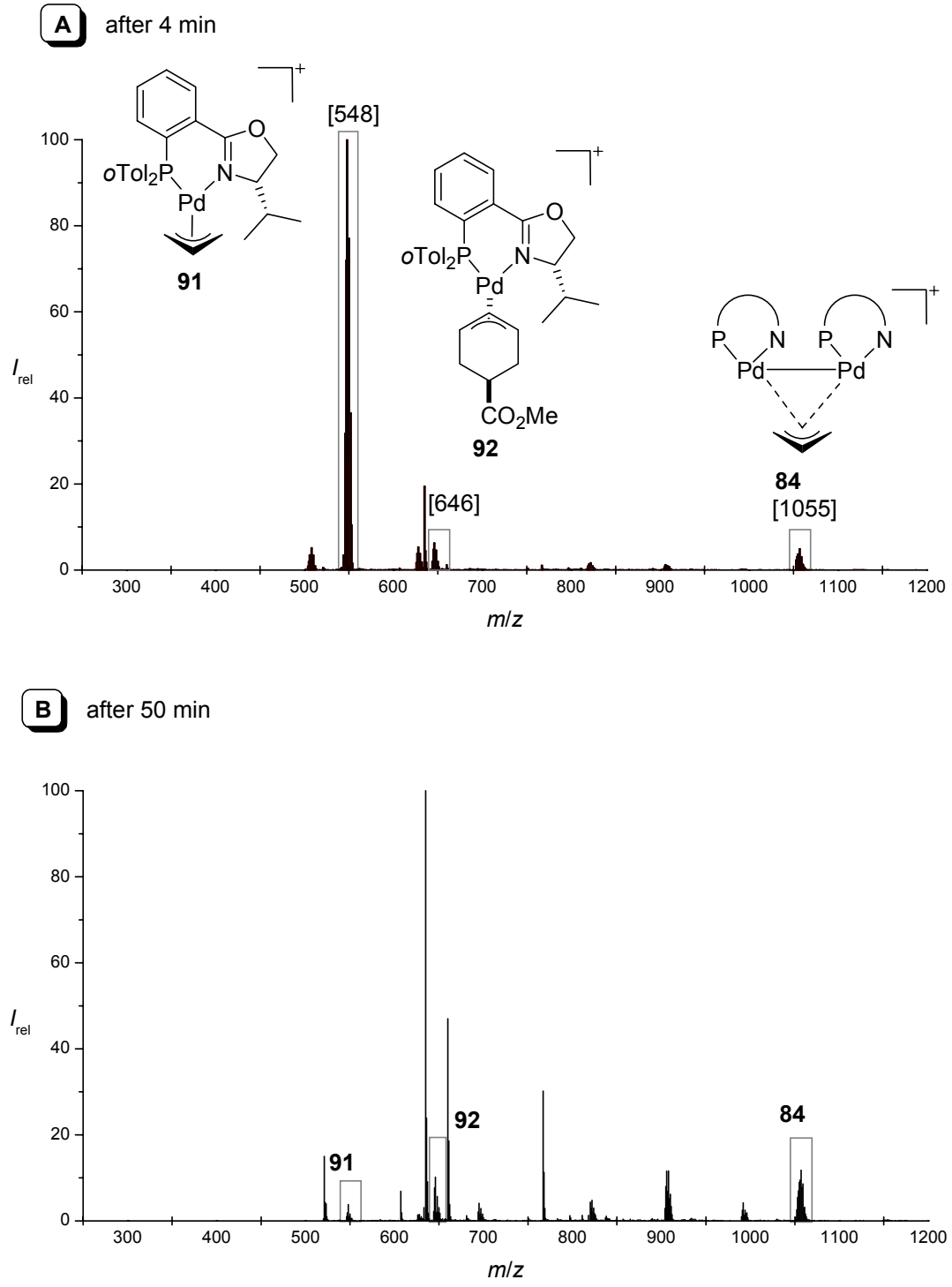


Figure 17. Back reaction screening of substrate **88a** at 50 °C using phox ligand **42**. Mass spectra recorded after 4 min (A) and 50 min (B).

When substrate **89a** was subjected to ESI-MS analysis no allyl-palladium intermediate **92** was detected using a large set of conditions and ligands.

The back reaction screening of compound **90a**, derived from 2-methylcyclohexane-1,3-dione, was also carried out at both room temperature and 50 °C. The mass spectrum was dominated

by the precatalyst **91** at lower temperatures, whereas the allyl-palladium intermediate **92** was observed as the main signal after 30 seconds at 50 °C (Figure 18). However, a significant amount of the dinuclear complex **84** was also detected.

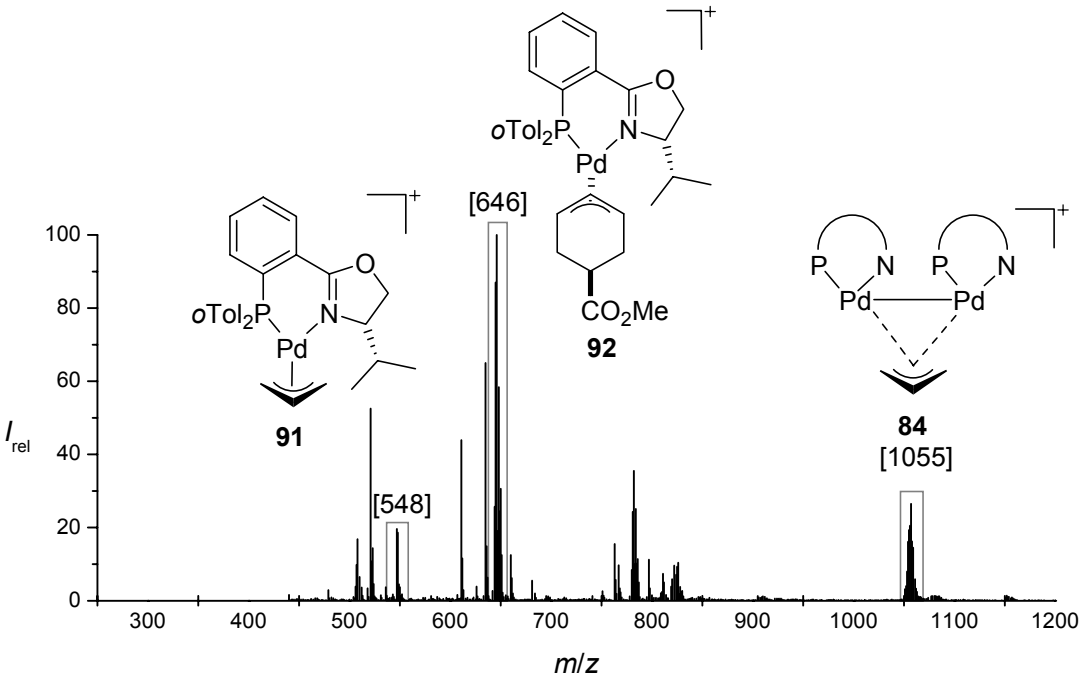
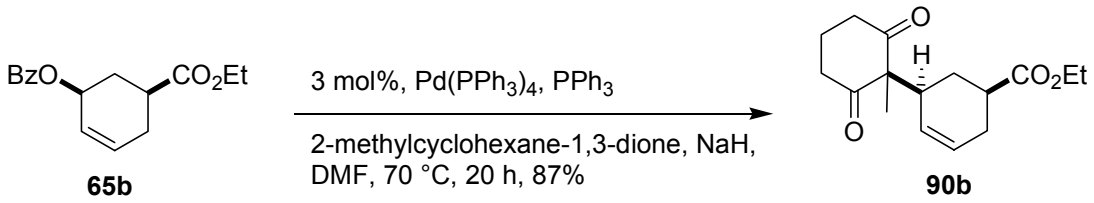


Figure 18. Back reaction screening at 50 °C using substrate **90a** and phox ligand **42**.

Compared to the Meldrum´s acid-based substrate **88a** the methylated derivative **90a** shows markedly higher reactivity. In the back reaction of **90a** the allyl-palladium intermediate **92** was clearly visible in the mass spectrum. Therefore a general screening method for cyclohexenyl carboxylates derived from 2-methylcyclohexane-1,3-dione was developed. For this an appropriate set of quasienantiomers was needed. The racemic ethyl ester **90b** was prepared as a single *cis*-diastereomer in high yield by palladium-catalysed allylic alkylation (Scheme 30).



Scheme 30. Synthesis of ethyl-labelled substrate **90b**.

The back reaction of an equimolar mixture of racemic methyl- and ethyl-labelled substrates **90a** and **90b** using phox ligand (*S*)-**28** was then analysed (Figure 19). The corresponding allyl-palladium complexes **63a** and **63b** were clearly detectable in a perfect 1:1 ratio in the mass spectrum as the two main species, along with precatalyst $[Pd(C_3H_5)L]^+$ and dinuclear complex **84**. This result demonstrates that the mass labels have no influence on the ratio of **63a** and **63b** and the reactivity of **62a** and **62b** is not affected.

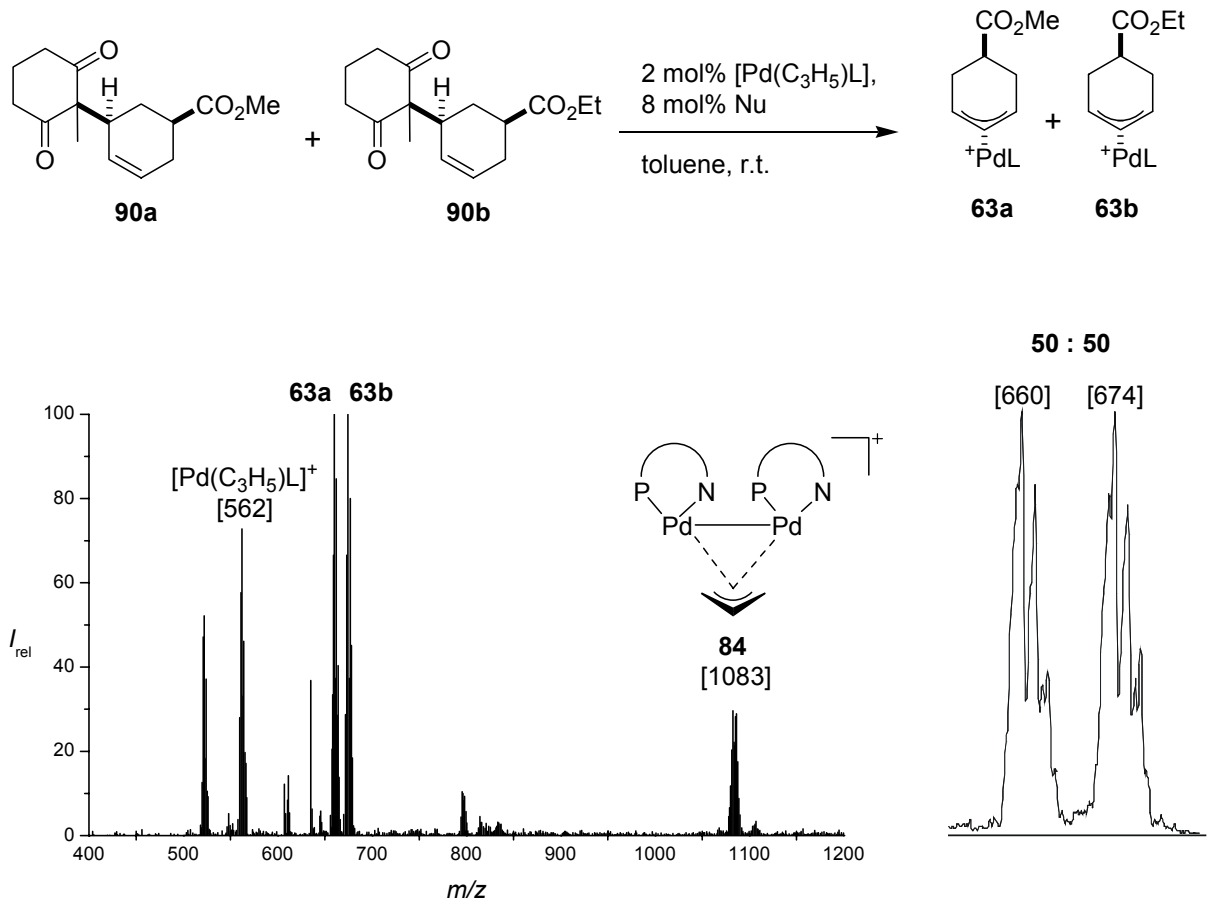


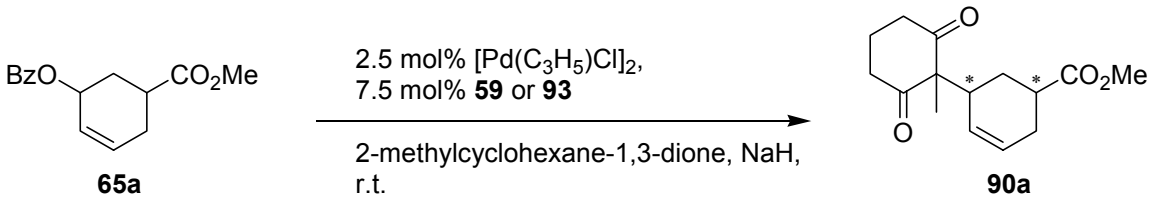
Figure 19. Back reaction using an equimolar mixture of racemic substrates **90a** and **90b** (L = (*S*)-**28**, Nu = [Na([15]crown-5)]CEt(CO_2Et)$_2$).

3.2.2 Synthesis of Quasienantiomeric Allylation Products

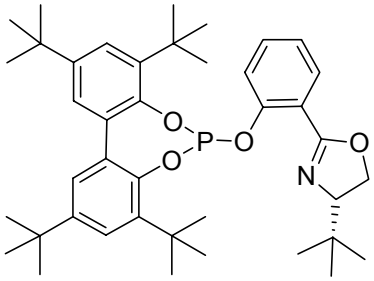
To measure the intrinsic selectivity of a chiral catalyst directly by ESI-MS enantiomerically pure quasienantiomeric substrates **90a** and **90b** were needed. Palladium-catalysed asymmetric allylic alkylations of benzoate **65a** were carried out in the presence of phosphite-oxazoline **59** or Trost ligand **93** as these are known to induce high selectivities for carbocyclic substrates.[92-95]

The transformations were carried out using 2.6 equivalents of the sodium salt of 2-methylcyclohexane-1,3-dione in presence of the 2.5 mol% of the respective palladium catalyst (Table 7).

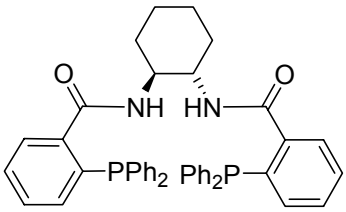
Table 7. Preparation of enantiomerically enriched quasienantiomer **90a**.



65a **90a**



59



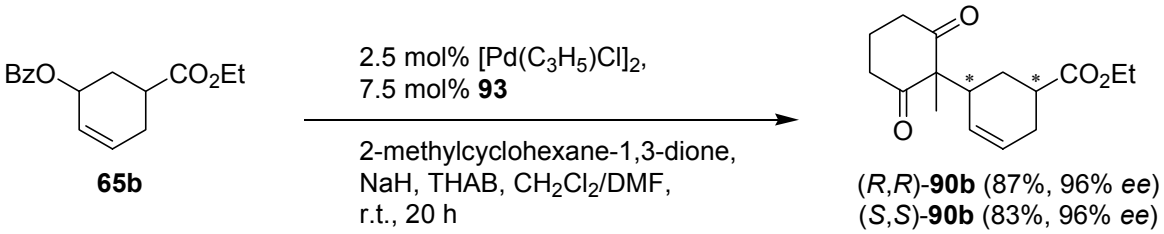
(*S*,*S*)-**93**

Entry	Ligand	Additive	Solvent	Time [h]	Yield [%]	Product	*ee* [%][a]
1	**59**	–	DMF	21	56	(*R*,*R*)-**90a**	78
2	(*S*,*S*)-**93**	–	DMF	39	65	(*S*,*S*)-**90a**	50
3	(*R*,*R*)-**93**	–	DMF	29	92	(*R*,*R*)-**90a**	50
4	(*S*,*S*)-**93**	THAB	CH_2Cl_2/DMF	24	65	(*S*,*S*)-**90a**	96
5	(*R*,*R*)-**93**	THAB	CH_2Cl_2/DMF	24	70	(*R*,*R*)-**90a**	96

[a] HPLC analysis (Daicel Chiracel AD-H, heptane/isopropanol 98:2, 0.5 mL*min^{-1}, 30 °C, 220 nm): t_R = 51.7 (*S*), 56.3 (*R*) min.

(*R,R*)-**90a** was obtained with a moderate enantioselectivity of 78% when the reaction was accomplished with Claver-type ligand **59** in dimethylformamide (Table 7, entry 1). This selectivity is significantly lower compared to the established reaction between cyclohexenyl acetate and dimethyl malonate.[94]

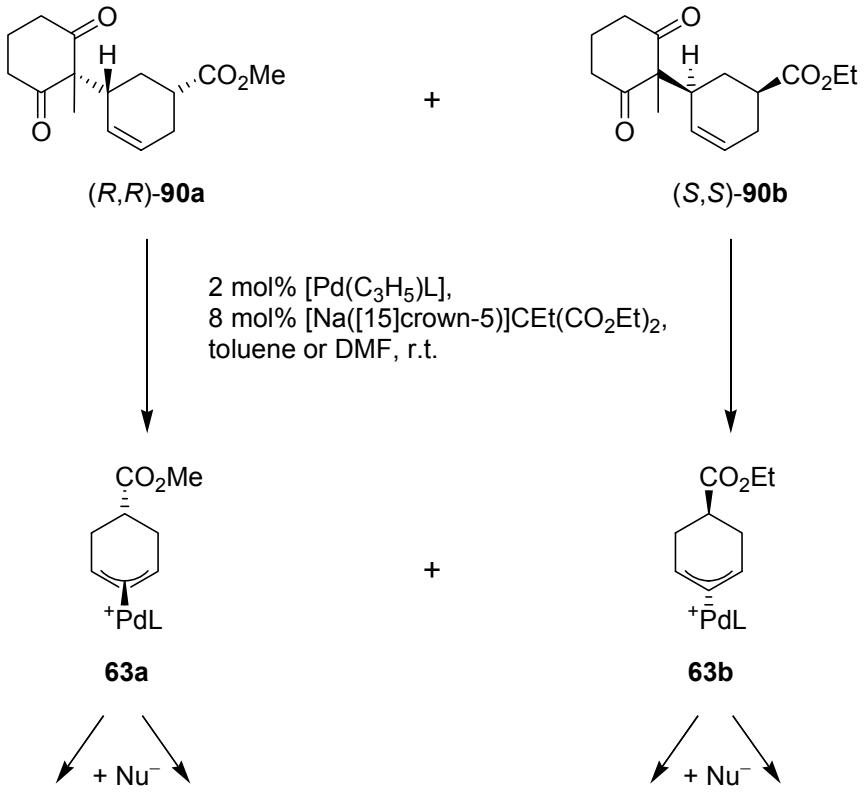
Ligand **93** was less efficient when similar conditions were applied and product **90a** was isolated with an enantiomeric excess of 50% (Table 7, entries 2 and 3). Trost and coworkers discovered that in some cases the selectivity can be increased by adding tetrahexylammonium bromide (THAB) to the reaction mixture.[97, 106] The allylic alkylations were repeated using 2.6 equivalents of THAB in a mixture of dichloromethane and dimethylformamide (Table 7, entries 4 and 5) with **93**. Both ligand enantiomers gave the product in good yields and very high enantiomeric excesses of 96%. By applying these improved reaction conditions both enantiomers of the ethyl-labelled substrate (*R,R*)- and (*S,S*)-**90b** were prepared in 96% *ee* (Scheme 31).



Scheme 31. Synthesis of enantiomerically enriched quasienantiomer **90b**.

3.2.3 Mass Spectrometric Evaluation of Chiral Ligands

With quasienantiomers (*R,R*)-**90a** and (*S,S*)-**90b** a back reaction screening was performed to evaluate the intrinsic selectivities of several catalysts in the palladium-catalysed allylic alkylation of carbocyclic substrates (Scheme 32). The complexes were prepared *in situ* from stoichiometric amounts of $[Pd(C_3H_5)(MeCN)_2]OTf$ and the corresponding chiral ligands in toluene. An equimolar mixture of (*R,R*)-**90a** and (*S,S*)-**90b** (25 equivalents based on Pd each) was added and the reaction initiated by activation of the precatalyst with the crown ether sodium salt of diethyl ethylmalonate (4 equivalents based on Pd). Satisfactory results were obtained only with phox ligands **42** and **28**, whereas most other derivatives gave no or very small quantities of allyl-palladium intermediates **63a** and **63b** under these conditions.



Scheme 32. Back reaction screening to determine the efficieny of chiral catalysts for cyclohexenyl benzoates as substrates.

The synthesis of substrate **88a**, derived from Meldrum's acid, showed that dimethylformamide is needed to achieve conversion of benzoate **65a** to the product. For this reason the influence of dimethylformamide in the back reaction of quasienantiomers (*R,R*)-**90a** and (*S,S*)-**90b** using Josiphos-type ligand **50** was studied under identical conditions. Comparison of these results with those obtained in toluene showed a significant increase in reactivity when the reaction was carried out in dimethylformamide. Allyl-palladium complexes **63a** and **63b** were detected as the main signals after five minutes (Figure 20, A), whereas the mass spectrum of the reaction in toluene was dominated by the precatalyst $[Pd(C_3H_5)L]^+$ (Figure 20, B).

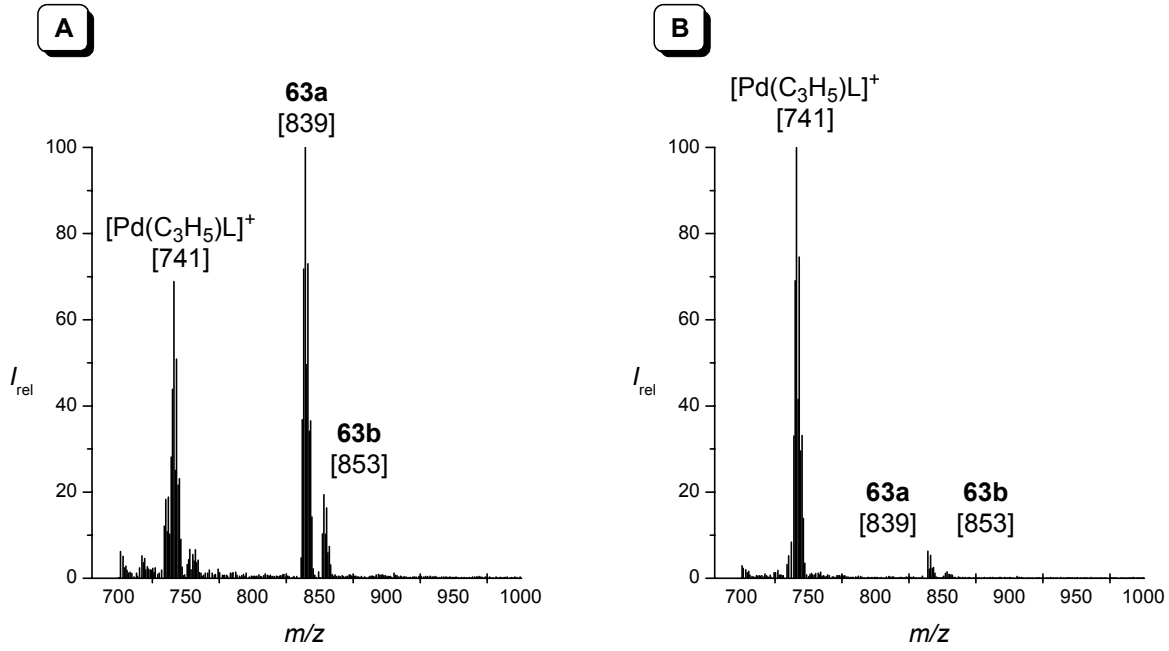
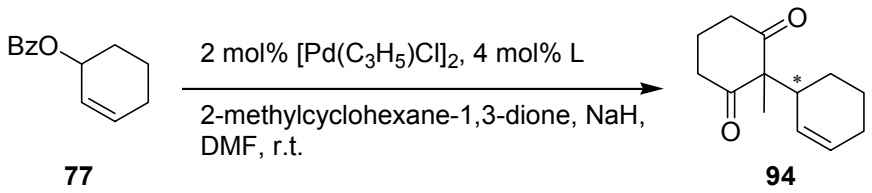


Figure 20. Back reactions of quasienantiomers (*R*,*R*)-**90a** and (*S*,*S*)-**90b** using ligand **50** in dimethylformamide (A) or toluene (B).

A new set of screenings was therefore carried out in dimethylformamide (Table 8). In all cases where allyl-palladium intermediates **63a** and **63b** could be detected, the calculated selectivities were compared with the results obtained from HPLC analyses of the corresponding preparative reactions, using cyclohexenyl benzoate **77** as substrate (Scheme 33). These transformations were conducted in dimethylformamide with 2 mol% of the catalysts prepared *in situ* from $[Pd(C_3H_5)]Cl]_2$ and the respective chiral ligands. In both dichloromethane and toluene no conversion of substrate **77** was achieved.



Scheme 33. Preparative allylic substitutions of cyclohexenyl benzoate **77** with 2-methylcyclohexane-1,3-dione.

With entry 5 in Table 8 being the only exepction, the enantiomeric ratios measured by ESI-MS correlate very well with the results of the product analysis for all the other preparative reactions. Importantly the screening reveals the correct selectivity order and therefore allows

reliable identification of the most efficient ligand. It is noteworthy that although intermediates **63a** and **63b** are only visible in a small amount the correlation is not affected.

Table 8. Results of the back reaction screening using quasienantiomers (*R*,*R*)-**90a** and (*S*,*S*)-**90b**.

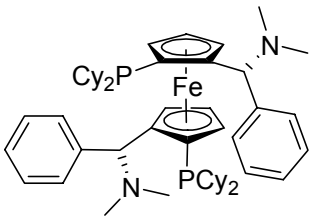
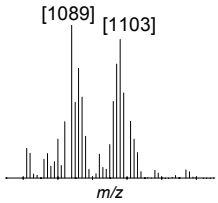
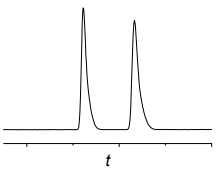
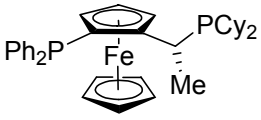
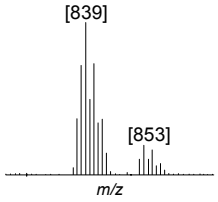
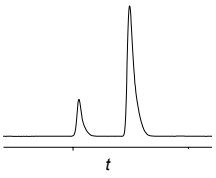
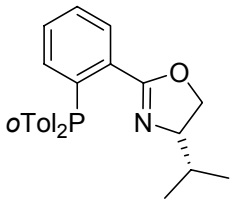
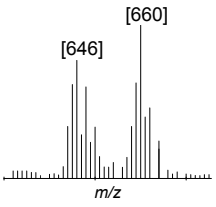
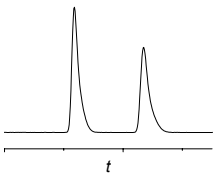
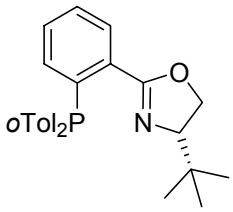
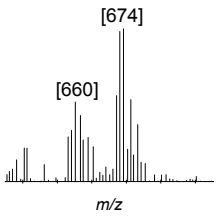
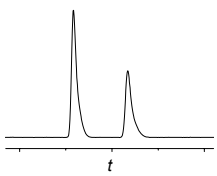
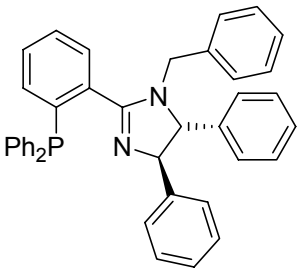
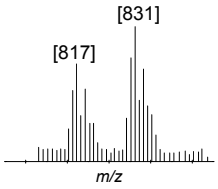
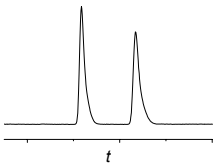
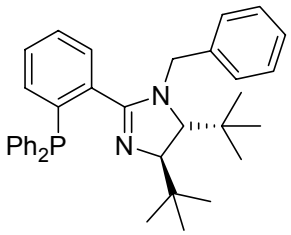
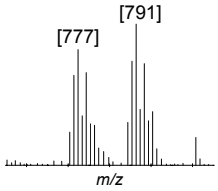
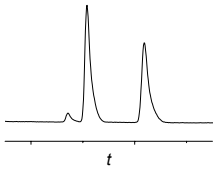
Entry	Ligand	Screening **63a** : **63b**	Preparative Reaction[a] (*S*)-**94** : (*R*)-**94**
1	 **44** (SL-M002-1)	52 : 48 	48 : 52 
2	 **50** (SL-J001-1)	82 : 18 	18 : 82 
3	 **42**	44 : 56 	56 : 44 
4	 **28**	39 : 61 	61 : 39 

Table 8. Continued.

Entry	Ligand	Screening **63a** : **63b**	Preparative Reaction[a] (*S*)-**94** : (*R*)-**94**
5	 **56**	42 : 58 	51 : 49 
6	 **57**	45 : 55 	54 : 46 

[a] HPLC analysis (Daicel Chiracel AD-H, heptane/isopropanol 98:2, 0.8 mL*min^{-1}, 20 °C, 254 nm): t_R = 10.9 ((*S*)-**94**), 13.2 ((*R*)-**94**) min. The absolute configuration of **94** was assigned by analogy.

Low enantioselectivities were induced with phox and phim ligands (Table 8, entries 3-6) in the palladium-catalysed allylic alkylation of cyclohexenyl benzoates. Josiphos-type ligand **50** was found to be the most efficient ligand so far, giving the allyl-palladium complexes **63a** and **63b** in a ratio of 82:18. Although the obtained selectivities are rather low the results clearly show the viability of this approach. As long as some reactivity in the back reaction is observed, the screening method presented can be used as an efficient tool for the development of new ligand systems.

3.3 Back Reactions of 3-(1',3'-Diphenylallyl)-pentane-2,4-dione Reinvestigated

As described in Chapter 2.2.5 no back reaction was obtained with mass-labelled 3-(1',3'-diarylallyl)-pentane-2,4-diones **30a** and **30b** in the ESI-MS analysis of several ligands. After discovering the deprotonation of acetyl acetone-derived cyclohexenyl ester **80a** under screening conditions, the mass spectra recorded with linear substrates were reinterpreted. No allyl-palladium intermediates **39a** and **39b** were detected for the Walphos-type ligands and formation of substrate palladium complexes, produced by the deprotonation of the acetyl acetone moiety, were observed in these cases, too. A preparative back reaction of substrate **24** with sodium dimethyl malonate in the presence of tetrakis(triphenylphosphine)palladium and triphenylphosphine in tetrahydrofuran at room temperature was conducted and analysed by ESI-MS.

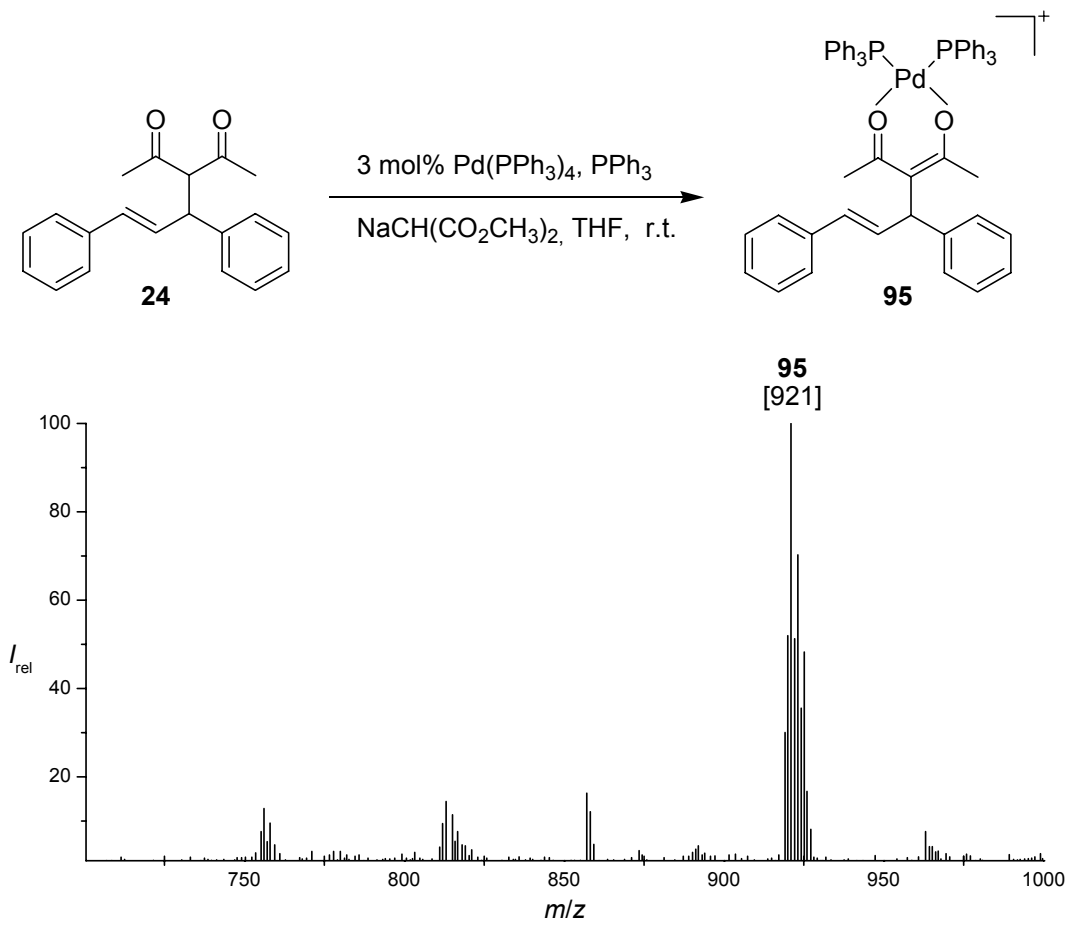


Figure 21. Substrate deprotonation followed by complex formation observed in several cases.

The intense signal at m/z = 921 corresponding to complex **95** represented the main species whereas no conversion of the starting material was observed. This demonstrates that deprotonation of the acetyl acetonate moiety can presumably inhibit the back reaction of substrates **30a** and **30b**, depending on the reactivity of the ligand under investigation.

3.4 Conclusion and Outlook

After having established a reliable protocol for the evaluation of chiral palladium catalysts in allylic substitutions of linear diarylallyl substrates, the methodology was extended to carbocyclic derivatives.

An efficient catalyst screening for the kinetic resolution of cyclohexenyl benzoate was developed by mass spectrometric monitoring of cyclic allyl esters. The data was compared with the corresponding results from kinetic analyses of the preparative reactions and an excellent correlation of the respective *s* values was found.

Based on the principle of microscopic reversibility a method for determining the efficiency of the overall allylic substitution process was developed. After the extensive analysis of several substrates for reactivity in the back reaction, allylation products derived from 2-methylcyclohexane-1,3-dione were identified as optimum quasienantiomers and a screening protocol was optimised. Although the applicability of this method is somewhat limited, the enantiomeric ratios determined by ESI-MS correlate very well with the results observed from the product analysis of the corresponding preparative reactions.

CHAPTER 4

DEVELOPMENT OF NEW CHIRAL LIGANDS USING ESI-MS AS ANALYTICAL TOOL

4 Development of New Chiral Ligands using ESI-MS as Analytical Tool

After having established a fast and reliable protocol for the evaluation of chiral palladium catalysts for the allylic substitution of both linear diarylallyl and carbocyclic substrates, the screening method was used for the development of new ligand systems.

4.1 Chiral Bis(*N*-sulfonylamino)phosphine-Oxazoline and Pyridyl-Phosphite Ligands

Within the scope of Franke's master thesis new ligands were prepared and evaluated by ESI-MS and conventional catalytic reactions.[107]

As the phosphite-oxazolines **96** proved to be highly efficient in palladium-catalysed allylic substitutions of unhindered linear and cyclic substrates, their structural motive was used as a starting point for the development of new derivatives as shown in Figure 22.[94]

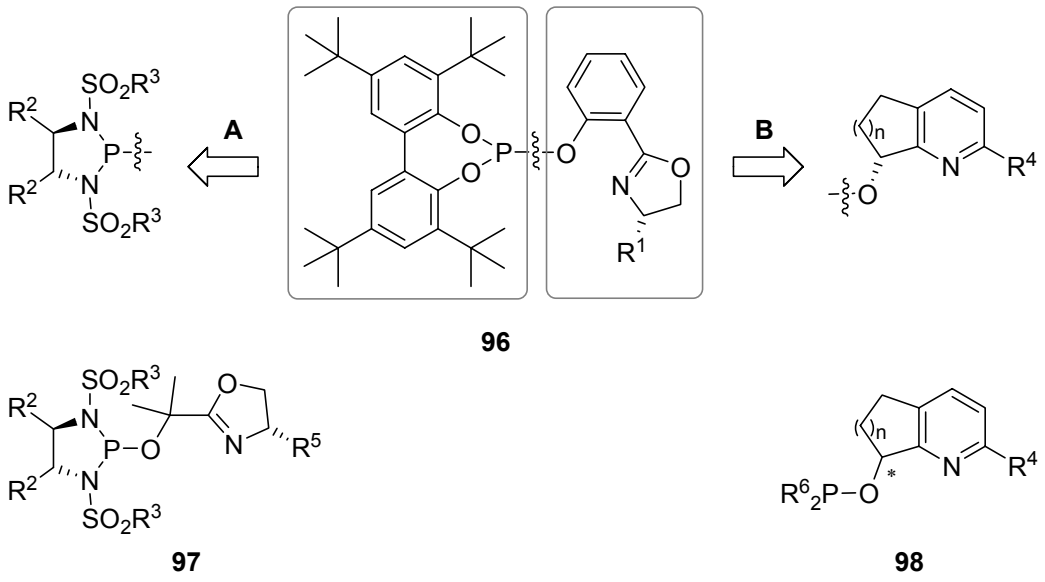
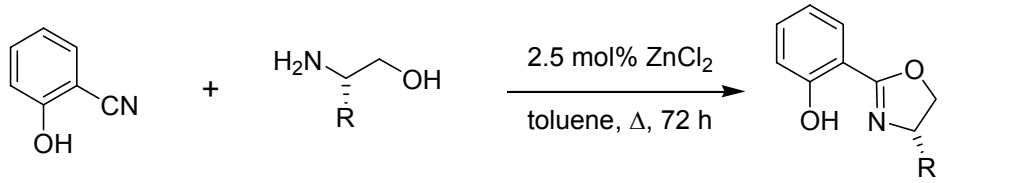


Figure 22. Approach for new ligand structures.

Previous work by Hilgraf and Kaiser demonstrated that ligands of the types **97** and **98** can induce high enantioselectivity in palladium-catalysed allylic alkylations and iridium-catalysed asymmetric hydrogenations, respectively.[108, 109] Therefore either the phosphite unit of **96** was replaced by sulfonyl-diazaphospholidines (Figure 22, A) or the oxazoline was substituted by a chiral pyridyl alcohol (Figure 22, B).

4.1.1 Ligand Synthesis

For the preparation of chiral bis(*N*-sulfonylamino)phosphine-oxazoline ligands the respective phenolic precursors **99-101** were synthesised in high yields from 2-hydroxybenzonitrile **102** and aminoalcohols **103-105** in the presence of catalytic amounts of zinc(II) chloride (Scheme 34).[110]



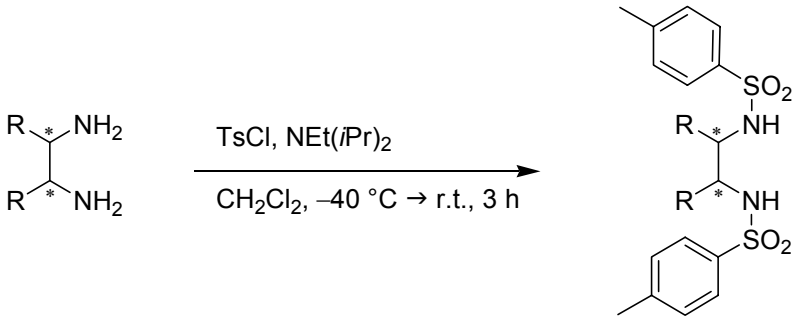
102

R = *i*Pr: **103**
R = *t*Bu:**104**
R = Ph: **105**

R = *i*Pr: **99** (93%)
R = *t*Bu: **100** (98%)
R = Ph: **101** (95%)

Scheme 34. Oxazoline synthesis.

Sulfonyldiamines **106** and **107** were obtained under mild conditions as shown in Scheme 35.

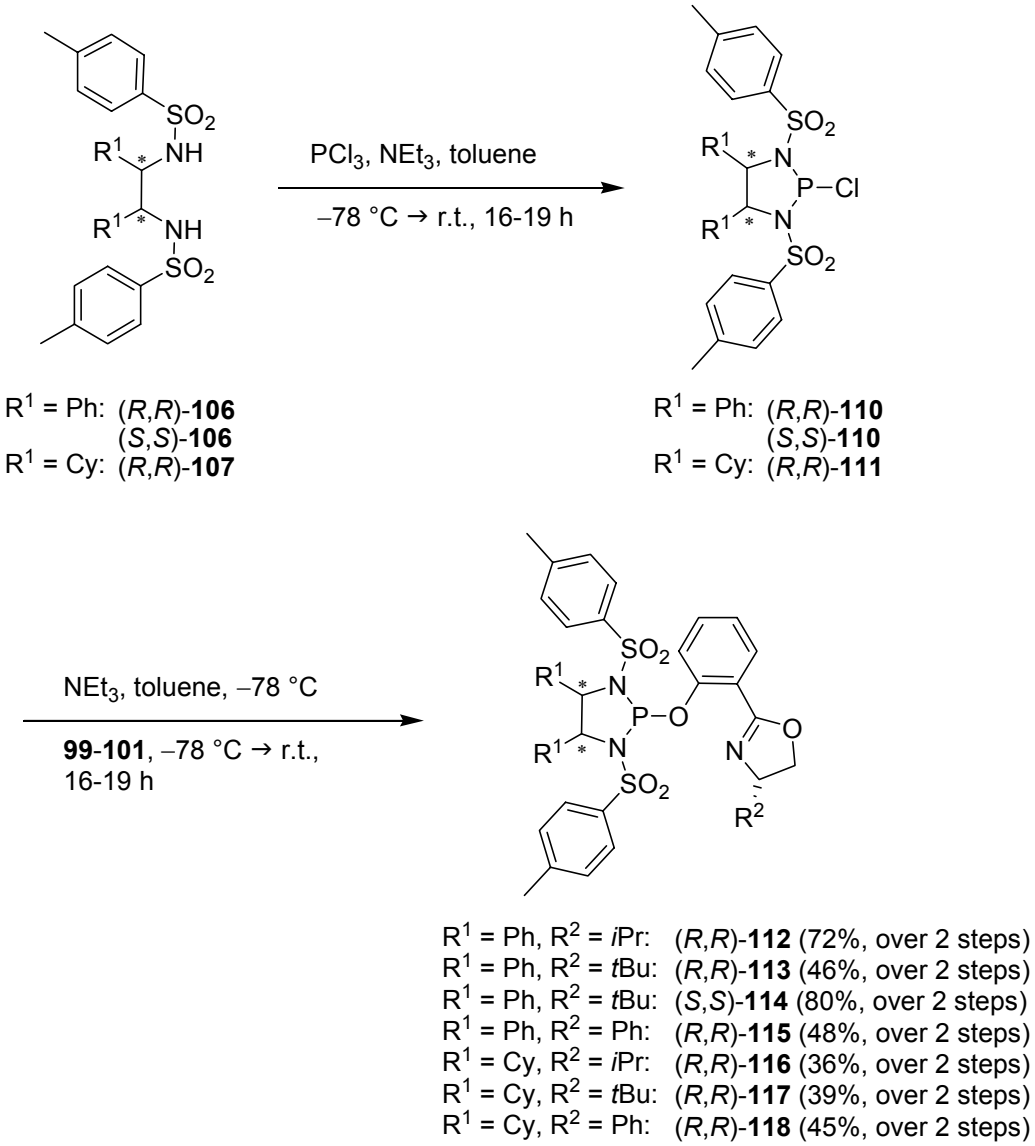


R = Ph: (*R*,*R*)-**108**
(*S*,*S*)-**108**
R = Cy: (*R*,*R*)-**109**

R = Ph: (*R*,*R*)-**106** (94%)
(*S*,*S*)-**106** (89%)
R = Cy: (*R*,*R*)-**107** (34%)

Scheme 35. Preparation of chiral sulfonyldiamines.

Treatment of **108** or **109** with phosphorus trichloride in toluene at −78 °C gave the corresponding *P*-chlorodiazaphospholidines **110** and **111** as pale yellow solids (Scheme 36). These moisture- and air-sensitive intermediates were directly converted to the desired ligands **112-118** by reaction with the respective oxazolines **99-101** and triethylamine. In contrast to similar derivatives reported in previous work, **112-118** are stable on deactivated silica gel and were obtained in good yields after column chromatography under argon.[108]



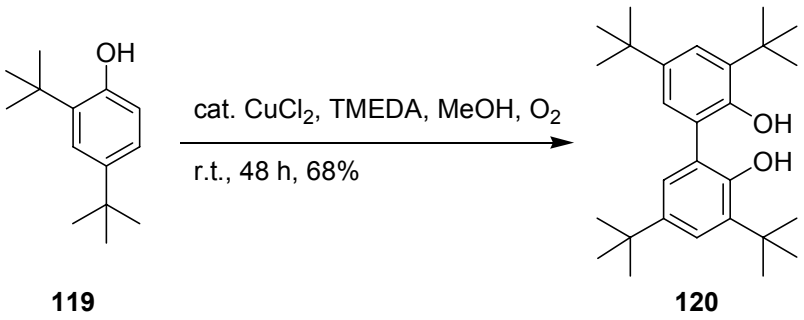
R^1 = Ph: (*R*,*R*)-**106**
(*S*,*S*)-**106**
R^1 = Cy: (*R*,*R*)-**107**

R^1 = Ph: (*R*,*R*)-**110**
(*S*,*S*)-**110**
R^1 = Cy: (*R*,*R*)-**111**

R^1 = Ph, R^2 = *i*Pr: (*R*,*R*)-**112** (72%, over 2 steps)
R^1 = Ph, R^2 = *t*Bu: (*R*,*R*)-**113** (46%, over 2 steps)
R^1 = Ph, R^2 = *t*Bu: (*S*,*S*)-**114** (80%, over 2 steps)
R^1 = Ph, R^2 = Ph: (*R*,*R*)-**115** (48%, over 2 steps)
R^1 = Cy, R^2 = *i*Pr: (*R*,*R*)-**116** (36%, over 2 steps)
R^1 = Cy, R^2 = *t*Bu: (*R*,*R*)-**117** (39%, over 2 steps)
R^1 = Cy, R^2 = Ph: (*R*,*R*)-**118** (45%, over 2 steps)

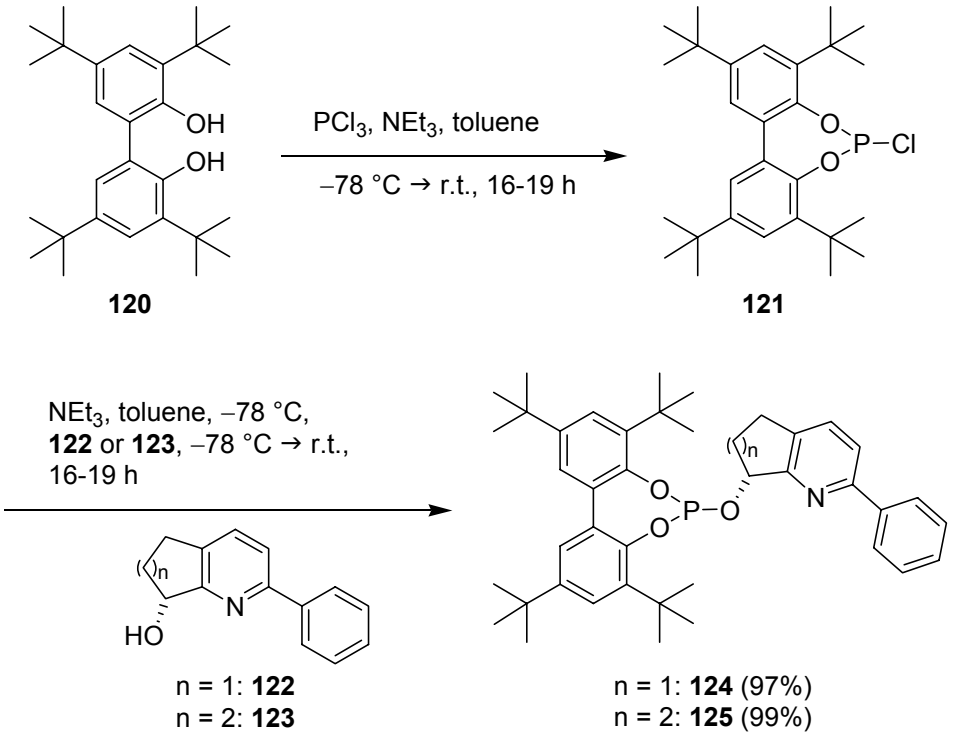
Scheme 36. Synthesis of bis(*N*-sulfonylamino)phosphine-oxazolines.

Along with bis(*N*-sulfonylamino)phosphine-oxazolines **112**-**118** new pyridyl-phosphites were prepared. Oxidative coupling of 2,4-di-*tert*-butylphenol **119** in the presence of catalytic amounts of copper(II) chloride and *N*,*N*,*N'*,*N'*-tetramethylethylenediamine gave diol **120** (Scheme 37).[111]



Scheme 37. Oxidative coupling of 2,4-di-*tert*-butylphenol.

The ligands were prepared in similar manner to derivatives **112**-**118**. Phosphorochloridite **121** was synthesised from diol **120** and phosphorus trichloride in the presence of triethylamine.[111] This intermediate was directly reacted with the respective pyridyl alcohols **122** or **123** to give ligands **124** and **125** in very high yields after column chromatography on deactivated silica gel under argon.

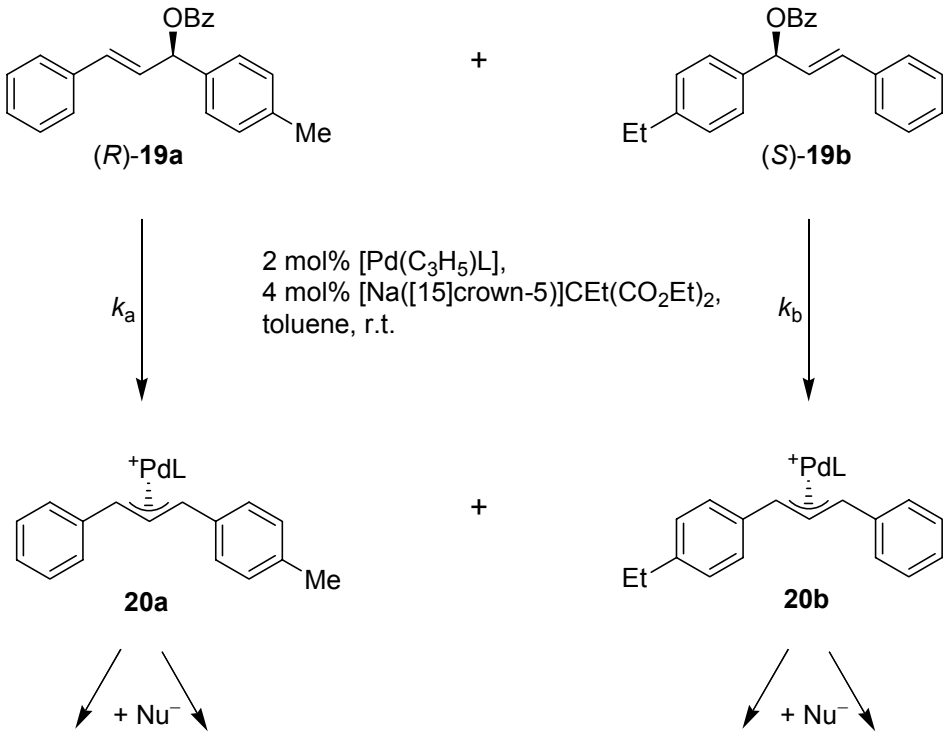


Scheme 38. Preparation of pyridyl-phosphite ligands.

4.1.2 ESI-MS Screening

In order to evaluate the efficiency of ligands **112-118**, **124** and **125** in palladium-catalysed allylic substitution reactions an ESI-MS analysis was carried out, in similar manner, as described in the two previous chapters. Allylic alkylations and aminations of diarylallyl substrates with acetyl acetone and phthalimide were investigated by studying the corresponding back reactions (Schemes 11 and 17, Chapter 2). However, no allyl-palladium complexes **39a** and **39b** were detected in the mass spectra using several conditions and it was not possible to initiate the back reaction.

As previously described quasienantiomeric allyl benzoates and phenolates proved to be much more reactive and the corresponding allyl-palladium complexes therefore easier to detect, a screening with these substrates was carried out.[104] The kinetic resolution of mass-labelled benzoates (*R*)-**19a** and (*S*)-**19b** was investigated first (Scheme 39).



Scheme 39. ESI-MS screening of palladium catalysts for the kinetic resolution of (*R*)-**19a** and (*S*)-**19b**.

Even in this reaction the respective allyl-palladium complexes **20a** and **20b** were not observed for all ligands. The results for the more efficient derivatives are shown in Figure 23.

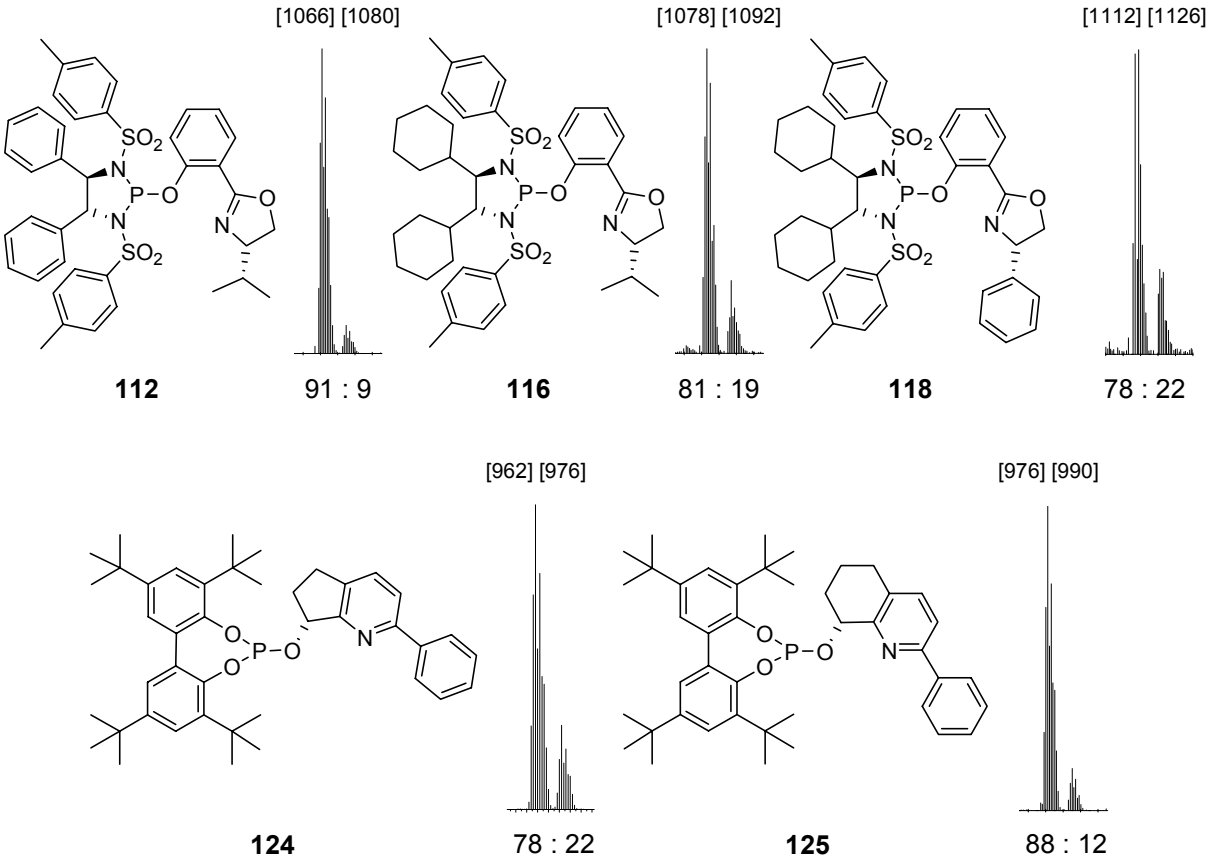
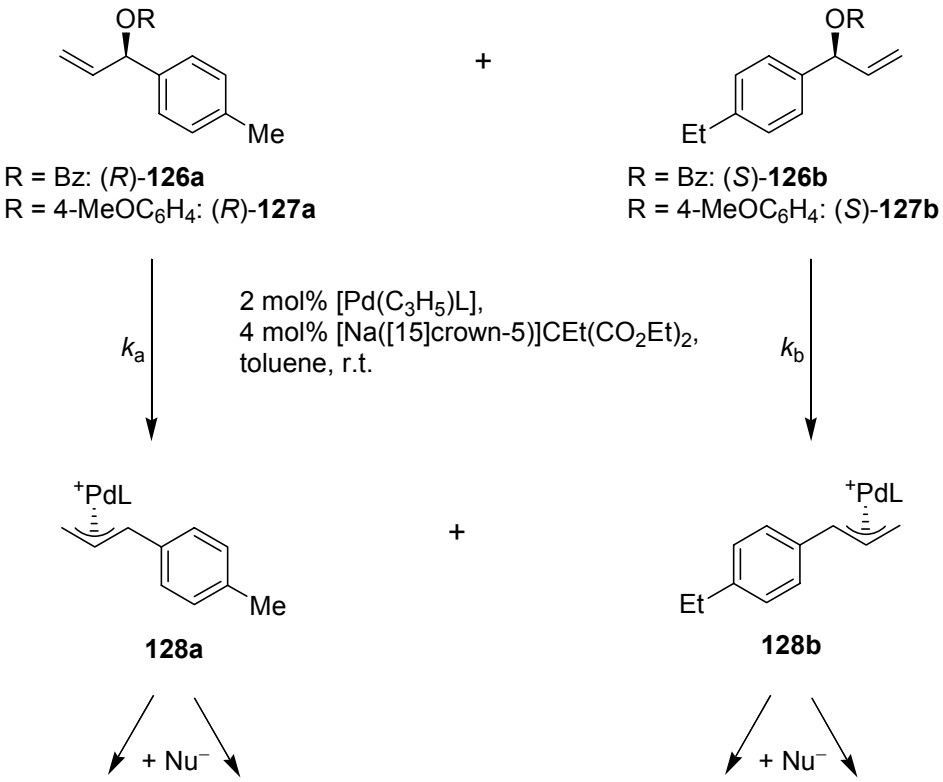


Figure 23. Screening results for the kinetic resolution according to Scheme 39.

Bis(*N*-sulfonylamino)phosphine-oxazoline **112** proved to be the most efficient ligand. The intermediates **20a** and **20b** were observed in a ratio of 91:9, corresponding to a *s* factor of 10.1, whereas only moderate selectivities were observed with the cyclohexyl derivatives **116** and **118**. These results compare favourably with those obtained with analogous ligands in earlier studies of this kinetic resolution.[104, 108] In case of derivatives **124** and **125**, the compound with the six-membered ring was slightly better.

Since palladium-catalysed allylic alkylations of unsymmetrical monosubstituted substrates are of particular interest, the ESI-MS analysis of such a reaction was performed.[104]

As shown in Scheme 40 both quasienantiomeric benzoates (*R*)-**126a**/(*S*)-**126b** and phenolates (*R*)-**127a**/(*S*)-**127b** were tested. By analysing the former substrates the selectivity of the kinetic resolution can be estimated. The latter serve as model compounds for the allylic substitution with phenolate as nucleophile, since the process monitored by ESI-MS corresponds to the back reaction.



Scheme 40. Catalyst screening using mass-labelled arylallyl benzoates (*R*)-**126a**/(*S*)-**126b** or phenolates (*R*)-**127a**/(*S*)-**127b**.

The results for this kinetic resolution are shown in Figure 24. Allyl-palladium complexes **128a** and **128b** were only formed with the oxazoline derivatives **112**, **116**, **118** which also showed reactivity in the screening of diarylallyl benzoates (Scheme 39), but the selectivities were considerably lower. The selectivity order was reversed though and the cyclohexyl derivative **118** proved to be the best ligand. The selectivities for ligands **124** and **125** were also somewhat diminished, but the order remained the same.

Markedly decreased reactivities were observed in the analysis of the back reaction of quasienantiomeric phenolates (*R*)-**127a** and (*S*)-**127b** as shown in Figure 25. Along with the pyridine derivatives **124** and **125**, intermediates were only detected for **112** with rather low selectivities measured in all three cases.

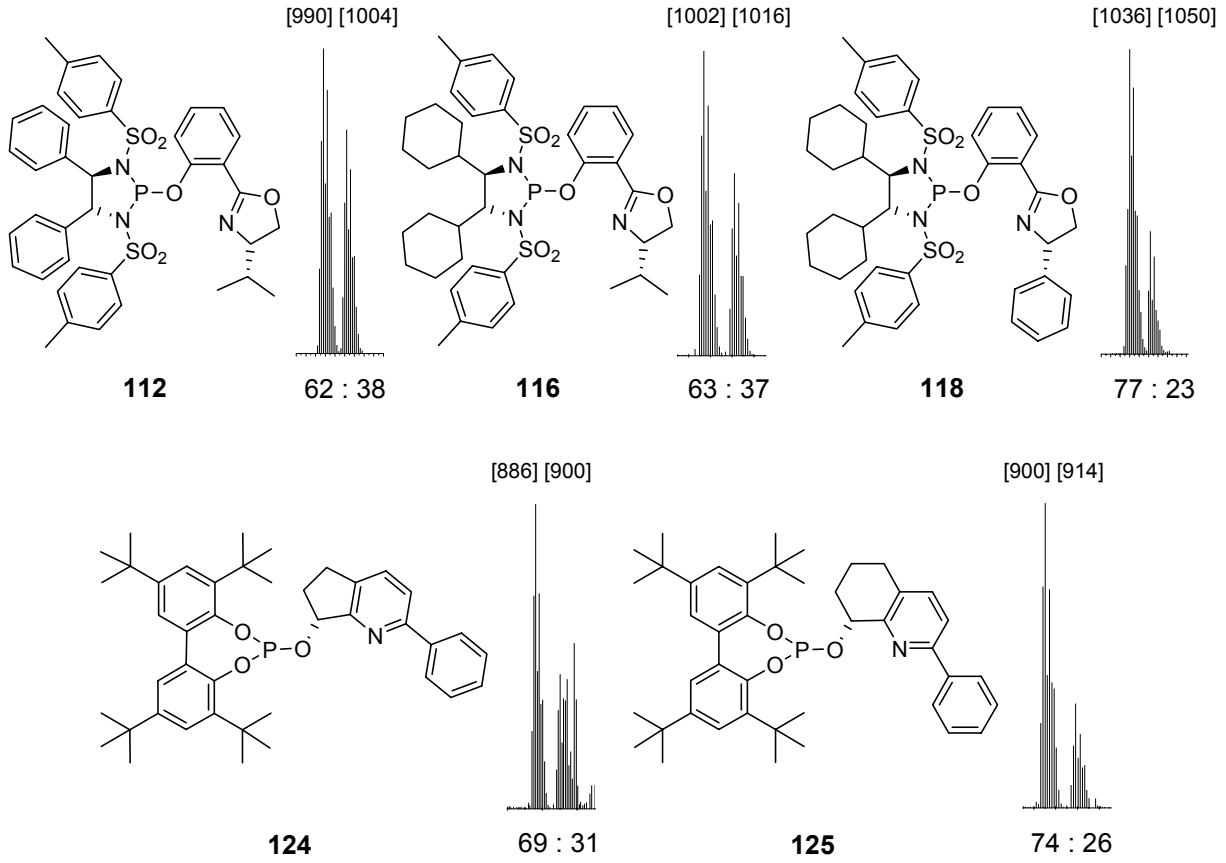


Figure 24. Screening results for the kinetic resolution depicted in Scheme 40.

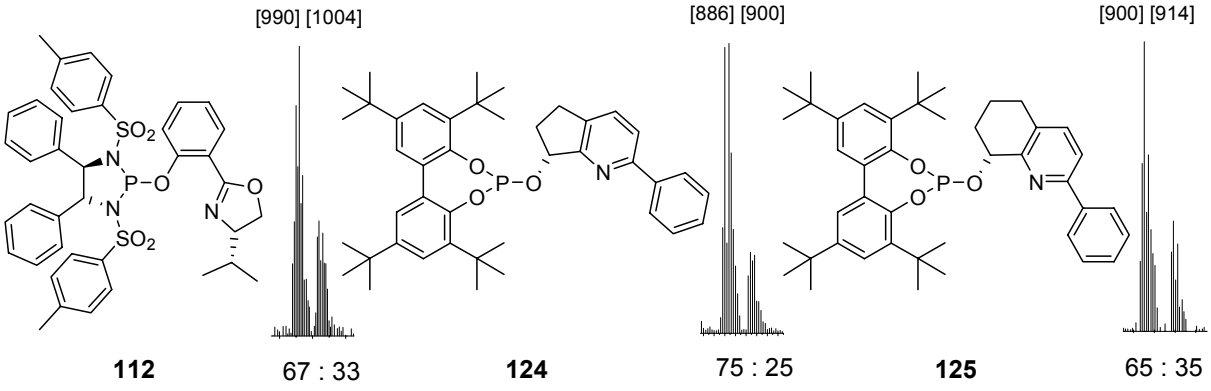


Figure 25. Results of the back reaction screening depicted in Scheme 40.

Finally, ligands **112-117**, **124** and **125** were applied in the kinetic resolution of cyclic allyl esters **65a** and **65b** according to Scheme 22 (Chapter 3.1.3). As it is evident from Figure 26, no significant selectivities were induced with **115**, **118** and **124**.

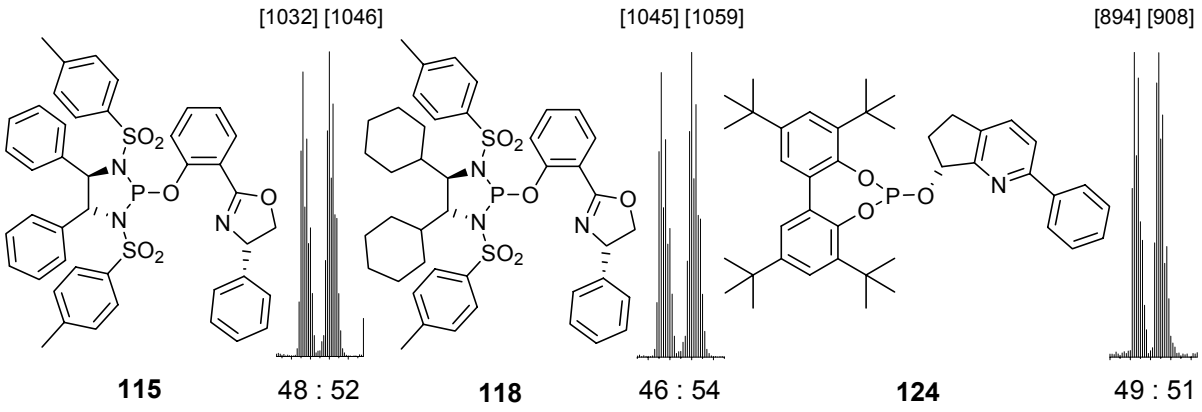


Figure 26. Screening results for the kinetic resolution according to Scheme 22 (Chapter 3.1.3).

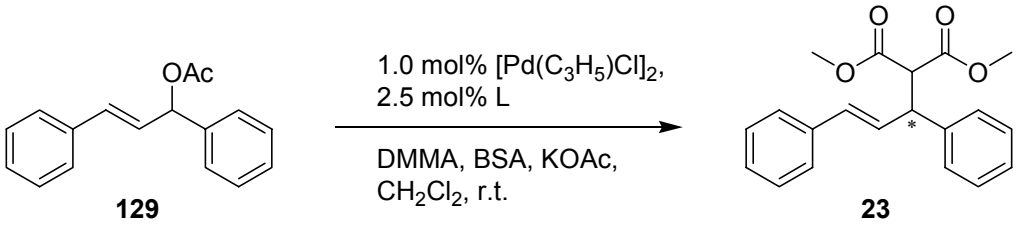
In the following, both new ligand classes were evaluated in conventional catalytic reactions, as the ESI-MS screening did not provide sufficient data for estimating the efficiency of all derivatives.

4.1.3 Preparative Allylic Alkylations

All ligands were tested in three conventional preparative transformations. The substitutions were carried out using dimethyl malonate as the nucleophile, 2 mol% of the catalyst, prepared *in situ* from $[Pd(C_3H_5)Cl]_2$ and the respective chiral ligand, *N*,*O*-bis(trimethylsilyl)acetamide and potassium acetate in dichloromethane at room temperature.

With (*E*)-1,3-diphenyl-2-propenyl acetate (**129**) only moderate enantioselectivities were achieved (Table 9), which are worse than those obtained with Claver-type ligands **96**.[94] The results of bis(*N*-sulfonylamino)phosphine-oxazolines **112**-**118** (entries 1-7) are similar to the corresponding data of previously described ligands derived from 2-[2'-(hydroxy)-prop-2'-yl]-oxazolines.[108] Except for **115**, the derivatives **112**-**114** with diphenyldiamine subunit (entries 1-3) are more efficient than the ligands with an analogous dicyclohexanediamine moiety **116**-**118** (entries 5-7). Catalysts prepared from **113** and **114** bearing a *tert*-butyl group on the oxazoline are the most selective (entries 2 and 3). In contrast to earlier studies, the diastereoisomer **114** derived from the (*S*,*S*)-diamine and the (*S*)-oxazoline is superior to the corresponding ligand **113** based on the (*R*,*R*)-diamine. Pyridyl-phosphites **124** and **125** (entries 7 and 8) show only low selectivity in this transformation giving enantiomeric excesses of less than 50%.

Table 9. Enantioselective allylic alkylation of (*E*)-1,3-diphenyl-2-propen-1-yl acetate (**129**).



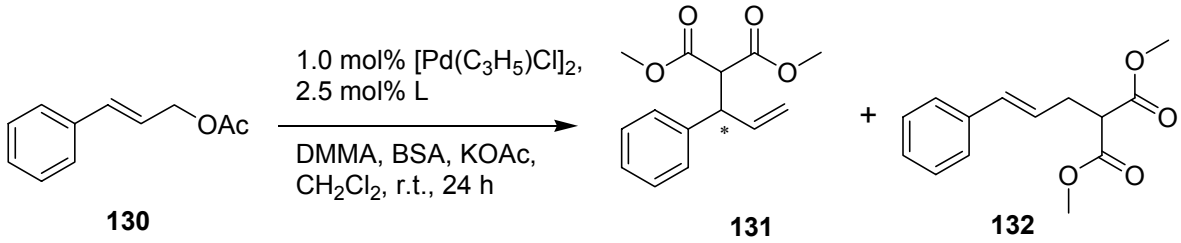
129 **23**

Entry	Ligand	Time [h]	Yield [%][a]	*ee* [%][b]
1	**112**	19	100	62 (*S*)
2	**113**	24	100	83 (*S*)
3	**114**	18	100	90 (*R*)
4	**115**	18	100	17 (*S*)
5	**116**	16	80	26 (*S*)
6	**117**	24	100	50 (*S*)
7	**118**	14	70	48 (*S*)
8	**124**	20	100	47 (*S*)
9	**125**	22	100	50 (*S*)

[a] Isolated yields after column chromatography; [b] determined by chiral HPLC analysis (Daicel Chiracel AD-H, heptane/isopropanol 97:3, 0.9 mL*min^{-1}, 20 °C, 220 nm): t_R = 26.2 (*R*), 37.2 (*S*) min.

Using (*E*)-3-phenyl-2-propen-1-yl acetate (**130**) as an unsymmetrical substrate, the new derivatives gave unsatisfactory results in comparison with previous work (Table 10).[94, 108] Formation of large amounts of the achiral linear substitution product **132** was observed with **113** being the only exception (entry 2). Ligands with diphenyldiamine backbone (entries 1, 2, and 4) are more efficient than the analogous derivatives with dicyclohexanediamine moiety (entries 5-7). The best result was obtained with a *tert*-butyl substituent on the oxazoline, but in this case ligand **113** derived from the (*R*,*R*)-diamine and the (*S*)-oxazoline shows the matched configuration (entry 2). A branched to linear ratio of 73:27 was observed and **131** isolated with 84% *ee* (*S*) whereas the diastereoisomer **114** based on the (*S*,*S*)-diamine only gave a low regioselectivity with 6% *ee* (*R*) (entry 3). Although **131** was obtained with 80% *ee* (*S*) using **124**, this derivative gave the linear isomer **132** as the major product (entry 8). Compound **125** bearing a more flexible six-membered ring is not efficient in terms of enantio- and regioselectivity (entry 9).

Table 10. Asymmetric allylic alkylation of (*E*)-3-phenyl-2-propen-1-yl acetate (**130**).



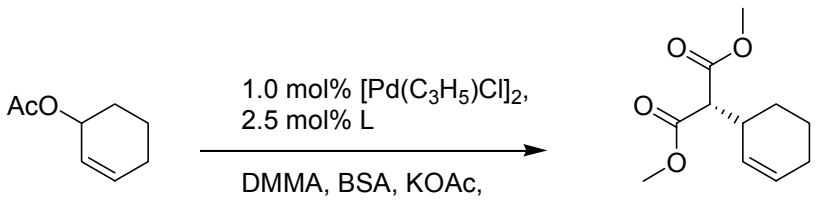
130 **131** **132**

Entry	Ligand	Yield [%][a]	*ee* [%][b]	br/l[c]
1	**112**	100	40 (*S*)	48 : 52
2	**113**	100	84 (*S*)	73 : 27
3	**114**	17	6 (*R*)	57 : 43
4	**115**	100	80 (*S*)	37 : 63
5	**116**	79	28 (*S*)	31 : 69
6	**117**	99	72 (*S*)	56 : 44
7	**118**	90	19 (*S*)	5 : 95
8	**124**	100	80 (*S*)	11 : 88
9	**125**	100	6 (*S*)	6 : 94

[a] Isolated yields after column chromatography; [b] determined by chiral HPLC analysis (Daicel Chiracel OJ, heptane/ethanol 97:3, 0.5 mL*min^{-1}, 20 °C, 210 nm): t_R = 43.7 (*S*), 50.9 (*R*) min; [c] determined by GC (Restek Rtx-1701, 50/0/10/250/10): t_R = 16.9 (br), 19.8 (l) min.

Finally, the allylic alkylation of the more demanding cyclohex-2-enyl acetate **60** was investigated (Table 11). No product formation was observed with bis(*N*-sulfonylamino)-phosphine-oxazolines **112**-**118**. Ligands **124** and **125** catalysed the reaction in rather low selectivity. Derivative **124** was found to be more efficient yielding allylation product **78** in 42% *ee* (*R*) (entry 1).

Table 11. Enantioselective allylic alkylation of cyclohex-2-enyl acetate (**60**).



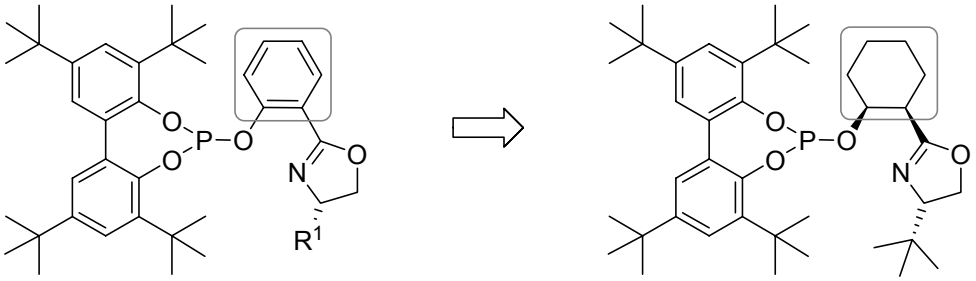
60 (*R*)-**78**

Entry	Ligand	Yield [%][a]	*ee* [%][b]
1	**124**	76	42
2	**125**	59	29

[a] Isolated yields after column chromatography; [b] determined by chiral GC analysis (γ-CD, G-TA, 95/0/0.1/120/0/15/180): t_R(*R*) = 67.7 min, t_R(*S*) = 69.0 min.

4.2 Cyclohexyl-Based Phosphite-Oxazoline Ligands

Apart from the variations of Claver-type ligand **96**, described in the preceding chapter, the influence of additional chirality elements in the backbone was also investigated. In order to keep rigidity of the original ligand **96** at the same time, the bridging aryl subunit was substituted by an aliphatic ring structure. As a first example ligand **133** with a *cis*-disubstituted cyclohexane ring was prepared for the application in palladium-catalysed allylic alkylations (Figure 27).

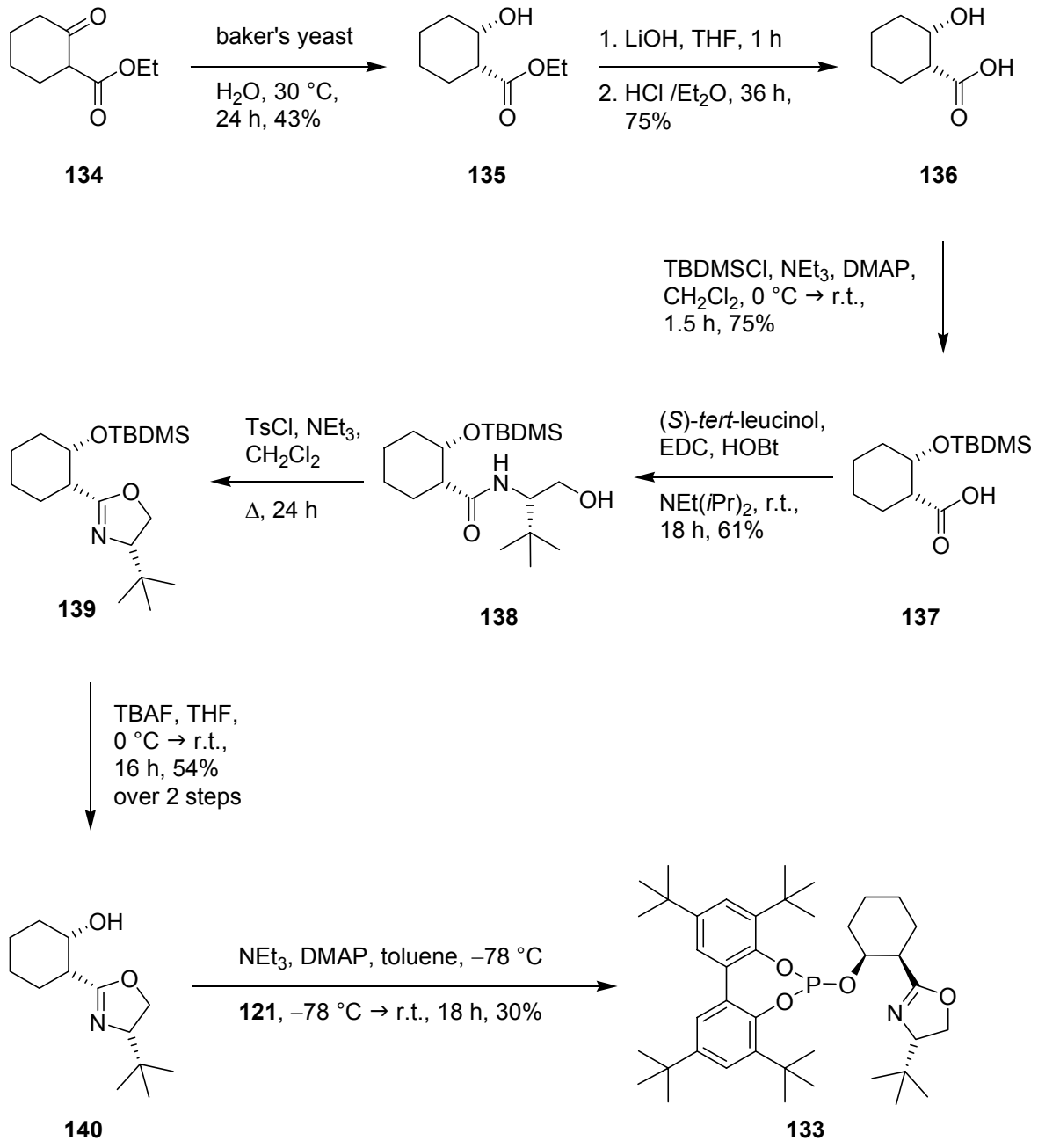


96 **133**

Figure 27. Development of new phosphite-oxazolines with aliphatic backbones.

4.2.1 Ligand Synthesis

Ligand **133** was prepared in seven steps from ethyl-2-oxocyclohexanecarboxylate (**134**) as shown in Scheme 41. Reduction of **134** with baker's yeast yielded the enantioenriched secondary alcohol **135** in good yield.[112] After saponification of the ester the resulting carboxylic acid **136** was treated with *tert*-butyldimethylsilyl chloride to selectively protect the alcohol.[113] The following condensation of carboxylic acid **137** with *tert*-leucinol was carried out using established amide coupling conditions.[114] After cyclisation to the oxazoline, **139** was deprotected with tetrabutylammonium fluoride without purification to yield oxazoline **140**.[115]

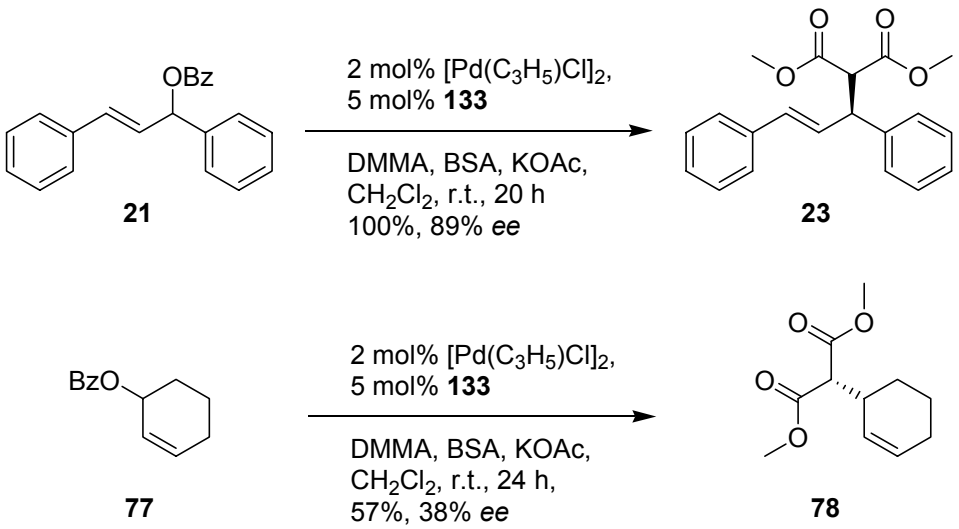


Scheme 41. Synthesis of phosphite-oxazoline **133**.

The phosphorylation was accomplished in analogy to the synthesis of derivatives **124** and **125** with phosphorochloridite **121**, which was prepared *in situ* from diol **120** and phosphorus trichloride.[111] Ligand **133** was isolated in moderate yield after column chromatography under argon. No conversion of the starting material was observed without the addition of 4-(dimethylamino)pyridine.

4.2.2 Ligand Screening and Catalytic Reactions

In order to evaluate the efficiency of ligand **133** in the palladium-catalysed allylic substitutions, it was subjected to ESI-MS analysis. Allylic alkylations and aminations of diarylallyl substrates were investigated by the analysis of the corresponding back reactions (Schemes 11 and 17, Chapter 2). The kinetic resolution of cyclic allyl esters was also studied (Scheme 22, Chapter 3). However, apart from the precatalyst $[Pd(C_3H_5)L]^+$ no allyl-palladium complexes were observed in the corresponding mass spectra using a range of conditions. The ligand was therefore used in the conventional preparative allylic alkylations of both (*E*)-1,3-diphenyl-2-propenyl benzoate (**21**) and cyclohex-2-enyl benzoate (**77**) (Scheme 42). The products **23** and **78** were isolated with promising enantiomeric excesses of 89% (*S*) and 38% *ee* (*R*), respectively.



Scheme 42. Preparative allylic alkylations using phosphite-oxazoline **133**.

4.3 Conclusions and Outlook

In the course of Franke's master thesis new bis(*N*-sulfonylamino)phosphine-oxazolines and pyridyl-phosphites were prepared and evaluated by ESI-MS and conventional catalytic reactions. It was observed, that these ligands exhibit a poor tendency to form allyl-palladium intermediates and therefore their analysis using ESI-MS was hampered. No back reactions were observed using quasienantiomeric substrates derived from acetyl acetone or phthalimide and a comparison with the corresponding preparative allylic alkylations and aminations was

not possible. By using more reactive mass-labelled benzoates and phenolates the formation of reaction intermediates was detected, but the selectivities were only moderate.

All new ligands were further tested in conventional allylic alkylations with the main focus on unhindered linear and cyclic substrates. Low to moderate selectivities were obtained and the results can not compete with the values of previously developed derivatives.

Finally a new phosphite-oxazoline with a chiral cyclohexyl backbone was synthesised. As first catalytic results are promising for this ligand the preparation of other diastereomeric derivatives, in particular with a *trans*-stereochemistry in the bridging ring, and compounds with different ring sizes in the backbone could be of interest to study the influence of the ligand geometry on its selectivity.

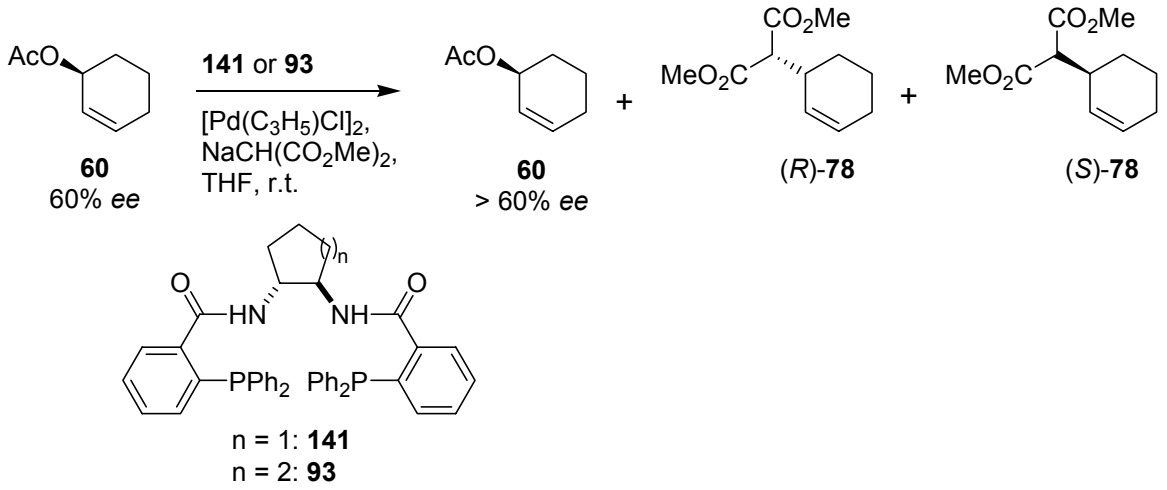
CHAPTER 5

SCREENING OF RACEMIC CATALYSTS

5 Screening of Racemic Catalysts

5.1 Introduction

In 2001, Lloyd-Jones introduced a method for estimating the efficiency of a chiral catalyst in a kinetic resolution by testing the racemic form of the ligand.[83] Qualitative information regarding the selectivity factor *s* can be obtained by employing a *scalemic* substrate ($0 < ee < 100$) and monitoring the change in enantiomeric excess with conversion. In this fashion, racemic ligands **141** and **93** were screened in the palladium-catalysed substitution of **60** (60% *ee*) with sodium dimethylmalonate (Scheme 43).



Scheme 43. Evaluation of racemic catalysts in the kinetic resolution of cyclohex-2-enyl acetate (**60**).

Several curves for the change in *ee* with conversion were calculated and then compared with the experimental data (Figure 28). The results clearly show that ligand **141** is more selective in this reaction than **93**.

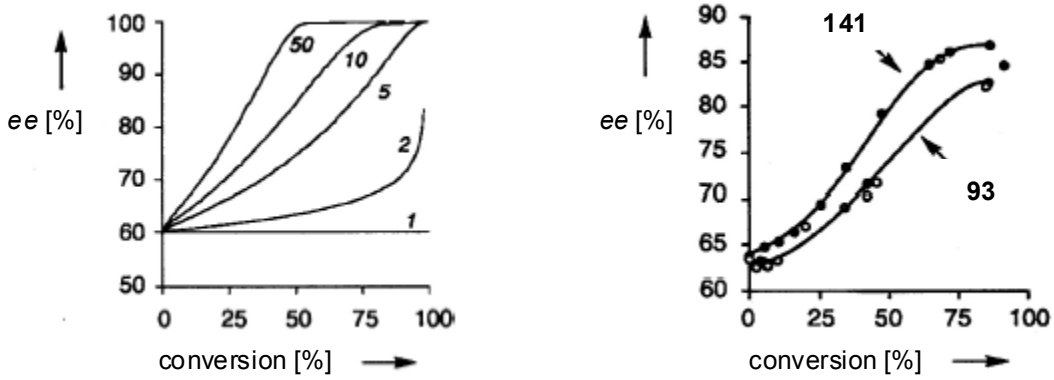
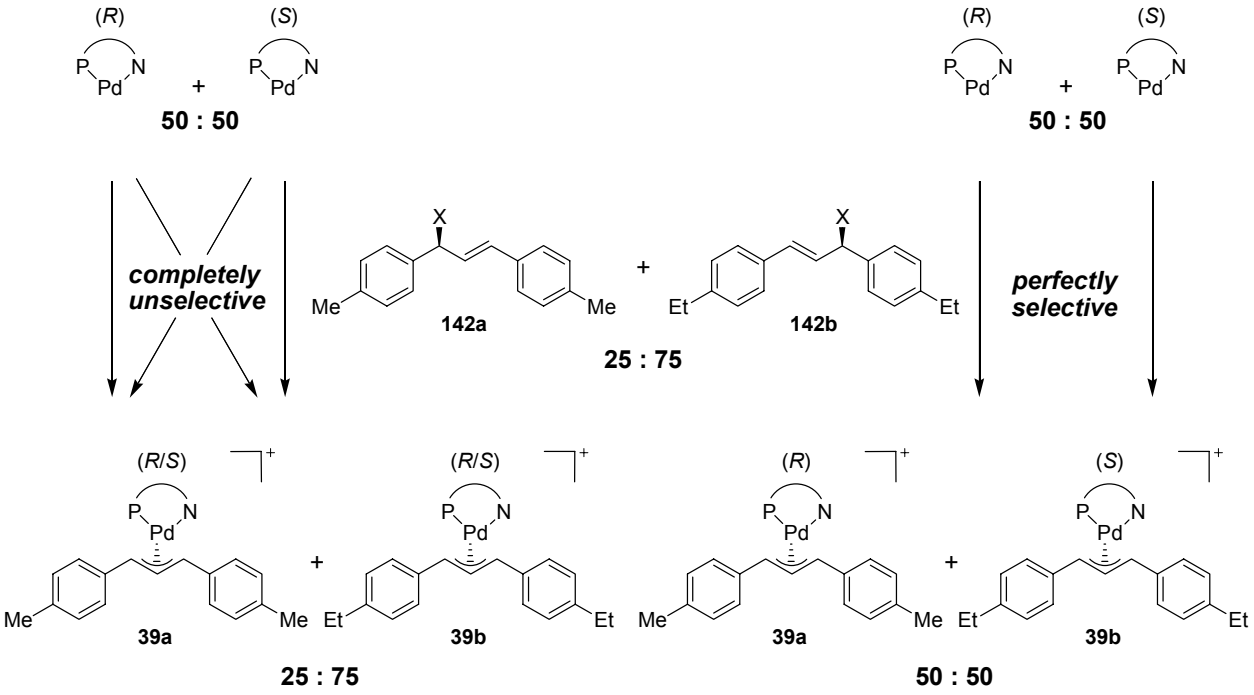


Figure 28. Predicted enantiomeric excess of **60** for several *s* values as a function of conversion with ee_{init} = 60% (left) and experimental data (right).[83]

The ability to test for selectivity using racemic ligands is very useful, as no enantioselective ligand synthesis or resolution processes are required. In order to increase the scope of the back reaction screening, this methodology was adopted for mass spectrometric evaluation of chiral ligands. It was previously demonstrated that the selectivity of racemic catalysts in the kinetic resolution of allyl esters can be determined in this way using a scalemic mixture of quasienantiomers.[104] The two borderline cases are depicted in Scheme 44.



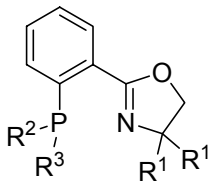
Scheme 44. Concept for screening racemic ligands with ESI-MS.

For an achiral or completely unselective chiral catalyst the relative rates of consumption of quasienantiomers are only dependent on the relative concentrations of the latter. Thus a 25:75 ratio of allyl intermediates **39a** and **39b** is detected by ESI-MS. If the catalyst is perfectly selective, each enantiomer of the catalyst reacts exclusively with the corresponding substrate enantiomer and, consequently, the palladium complexes **39a** and **39b** are observed in equimolar amounts of 50:50. Since the majority of ligands exhibits properties in between, the ratio of intermediates **39a**/**39b** is correlated with the selectivity factor *s* by Equation **3**. This allows for the simple evaluation of the respective catalysts.[104]

$$\text{Ratio of allyl intermediates} = 50 \cdot \left(\frac{s}{s+3} + \frac{1}{3s+1} \right) : 50 \cdot \left(\frac{3}{s+3} + \frac{3s}{3s+1} \right) \qquad \textbf{[3]}$$

5.2 Phox Ligands with Stereogenic Phosphorus

Since the influence of stereogenic phosphorus atoms in phosphinooxazolines (Figure 29) has not intensely been investigated in allylic substitution reactions so far,[116-118] the method developed by Lloyd-Jones seemed promising to evaluate the selectivity of these ligands.



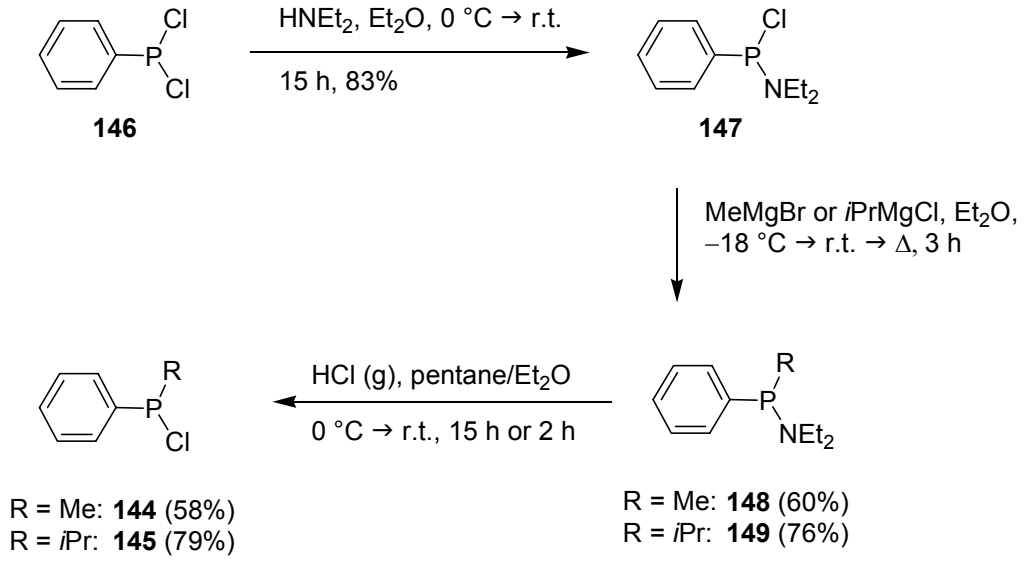
143

Figure 29. Phox ligand with a stereogenic phosphorus atom.

The synthesis of enantiomerically pure derivatives **143** with chiral phosphorus donors and achiral oxazoline moieties is not straightforward, but their racemates are easily accessible. Hence, the evaluation of the racemic catalysts by ESI-MS would be advantageous.

5.2.1 Synthesis of Dialkyl- and Alkylaryl-Substituted Phosphinooxazolines

The synthesis of phox ligands derived from dialkyl- or alkylarylchlorophosphines was pursued first.



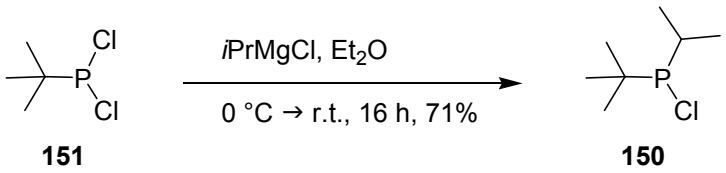
146 **147**

R = Me: **144** (58%)
R = *i*Pr: **145** (79%)

R = Me: **148** (60%)
R = *i*Pr: **149** (76%)

Scheme 45. Synthesis of chlorophosphines **144** and **145**.

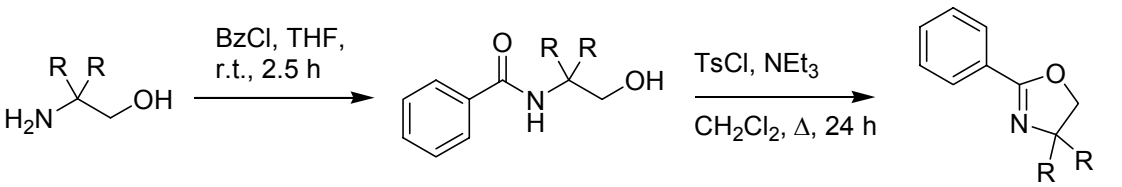
For this purpose, chlorophosphines **144** and **145** were synthesised in three steps starting from commercially available dichlorophenylphosphine **146** (Scheme 45).[119] Since clean monoalkylations of **146** are not possible, diethylamine was used as a surrogate for one of the chlorides and the obtained aminochlorophosphine **147** was reacted with the respective Grignard reagents. Treatment with anhydrous hydrogen chloride gave chlorophosphines **144** and **145** in moderate yields after distillation. Because of its increased steric bulk, the *tert*-butyl-chloro-isopropylphosphine **150** could be prepared directly from **151** and isopropylmagnesium chloride in good yield (Scheme 46).[117]



151 **150**

Scheme 46. Preparation of *tert*-butyl-chloro-isopropylphosphine **150**.

Oxazolines **152** and **153** were obtained in high overall yields starting from amino alcohols **154** and **155**, by benzoylation and subsequent ring closure with tosyl chloride.[115, 120]



R = H: **154**
R = Me: **155**

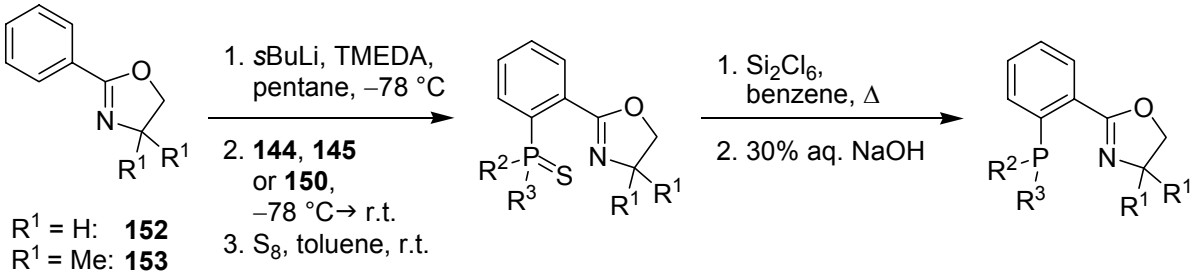
R = H: **156** (81%)
R = Me: **157** (79%)

R = H: **152** (85%)
R = Me: **153** (70%)

Scheme 47. Synthesis of oxazolines **152** and **153**.

Racemic phox derivatives with stereogenic phosphorus atoms were prepared by ortholithiation of phenyl-substituted oxazolines **152** or **153** and subsequent reaction with chiral chlorophosphines **144**, **145** or **150** (Table 12).[117] Sulfur was used to protect the air-sensitive phosphine moiety.[117, 121] Racemic phosphine sulfides **158a**-**163a** were isolated in 20-90% yield after column chromatography.

Table 12. Synthesis of phosphinooxazolines with stereogenic phosphorus atoms.



Entry	R^1	R^2	R^3	Phosphine Sulfide	Yield [%]	Free Ligand	Yield [%]
1	H	Ph	Me	**158a**	67	**158**	21
2	H	Ph	*i*Pr	**159a**	79	**159**	44
3	H	*t*Bu	*i*Pr	**160a**	89	**160**	43
4	Me	Ph	Me	**161a**	64	**161**	37
5	Me	Ph	*i*Pr	**162a**	31	**162**	33
6	Me	*t*Bu	*i*Pr	**163a**	64	**163**	51

The protecting groups were removed with hexachlorodisilane in benzene in order to avoid the racemisation of the stereogenic phosphorus atoms.[122, 123] Moderate yields were obtained and in some cases the procedure had to be repeated to achieve full conversions. The structures of all new derivatives are depicted in Figure 30.

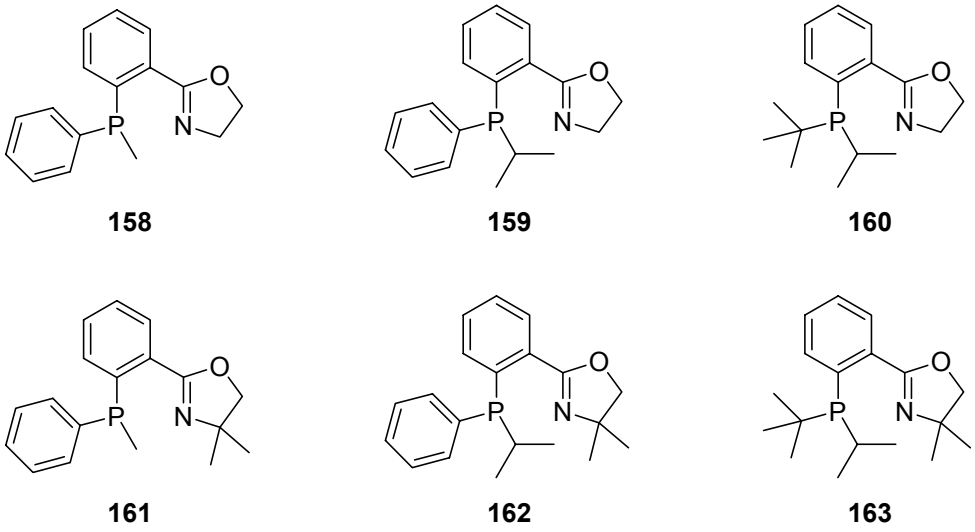
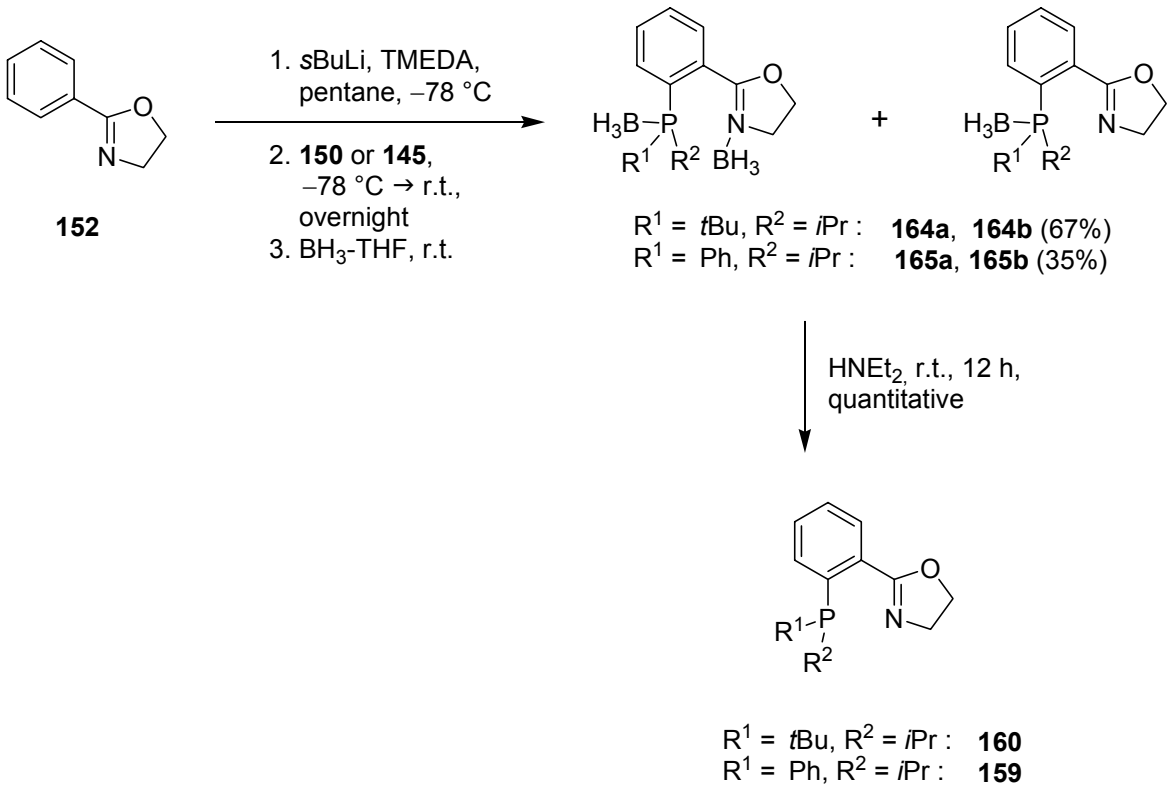


Figure 30. New phosphinooxazolines with stereogenic phosphorus atoms.

Due to the difficult removal of sulfur, borane was tested as alternative protecting group as well (Scheme 48).[124]



Scheme 48. Synthesis of phosphinooxazolines using the borane protecting group.

However, when the reaction was carried out with two equivalents of borane, partial protection of the nitrogen atom was observed. This took place even when substoichiometric amounts of protecting agent were used. The protected ligands **164** and **165** were obtained in high purity after column chromatography and the borane moiety was easily removed by treatment with an excess of diethylamine. However, separation of the enantiomers of the borane-protected ligands **164** and **165** by semipreparative HPLC was not possible, since the ligands partially decomposed. Therefore, the borane protection method was discarded.

Portions of the racemic phosphine sulfides **158a**-**163a** were separated into their enantiomers by semipreparative HPLC on a chiral column without difficulty. Single crystals suitable for X-ray analysis were obtained for the ligands **159a**, **160a**, and **162a** (Figure 31) and the resulting crystal structure data enabled the assignment of configurations at phosphorus.

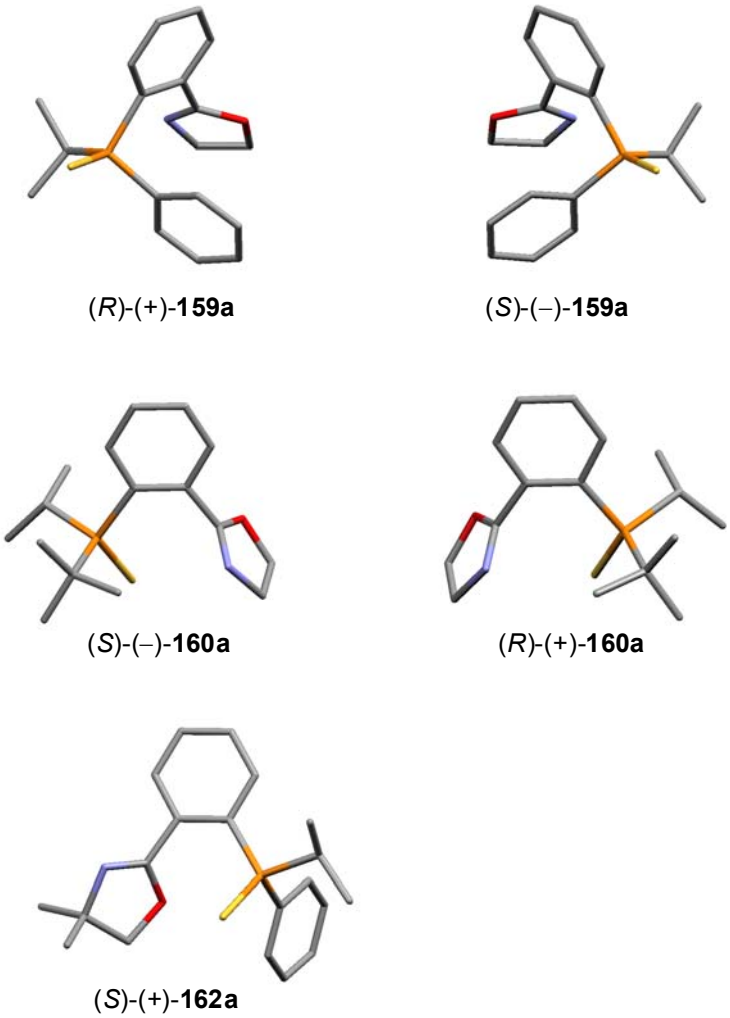


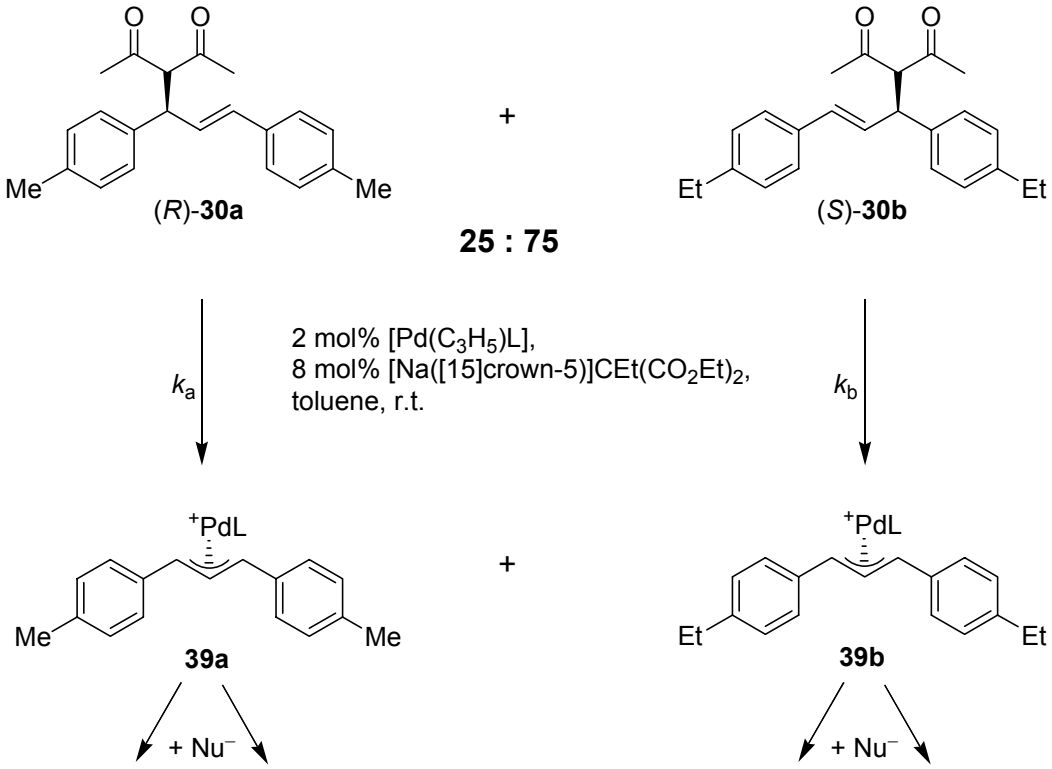
Figure 31. Crystal structures of the phosphine sulfides **159a**, **160a** and **162a**.

The sulfides were deprotected with hexachlorodisilane, as described above. This method is known to proceed with retention of configuration at phosphorus.[122, 123]

During synthesis, it became clear that phox ligands possessing one or two alkyl-groups on the phosphorus donors are less stable than their aryl-substituted counterparts. Decomposition was observed, even when these derivatives were stored in an air- and moisture-free environment. Similar observations have previously been reported.[117]

5.2.2 Ligand Screening

After having prepared racemic ligands **158**-**163** a back reaction screening was carried out under the conditions described in Chapter 2, but a scalemic mixture of quasienantiomers (*R*)-**30a** and (*S*)-**30b** was used (Scheme 49). The precatalysts were prepared *in situ* from $[Pd(C_3H_5)(MeCN)_2]OTf$ and the respective racemic ligands. In contrast to the established phosphinooxazolines **27**, **28** and **40**-**42** only moderate precomplexation was achieved, as indicated by low signal intensities in the mass spectra. This might be attributed either to impurities from the reduction of the sulfides to the free ligands or to subsequent partial decomposition of the latter.



Scheme 49. Back reaction screening of racemic ligands.

After activation of the precatalysts with the crown ether sodium salt of diethyl ethylmalonate, allyl intermediates **39a** and **39b** were solely generated with the catalyst derived from ligand **162** (Figure 32). The respective complexes **166a** and **166b** were detected in low intensity with a ratio of 25:75, indicating no selectivity of the catalyst at all.

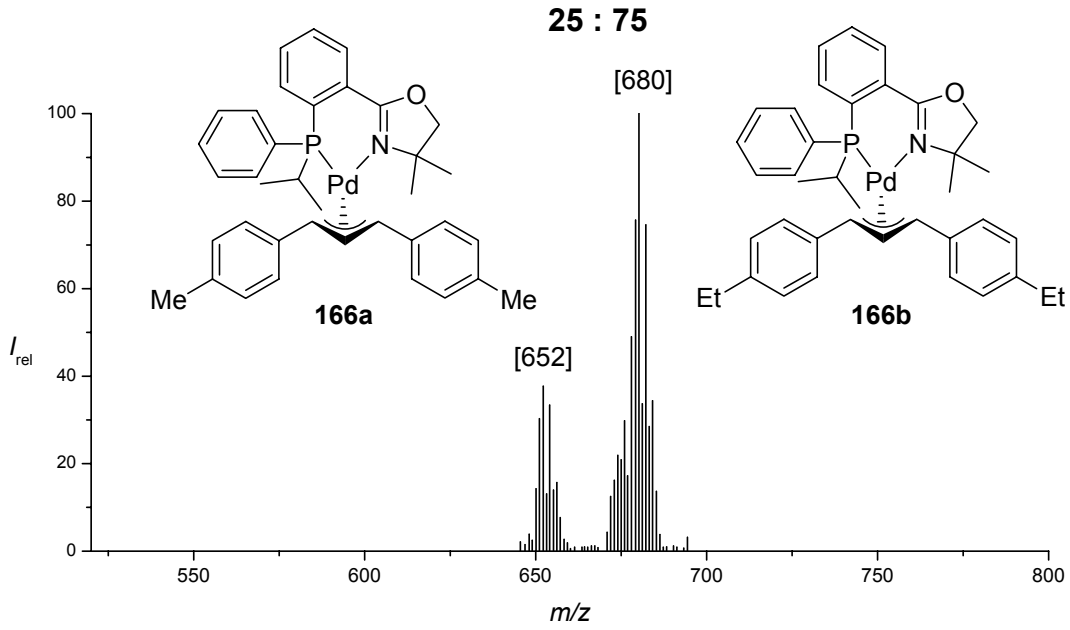
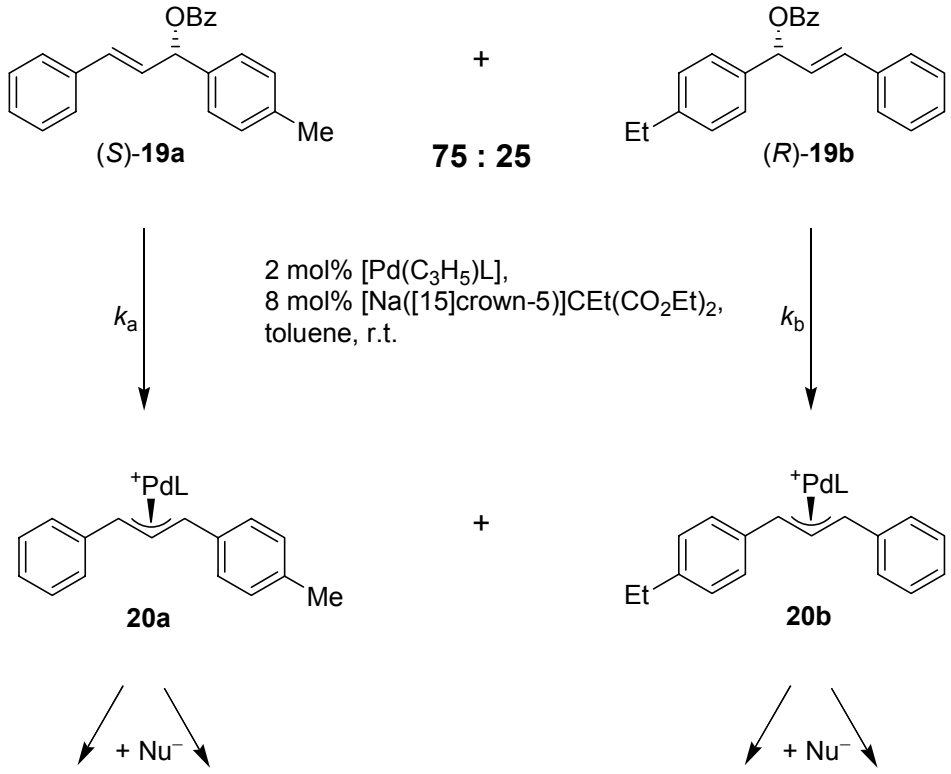


Figure 32. Evaluation of phox ligand **162** in the back reaction according to Scheme 49.

For comparison, the corresponding preparative reaction using the enantiomerically pure ligand **162** was carried out (Scheme 14, Chapter 2) and racemic product was isolated – a result consistent with the ESI-MS analysis. Similar results were obtained in the back reaction screening using phthalimide-based quasienantiomers (*R*)-**58a** and (*S*)-**58b**.

Racemic ligands **158**-**163** were also studied in the kinetic resolution of quasienantiomeric allyl esters using a mixture of **19a** and **19b** in a ratio of 75:25 (Scheme 50). Although these more reactive substrates were employed, the palladium complexes **20a** and **20b** were detected only when the ligands **161**-**163** derived from dimethyl-substituted oxazoline **153** were used. As evident from Figure 33, the signal intensities were poor and the mass spectra of generally low quality, a result which confirms the decreased ability of these ligands to form allyl intermediates **20a** and **20b**. The latter were observed in a ratio of about 75:25 with the phosphines **161** and **162**, again indicating that no resolution is taking place. Ligand **163** proved to be more efficient, but an exact determination of the *s* value was complicated by signal overlap.



Scheme 50. Screening of racemic ligands in the kinetic resolution of (*S*)-**19a** and (*R*)-**19b**.

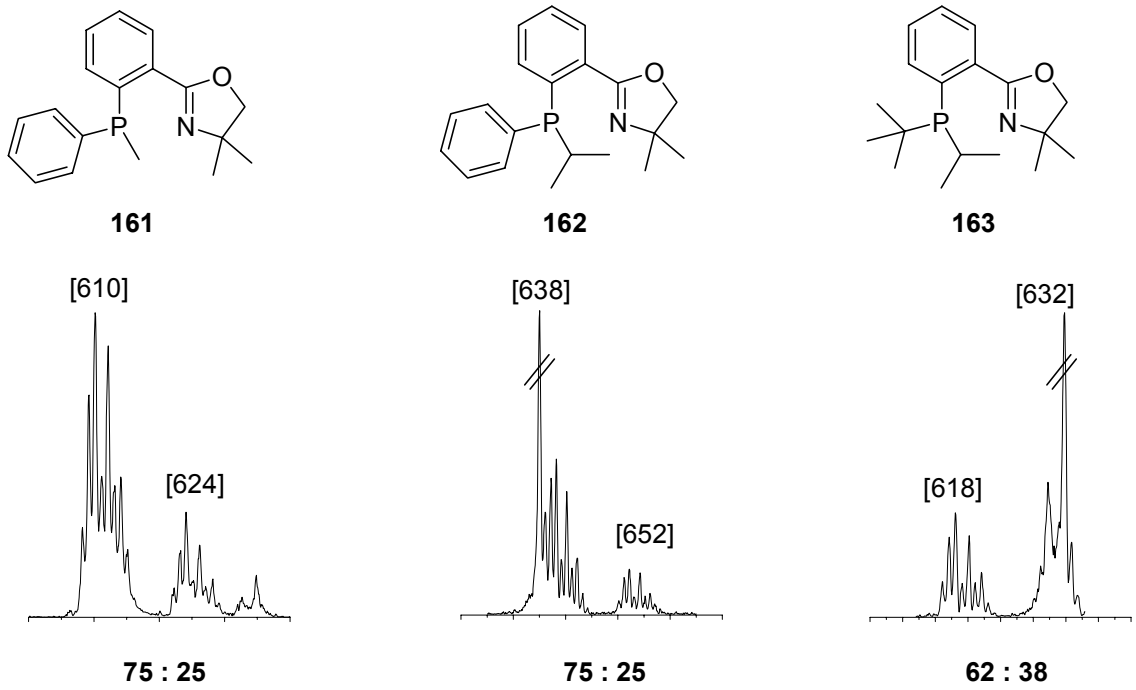
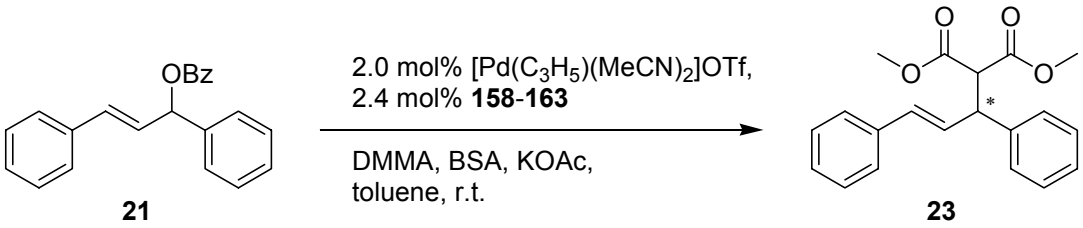


Figure 33. Evaluation of phox derivatives **161-163** in the kinetic resolution depicted in Scheme 50.

Since the ESI-MS screening did not provide sufficient data to estimate the efficiency of all derivatives, conventional allylic alkylations of (*E*)-1,3-diphenyl-2-propenyl benzoate (**21**) with dimethyl malonate were conducted with the enantiomerically pure ligands (Table 13). The allylation product **23** was obtained in high yields with moderate to low enantiomeric excesses, except for phosphines **158** and **161** (entries 1 and 4), which showed no selectivity. Methyl substitution on the oxazoline moiety was found to give superior results and **163** was identified as the most selective derivative in this series with 66% *ee* (*S*) (entry 6). Overall, the data demonstrate that stereogenic phosphorus atoms have a significant influence on selectivity, but the new phox derivatives are not competitive with their already established counterparts.

Table 13. Allylic alkylation of **21** with phox ligands **159**-**163**.



21 **23**

Entry	Ligand	Time [h]	Yield [%]	*ee* [%][a]
1	(+)-**158**	17	86	*rac*
2	(+)-(*R*)-**159**	19	80	24 (*R*)
3	(+)-(*R*)-**160**	16	79	15 (S)
4	(+)-**161**	63	100	6 (*R*)
5	(+)-(*S*)-**162**	18	84	46 (S)
6	(+)-**163**	41	100	66 (S)

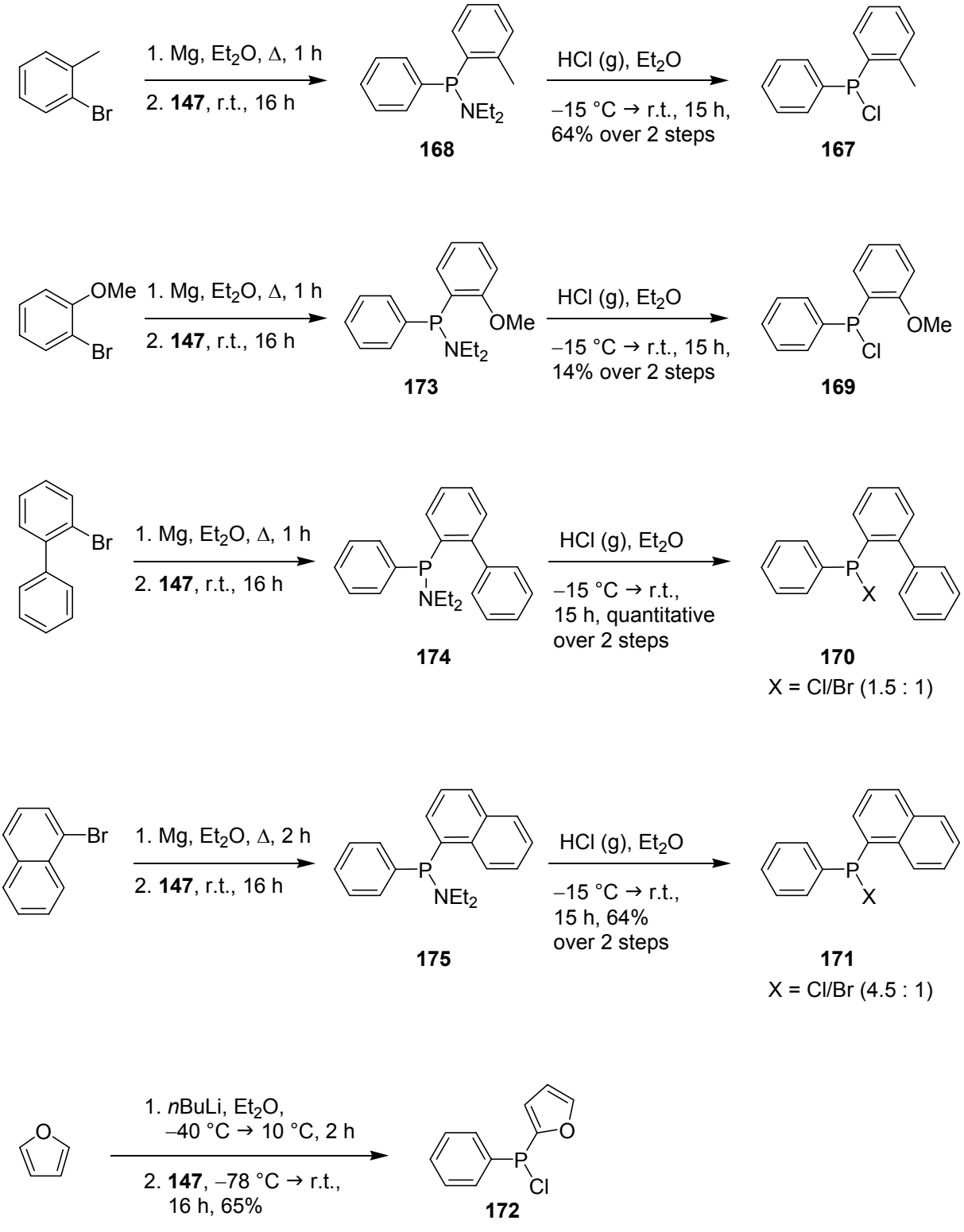
[a] determined by chiral HPLC analysis (Daicel Chiracel AD-H, heptane/isopropanol 97:3, 0.9 mL*min^{-1}, 20 °C, 220 nm): t_R = 26.2 (*R*), 37.2 (S) min.

5.2.3 Diaryl-Substituted Phosphinooxazolines

The investigations described above demonstrate that phox ligands with dialkyl-substitution at the phosphorus donor generally exhibit poor ability to form allyl-palladium intermediates **39a** and **39b**. In contrast, excellent results in allylic alkylations and aminations were obtained with diaryl-phosphines **27**, **28** and **40**-**42** (Chapter 2). Prompted by these findings, a series of phox ligands derived from chiral diarylphosphines was synthesised with the intent of improving efficiencies in the back reaction screening.

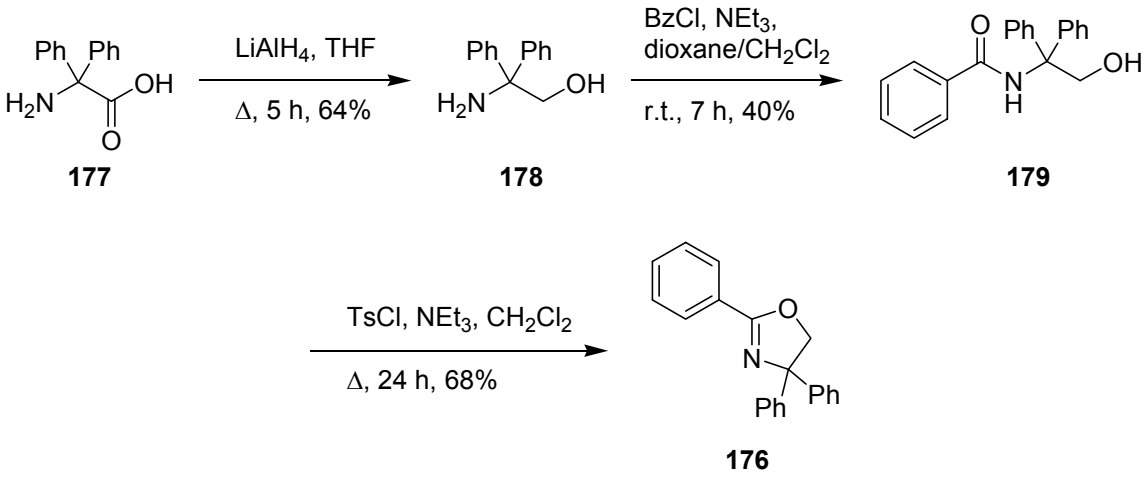
For this purpose, chiral phosphines were prepared according to Scheme 51. The synthesis of phosphine **167** involved the reaction of diethylamino derivative **147** with one equivalent of Grignard reagent.[116] As described in Section 5.2.1, the diethylamino group was used to avoid product mixtures. Intermediate **168** was treated with anhydrous hydrogen chloride to give the desired product **167** in good yield. Similar procedures were employed to obtain the *ortho*-anisyl-, 2-biphenyl- and 1-naphthylphenyl-derivatives **169**, **170**, and **171**. Phosphines **170** and **171** were isolated as mixtures of the corresponding chlorides and bromides, both of which are suitable electrophiles for ligand syntheses.

Furyl-substituted phosphine **172** was prepared from furan by ortholithiation and subsequent reaction with 0.8 equivalents of dichlorophenylphosphine. The product was obtained in good yield, but was contaminated by 10% of di(2-furanyl)phenylphosphine.[125]



Scheme 51. Synthesis of diaryl-chlorophosphines.

A phenyl-substituted oxazoline **176** was prepared from commercially available amino acid **177** in three steps (Scheme 52). The product was obtained in good overall yield after reduction of the acid followed by benzoylation and ring closure with tosyl chloride.[115, 126]

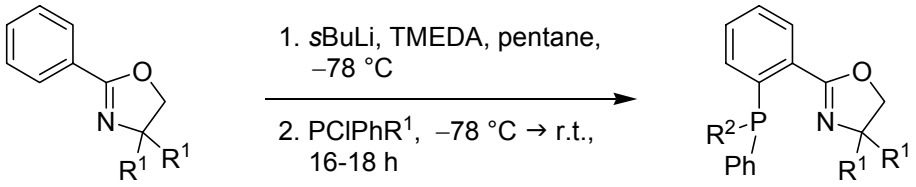


177 **178** **179** **176**

Scheme 52. Preparation of oxazoline **176**.

The ligand syntheses were accomplished using ortholithiation of the achiral oxazolines **152**, **153** and **176** with *sec*-butyllithium and subsequent addition of the chiral chlorophosphines. Compounds **180**-**190** were isolated in variable yields ranging from 14% to 71% after column chromatography under argon (Table 14).

Table 14. Synthesis of diarylphosphinooxazolines with stereogenic phosphorus atoms.



R^1 = H: **152**
R^1 = Me: **153**
R^1 = Ph: **176**

Entry	R^1	R^2	Ligand	Yield [%]
1	H	*o*Tol	**180**	25
2	H	*o*An	**181**	62
3	H	2-Bp	**182**	43
4	H	1-Np	**183**	71
5	H	1-Fu	**184**	42
6	Me	*o*Tol	**185**	40
7	Me	*o*An	**186**	28
8	Me	2-Bp	**187**	37
9	Me	1-Np	**188**	70
10	Me	1-Fu	**189**	22
11	Ph	2-Bp	**190**	14

In contrast to the alkylphosphine-based derivatives **158a-163a**, sulfur protection was not necessary due to increased ligand stability.

After their successful preparation, ligands **180-190** were evaluated by ESI-MS and the results are shown in Table 15.

Table 15. Mass spectrometric evaluation of racemic phox ligands **180**-**190**.

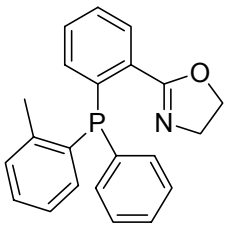
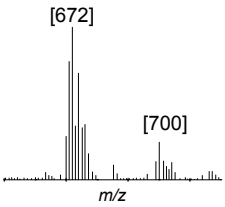
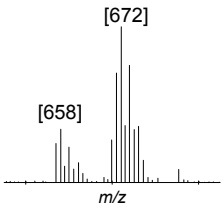
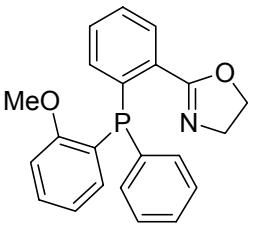
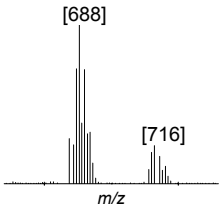
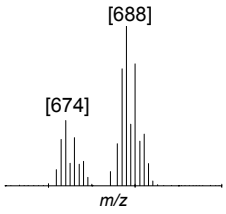
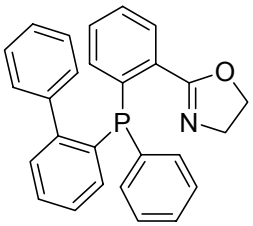
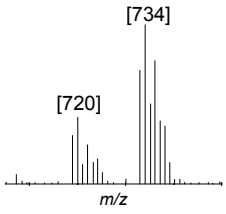
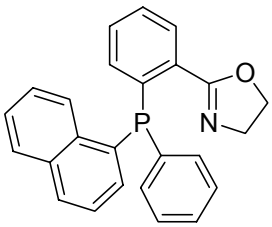
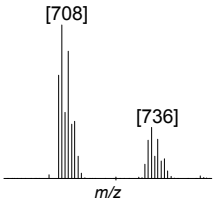
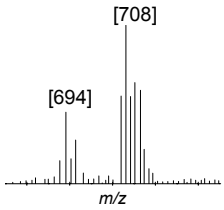
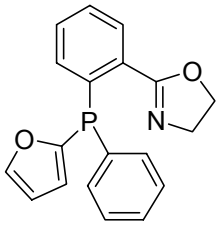
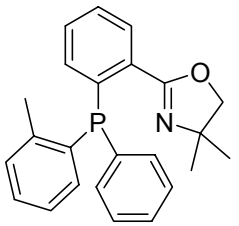
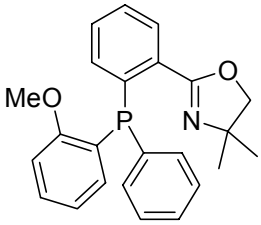
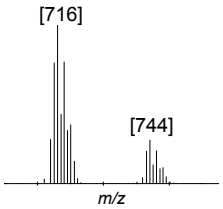
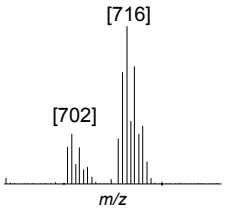
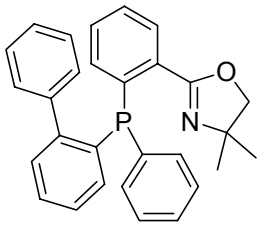
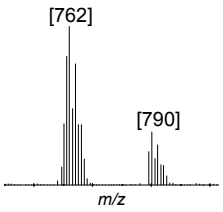
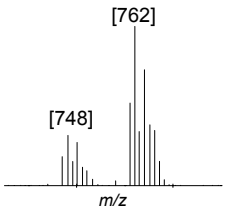
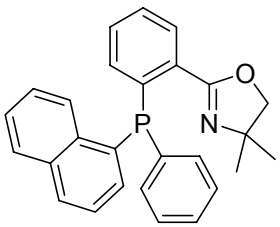
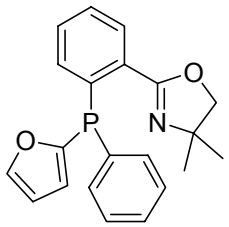
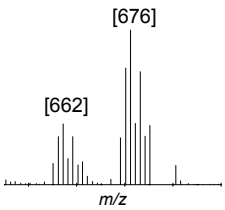
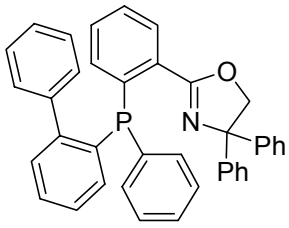
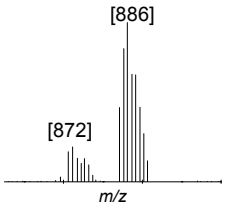
Entry	Ligand	Back Reaction[a]	Kinetic Resolution[b]
1	 **180**	75 : 25 	25 : 75 
2	 **181**	75 : 25 	28 : 72 
3	 **182**	–	30 : 70 
4	 **183**	76 : 24 	25 : 75 
5	 **184**	–	–

Table 15. Continued.

Entry	Ligand	Back Reaction[a]	Kinetic Resolution[b]
6	 **185**	–	–
7	 **186**	75 : 25 	25 : 75 
8	 **187**	75 : 25 	25 : 75 
9	 **188**	–	–
10	 **189**	–	28 : 72 
11	 **190**	–	25 : 75 

[a] according to Scheme 49; [b] according to Scheme 50.

Both the back allylic alkylation (Scheme 49) and the kinetic resolution (Scheme 50), using scalemic mixtures of quasienantiomers in ratios of 75:25, were investigated. The ligands with diaryl-substituted phosphorus atoms showed increased reactivity relative to the analogous alkyl derivatives. In the kinetic resolution of allylic benzoates **19a** and **19b**, the desired allyl intermediates **20a** and **20b** were observed in all cases, except for ligands **184**, **185**, and **188** (entries 5, 6, and 9). However, no or only weak asymmetric induction was observed in this reaction and intermediate ratios between 25:75 and 30:70 were obtained.

In accordance with previous results, a lower efficiency for the formation of allyl-palladium complexes **39a** and **39b** was observed, when the back reaction was analysed; no selectivities were obtained either.

In summary, the presented methodology for screening racemic catalysts efficiently demonstrates that phox derivatives with diaryl-substituted phosphorus atoms and achiral oxazoline moieties are unsuitable for allylic alkylation reactions, avoiding the time-consuming and labour-intensive preparation of enantiomerically pure ligands.

5.3 Conclusions and Outlook

In this chapter, the ESI-MS screening protocol was extended to determine the selectivities of chiral catalysts in allylic substitution reactions by testing their racemates. Based on the work of Lloyd-Jones, scalemic mixtures of quasienantiomers were employed.[83, 104] The method was applied to investigate the efficiency of phox ligands with stereogenic phosphorus atoms, as the synthesis of enantiomerically pure derivatives with chiral phosphorus subunits and achiral oxazoline moieties is not straightforward. The advantage of this approach is that selective catalysts can be identified by testing their easily accessible racemates.

First, ligands derived from dialkyl- and alkylaryl-chlorophosphines were successfully synthesised. However, the ESI-MS analysis of both kinetic resolution and the back allylic alkylation revealed a poor affinity for the formation of allyl-palladium intermediates and ligand evaluation was therefore not possible. For this reason conventional preparative allylic alkylations using the separated ligand enantiomers were carried out and the chiral phosphorus subunit was shown to have a significant influence on the reaction. However, the derivatives were not competitive with the easily accessible standard phox ligands derived from chiral amino alcohols.

In order to favour the back reaction racemic phox ligands derived from chiral diarylchorophosphines were synthesised and subjected to ESI-MS analysis. In most cases

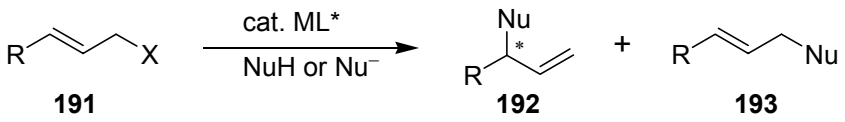
increased reactivities were observed for both the kinetic resolution and the back allylic alkylation. Without the time-consuming preparation of enantiomerically pure derivatives the results rapidly demonstrated that phox ligands with diaryl-substituted phosphine donors and achiral oxazolines are virtually unselective in allylic substitutions. Future work might be dedicated to the the evaluation of these ligands in other catalytic reactions, such as the iridium-catalysed asymmetric hydrogenations of unfunctionalised olefins.

CHAPTER 6

IRIDIUM-CATALYSED ASYMMETRIC ALLYLIC SUBSTITUTIONS

6 Iridium-Catalysed Asymmetric Allylic Substitutions

After having established a reliable ESI-MS based screening protocol for the evaluation of chiral palladium catalysts in allylic substitutions of both linear diarylallyl and carbocyclic substrates we became interested in reactions of monosubstituted allylic derivatives **191** (Scheme 53).[80, 81, 92] In the last years more and more research has been directed on finding catalysts, which favour the formation of the chiral branched product **192** with high selectivity.

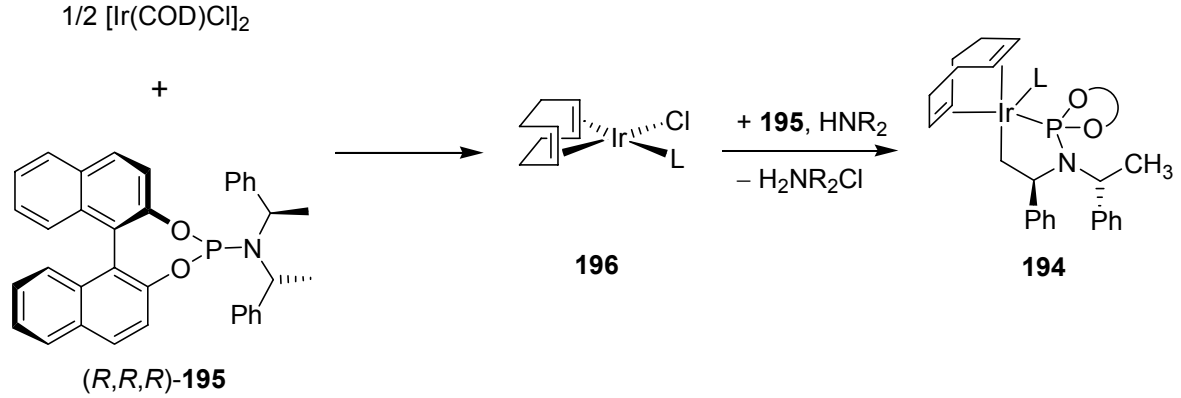


191 **192** **193**

Scheme 53. Allylic substitutions of monosubstituted allylic substrates **191**.

Palladium systems usually give the achiral linear product with few exceptions[94, 108, 127, 128] but iridium complexes of electron-poor ligands became the catalysts of choice for this purpose.[129] Precatalysts prepared from chloro-1,5-cyclooctadiene iridium(I) dimer and phosphoramidites derived from 2,2'-dihydroxybinaphtalene (BINOL) and 2-arylethylamines are the most efficient systems for allylic aminations,[130-135] etherifications[136] and alkylations.[137-139] The branched products are obtained in high yields with excellent regio- and enantioselectivities.

During their investigations on allylic aminations Hartwig and coworkers discovered that the active catalyst **194** contains a metallacycle, which ist generated *in situ* by reaction of chloro-1,5-cyclooctadiene iridium(I) dimer with the phosphoramidite ligand **195** in the presence of an amine base (Scheme 54).[140]



(*R*,*R*,*R*)-**195** **196** **194**

Scheme 54. Preparation of the activated catalyst **194**.

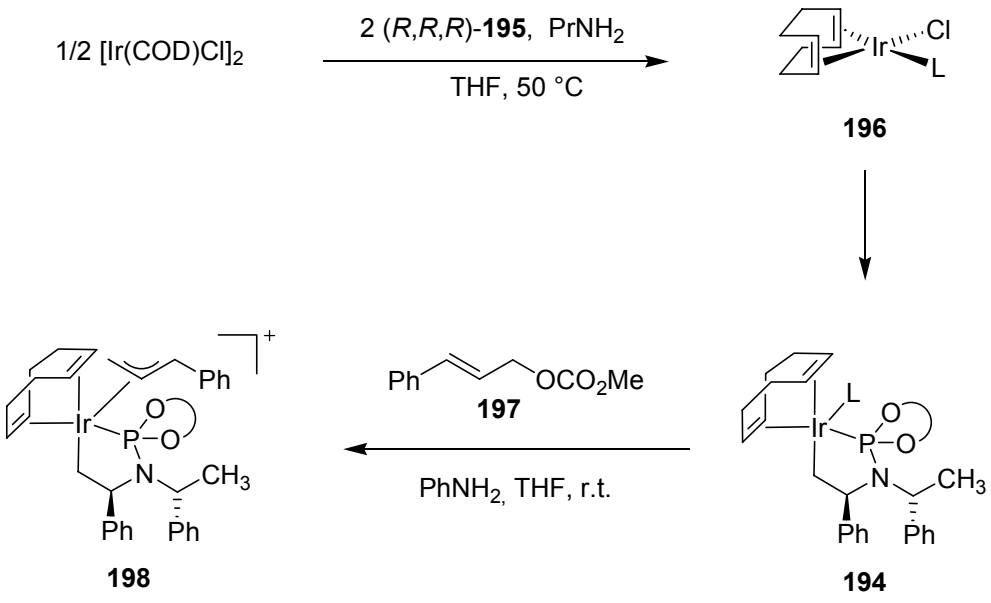
The transformation proceeds *via* the squareplanar iridium(I) complex **196**, which was found to be inactive on the time scale of catalytic reactions. Apart from these findings mechanistic data are scarce.[141, 142]

Due to the importance of iridium-catalysed allylic substitutions this reaction was investigated by ESI-MS in order to develop a screening method for the evaluation of alternative chiral ligands. Furthermore we hoped to get a closer insight into the catalytic cycle, whose intermediates have not been isolated or even detected to that date.

6.1 Mass Spectrometric Analysis

The evaluation of chiral catalysts by ESI-MS is only applicable to reactions, which proceed *via* charged intermediates that are related to the enantioselective step. Since no mechanistic data on iridium-catalysed allylic substitutions was available, it was unclear if the transformation would fulfil this criteria. Most assumptions on the mechanism were based on that for palladium, for which the identity of each species has been determined and the rate-limiting step has been identified.

The allylic amination of carbonate **197** with aniline was analysed, applying the conditions described in the literature (Scheme 55), to test if allyl-iridium intermediates analogous to the respective palladium species can be detected by ESI-MS.[131, 140]



Scheme 55. Mass spectrometric analysis of the allylic amination of carbonate **197** with aniline.

The activated catalyst **194** was formed by the reaction of 1 mol% of chloro-1,5-cyclooctadiene iridium(I) dimer with two equivalents of phosphoramidite **195** in a 1:1 mixture of propylamine and tetrahydrofuran at 50 °C. After 20 minutes an aliquot was diluted in methanol and analysed by ESI-MS (Figure 34, A).

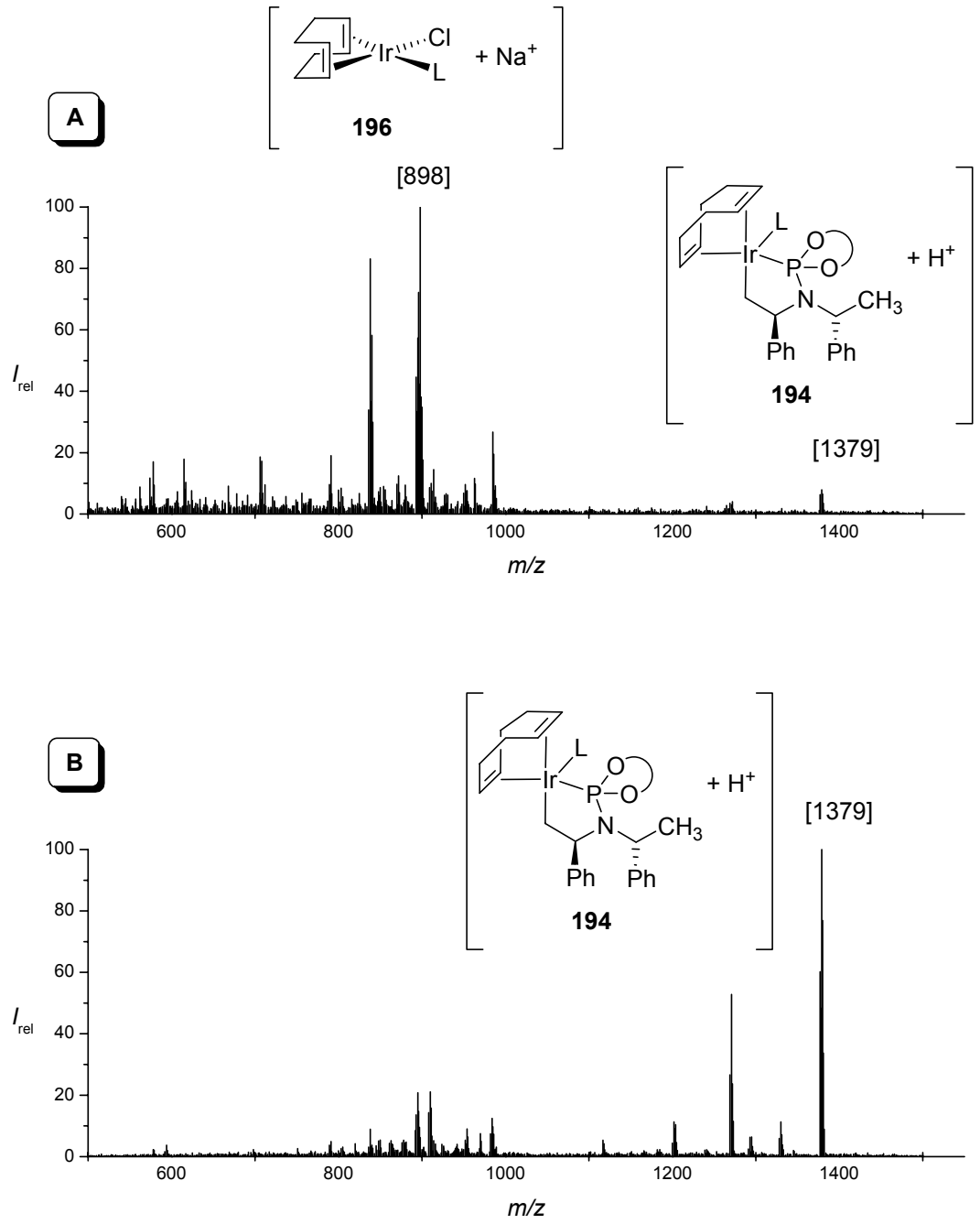


Figure 34. Mass spectra recorded during catalyst activation after 20 min (A) and 2 h (B).

The mass spectrum shows a major signal at m/z = 898 and a minor one at m/z = 1379 corresponding to the sodium adduct of iridium(I) complex **196** and the protonated activated derivative **194**. The spectra are of low quality, because **196** and **194** themselves are uncharged. The dilution in protic solvents like methanol or isopropanol was mandatory to detect these species by ESI-MS. After two hours another sample was analysed (Figure 34, B) and the signal of the cyclometallated derivative **194** was the most intensive one in the mass spectrum. Since a sodium adduct and a protonated species are compared a quantitative analysis is not possible, but the results clearly show the conversion of **196** to **194** over the course of the activation process. All volatiles were removed in high vacuum and the yellow residue was dissolved in tetrahydrofuran. The allylic carbonate **197** as well as aniline were added and the resulting mixture was stirred at room temperature.

After five minutes the reaction was analysed by ESI-MS and a clean spectrum was obtained (Figure 35, A). Besides some activated catalyst **194**, an intense signal at m/z = 956 corresponding to the allyl complex **198** was detected. The structure of this species was confirmed by MS/MS experiments. The signal at m/z = 848 is attributed to the loss of 1,5-cyclooctadiene. The mass spectrum recorded after 30 minutes indicated the complete consumption of the activated catalyst **194** (Figure 35, B).

These results proved the existence of allyl intermediate **198** for the first time. It is assumed, that dissociation of ligand **195** creates a free coordination site at the activated catalyst species **194** for oxidative addition of allylic carbonate **197**.

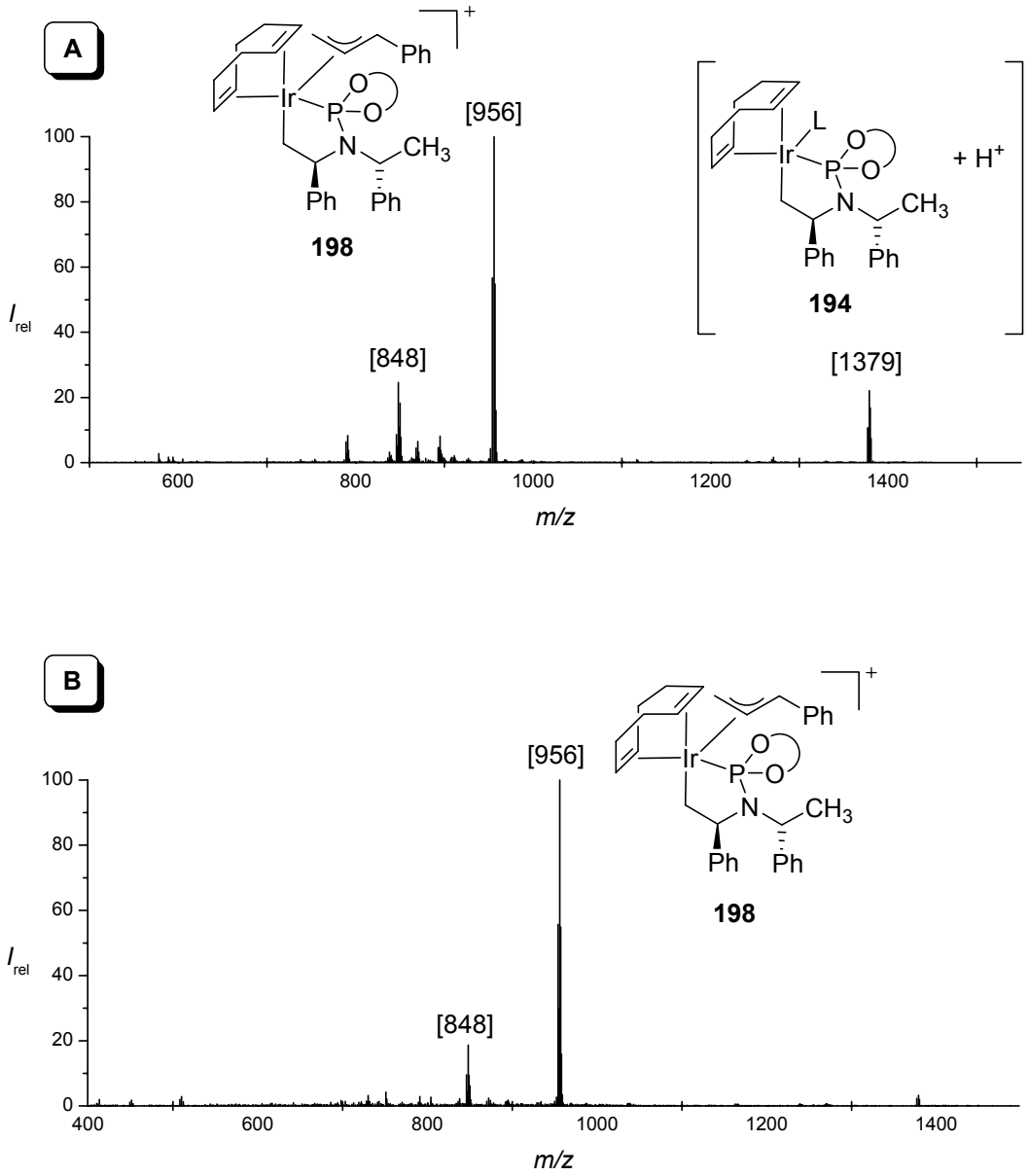
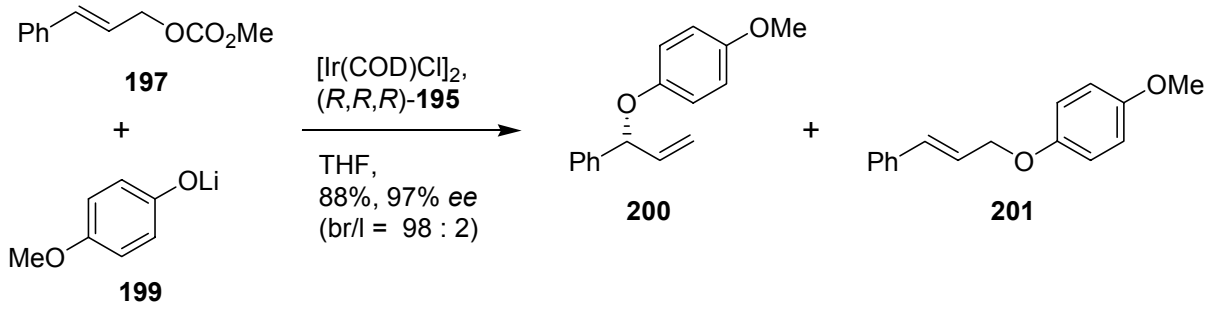


Figure 35. ESI-MS analysis of the reaction mixture 5 min (A) and 30 min (B) after the addition of **197**.

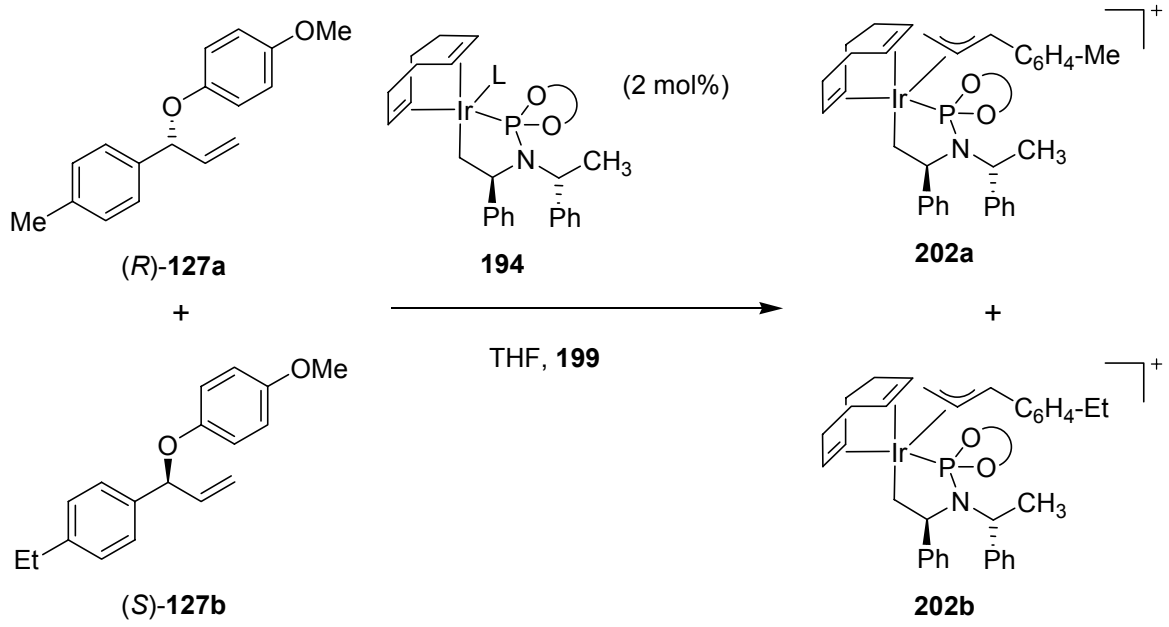
Since allyl-iridium intermediates could be detected by ESI-MS, the question arose if a screening protocol in analogy to palladium-catalysed allylic substitutions would allow the determination of the enantioselectivity for the overall reaction. Applying the principle of microscopic reversibility, the back reaction of quasienantiomeric products leading to the corresponding mass-labelled allyl-iridium complexes should be monitored. The results should be compared with the selectivities determined from product analysis of the corresponding preparative reactions.

The etherification of carbonate **197** with lithium phenolate **199** was tested first (Scheme 56),[136] since the quasienantiomeric allylation products were readily available in the group.[104]



Scheme 56. Allylic etherification of carbonate **197** with lithium phenolate **199**.

The precatalyst solution was prepared from 1 mol% of chloro-1,5-cyclooctadiene iridium(I) dimer and two equivalents of phosphoramidite (*R*,*R*,*R*)-**195** in tetrahydrofuran at 50 °C for four hours. Two equivalents lithium-*para*-methoxyphenolate (**199**) were used for generating the activated catalyst species **194** in this case. The metallacycle was added to an equimolar mixture of (*R*)-**127a** and (*S*)-**127b** (Scheme 57). After stirring the reaction mixture at room temperature for five minutes an aliquot was taken, diluted with methanol and analysed by ESI-MS.



Scheme 57. Back reaction using quasienantiomeric phenolates (*R*)-**127a** and (*S*)-**127b**.

As it is shown in Figure 36 the signals corresponding to the allyl intermediates **202a** and **202b** were detected at *m*/*z* = 970 and *m*/*z* = 984, respectively, with high intensities. However a ratio of 61:39 was observed, which is significantly lower compared to the product enantiomeric ratio of 98.5:1.5.[136]

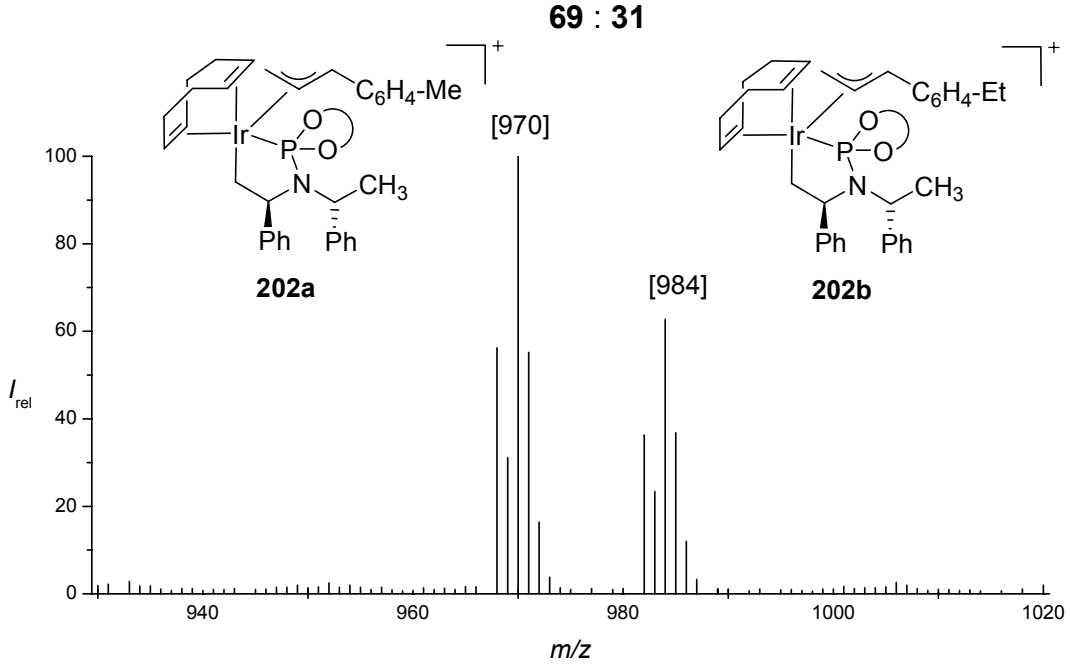


Figure 36. Back reaction screening using iridium complex **194** derived from ligand (*R*,*R*,*R*)-**195**.

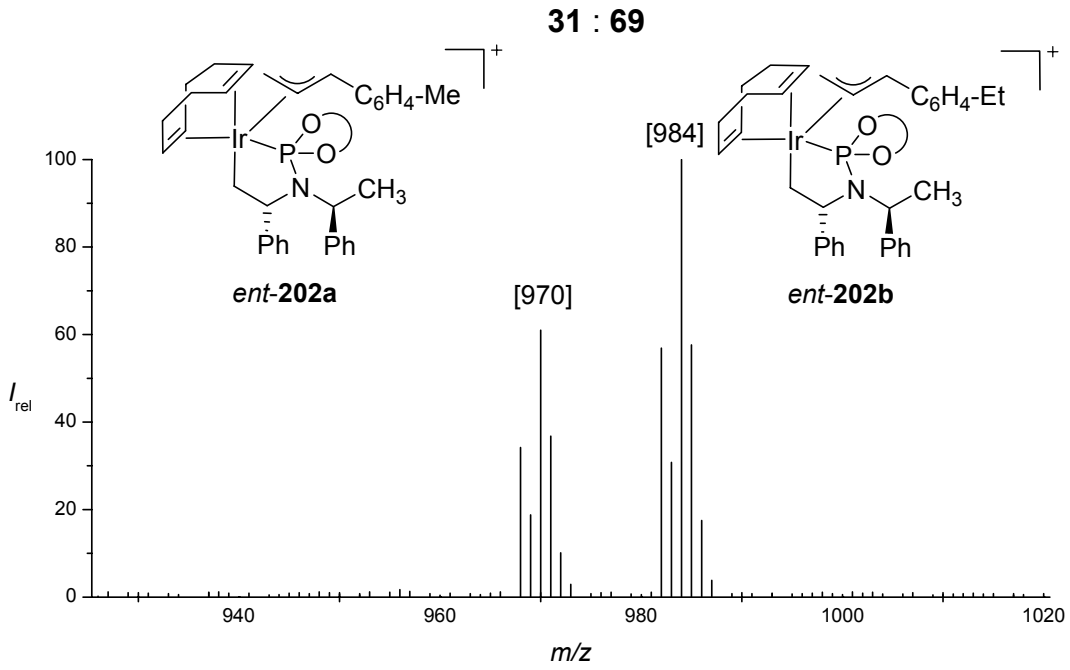


Figure 37. Back reaction screening using iridium complex *ent*-**194** derived from ligand (*S*,*S*,*S*)-**195**.

The reaction was carried out with the catalyst *ent*-**194** prepared from the enantiomeric phosphoramidite ligand (*S*,*S*,*S*)-**195** under otherwise identical conditions and the allyl complexes *ent*-**202a** and *ent*-**202b** were detected with the exact reverse ratio of 39:61.

It was reported in the literature that the base used for altering the catalyst can influence the enantioselectivity of this transformation.[136] Therefore the experiment was repeated in the presence of propylamine, but the same result was obtained. The ratio was not affected by the reaction temperature either and similar values were obtained at both 50 °C and −78 °C. Furthermore the ratio of intermediates remained constant for at least 50 minutes.

The selectivity of the forward reaction using an equimolar mixture of quasienantiomeric benzoates (*R*)-**126a** and (*S*)-**126b**, lithium phenolate **199** and the catalyst **194** in tetrahydrofuran (Figure 38) was investigated as well.

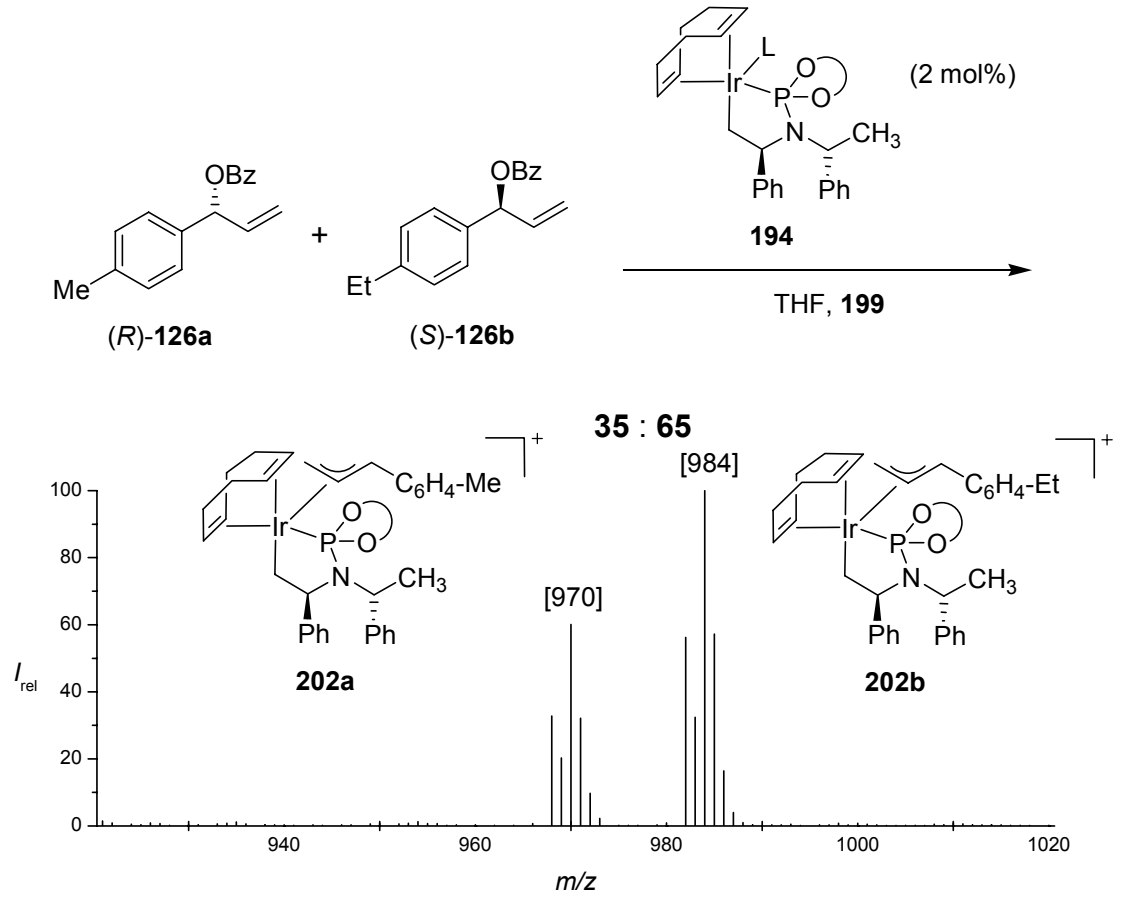


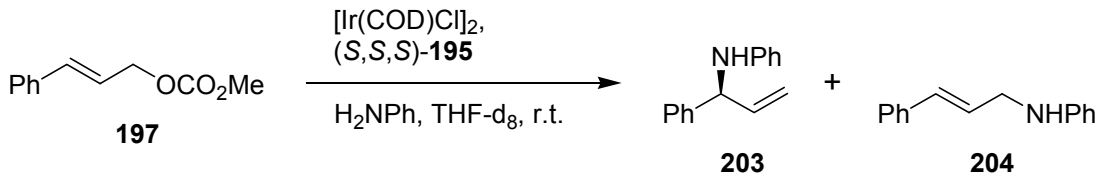
Figure 38. Forward reaction screening using quasienantiomeric benzoates (*R*)-**126a** and (*S*)-**126b**.

However the allyl intermediates **202a** and **202b** were observed with a reversed selectivity compared to the back reaction screening (Figure 36) and a ratio of 35:65 in favour of the consumption of the (*S*)-benzoate was detected. The reason for this outcome remains unclear.

Furthermore and in contrast to the back reaction analysis the peak ratio decreased when aliquots were taken after different reaction times (**202a**/**202b** ~ 1:1 after 50 min).

6.2 Combination of ESI-MS and NMR-Analysis

In order to obtain a better understanding of the allylic substitution process, the amination of carbonate **197** with aniline in the presence of iridium complex **194** was simultaneously investigated by ESI-MS and NMR analysis (Scheme 58). In analogy to the well established mechanism of palladium-catalysed allylic substitutions, the acquisition of data on the corresponding intermediates in the iridium-catalysed process was envisaged. The former process proceeds by oxidative addition of an allylic ester to the palladium centre, followed by attack of the nucleophile on the allyl intermediate.



Scheme 58. Allylic amination of carbonate **197** with aniline.

In the course of this combined experiment the catalytic cycle should be passed step by step. The results are depicted in Figure 39.

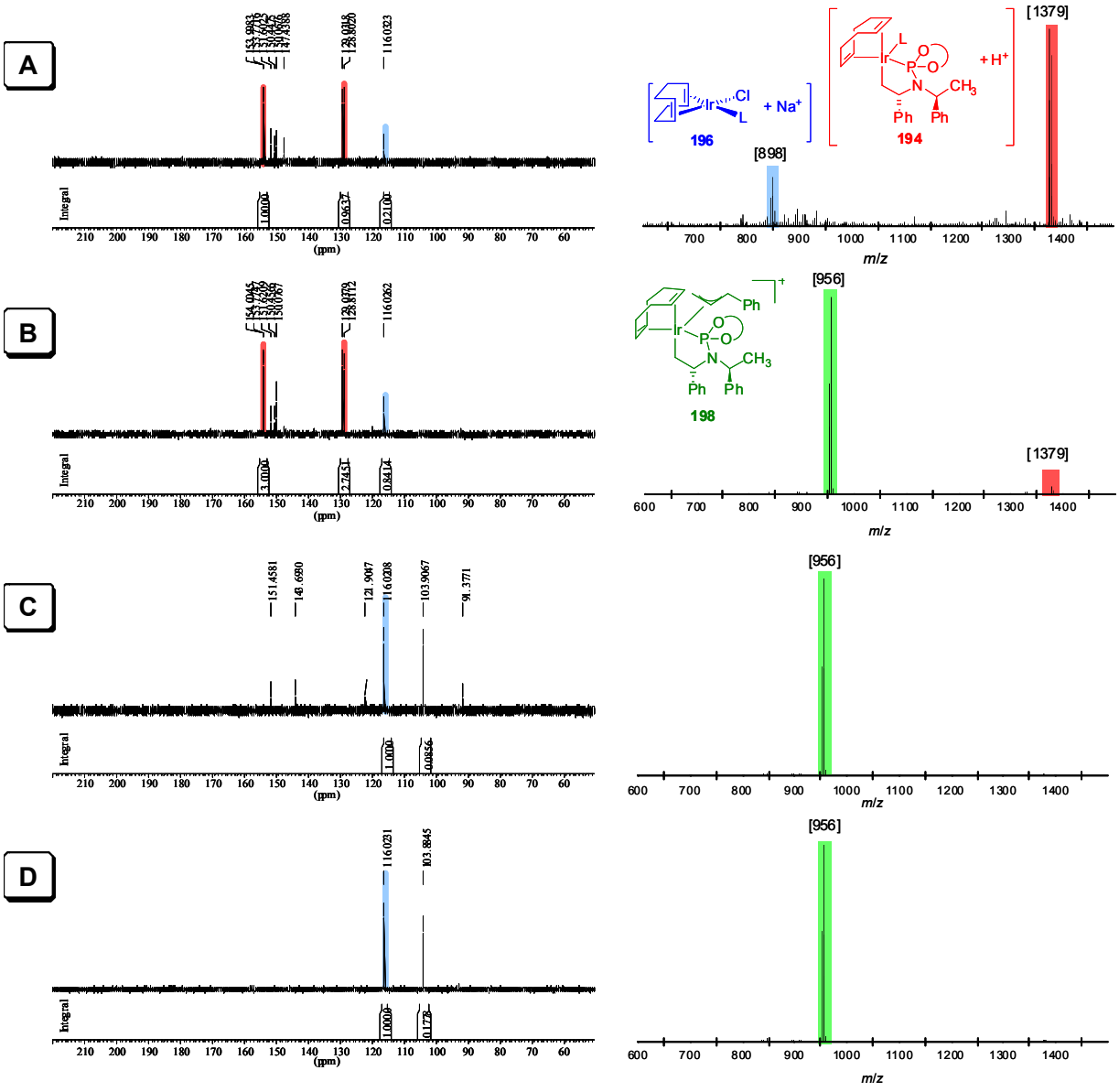


Figure 39. Analysis of an allylic amination by ^{31}P NMR spectroscopy and ESI-MS.

By applying the exact stoichiometry for the preparation of the activated catalyst **194**, a solution of a quarter equivalent of chloro-1,5-cyclooctadiene iridium(I) dimer and one equivalent of phosphoramidite ligand **195** was treated with propylamine in tetrahydrofuran-d_8. The mixture was heated at 50 °C for one hour. After it had been cooled to room temperature a sample was taken and analysed by ESI-MS and ^{31}P NMR (Figure 39, A). As it is described in the literature the catalyst activation proceeds *via* the squareplanar iridium(I) complex **196**.[140] The addition of the amine base leads to the formation of species **194** by cyclometallation of the phosphoramidite ligand at one methyl group of the amino substituent and elimination of amine hydrochloride. Coordination of a second phosphoramidite **195** generates the trigonal

bipyramidal complex **194**. The ^{31}P NMR spectrum was dominated by a singlet at δ = 116.0 ppm of **196** and two doublets at δ =153.9 ppm and δ = 128.9 ppm with $^{2}J_{P,P}$ = 46 Hz, which represent the cyclometallated complex **194**, as reported in the literature.[140] The other diastereoisomer was also observed in low amount of approximately 5%. Signals at *m*/*z* = 898 and *m*/*z* = 1379 for both iridium complexes were detected by ESI-MS as well, which correspond to the sodium adduct of **196** and protonated **194**.

After the activation process had been completed, all volatiles were removed in vacuo. The resulting orange solid was dissolved in tetrahydrofuran-d_8 and one equivalent of carbonate **197** was added. An aliquot of the reaction mixture was immediately taken and analysed by NMR spectroscopy and ESI-MS (Figure 39, B). However, the ^{31}P NMR spectrum remained unchanged, whereas a new intense signal at *m*/*z* = 956 was observed in the mass spectrum, which corresponds to allyl intermediate **198**. The ^{1}H NMR spectrum was also analysed, but no allyl intermediates were found. Since the structural analysis of complex **194** is known to be complicated by conformational changes on the NMR time scale, it was assumed that this problem probably might also occur in the case of allyl intermediate **198**.[140] Therefore the NMR spectra were recorded at both lower and higher temperatures, but no indication for the presence of an allyl intermediate was obtained.

It is known, that additional chloro-1,5-cyclooctadiene iridium(I) dimer increases the rate of the catalysis,[140] because it facilitates the dissociation of the phosphoramidite **195** from the activated catalyst to generate a free coordination site. For this reason another quarter equivalent of chloro-1,5-cyclooctadiene iridium(I) dimer was added (Figure 39, C). The mass spectrum still showed a single signal at *m*/*z* = 956, but the catalytically inactive complex **196** was detected by ^{31}P NMR as the only major species and the signals for **194** had disappeared. This indicates that the activated complex had completely decomposed. Furthermore a new signal at δ = 103.9 ppm arose, but a characterisation of this entity was not possible.

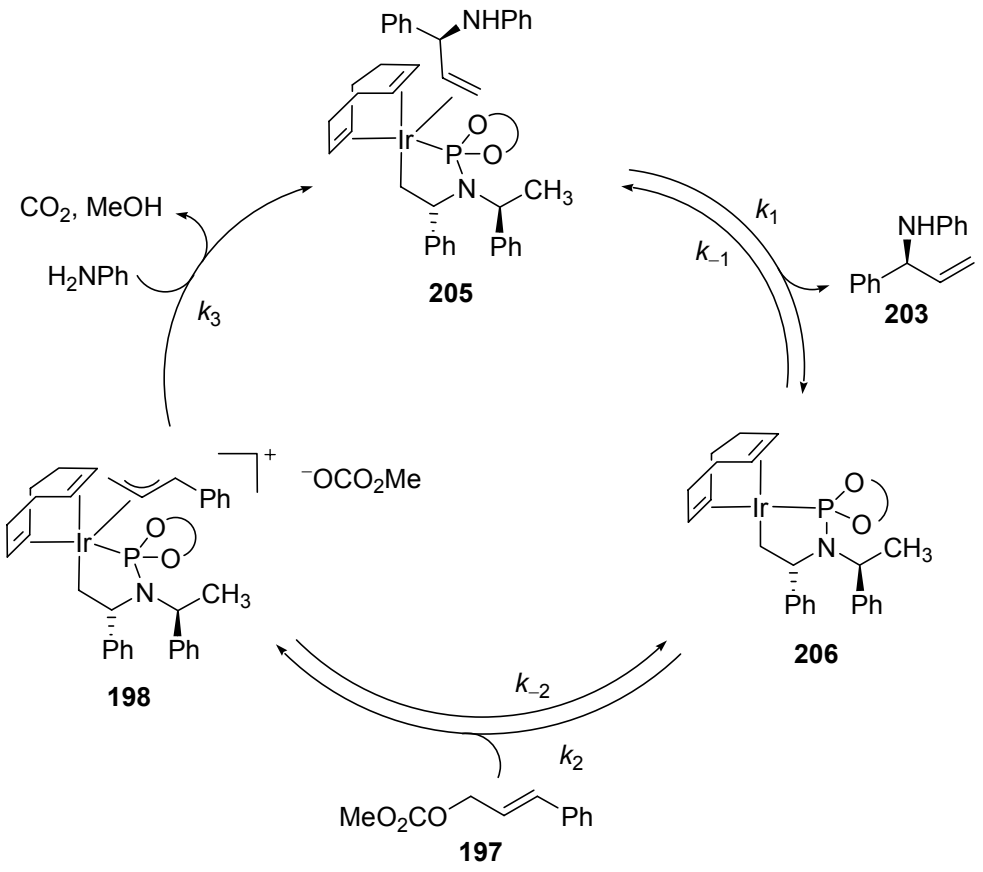
Finally aniline was added to the reaction mixture, but no product formation was observed in the ^{1}H NMR spectrum (Figure 39, D). This can most likely be ascribed to the fact that no activated catalyst was present any longer at this stage.

A similar experiment was carried out starting directly from half an equivalent of chloro-1,5-cyclooctadiene iridium(I) dimer and one equivalent of the phosphoramidite ligand **195**. After the catalyst activation both iridium complexes **196** and **194** were observed by ^{31}P NMR spectroscopy and ESI-MS. When carbonate **197** was added, the NMR spectrum remained unchanged. Consistent with the previous experiment the allyl intermediate **198** was exclusively detected by ESI-MS. After addition of aniline the signals of the activated complex

194 disappeared and only the singlet at δ = 116.0 ppm for **196** was found in the NMR spectrum, whereas allyl intermediate **198** was still visible by ESI-MS.

The results indicate that iridium-catalysed allylic substitutions do not proceed in exact analogy to the palladium-catalysed process. However with the data collected so far the poor correlation of the ESI-MS measurements and the results from the preparative reactions can not be explained. We assume that the allyl intermediates detected by ESI-MS are present only in very low concentration and the picture obtained by ESI-MS does not show the representative composition of the reaction mixture.

After having finished these preliminary investigations, a detailed study towards the reaction mechanism was published by Hartwig and coworkers.[143] The allylamine complex **205** was claimed to be the resting state of the transformation. Based on the isolation of this complex **205** and kinetic data for the process, a catalytic cycle was proposed (Scheme 59).



Scheme 59. Mechanism for iridium-catalysed allylic substitutions as proposed by Hartwig.

The catalytic cycle involves the formation of the proposed allyl complex **198** by an endothermic and reversible addition of the allylic carbonate **197** to the coordinatively unsaturated complex **206**. This process is followed by an irreversible formation of the

allylamine complex **205**. Furthermore it is assumed that the attack of the amine represents the 'enantio-determining' step and the enantioselectivity is furthermore connected to the relative stabilities of the diastereomeric allylamine complexes of type **205**, but no evidence is given.

In this work we were able to confirm the existence of allyl complex **198**, which was suggested by Hartwig and coworkers. The catalytic cycle shown in Scheme 59 allows the re-interpretation of the combined ESI-MS and NMR investigations. In the course of the activation process, both catalyst species **196** and **194** were detected by ^{31}P NMR as well as ESI-MS analysis (Figure 39, A). After the addition of allylcarbonate **197** the mass spectrum showed the clean formation of the allyl intermediate **198**, whereas the NMR spectrum remained unchanged (Figure 39, B). It is now assumed that **198** is formed in such a small amount, that it can not be observed by NMR spectroscopy. However the sensitivity of ESI-MS is much higher and enables the detection of charged species even in traces. This finding is consistent with Hartwig's mechanism, involving an equilibrium between allyl complex **198** and the substrate **197**, which is on the side of **197**. Since the activated catalyst **194** is only visible in its protonated form by ESI-MS, no quantitative information concerning the ratio of **194** and **198** can be given.

Chloro-1,5-cyclooctadiene iridium(I) dimer was added to activate the cyclometallated catalyst **194** by removal of the phosphoramidite ligand **195**. In the mass spectrum the signal of **198** was still found exclusively (Figure 39, C). However, in the corresponding ^{31}P NMR spectrum, only the catalytically inactive complex **196** was detected and the signals for **194** had disappeared. This can be explained with regard to the findings of Hartwig. The allyl complex **198** is formed in negligible amounts and the equilibrium predominantly lies on the side of the starting material. The overall reaction proceeds only when intermediate **198** reacts irreversibly with the nucleophile. Since no amine was present, the activated catalyst **194**, which is unstable after the removal of one phosphoramidite ligand, most likely decomposed before aniline was added after prolonged periods of reaction time (Figure 39, D).

Taken together it was demonstrated that the mechanism of iridium-catalysed allylic substitutions is more complex in comparison to analogous reactions involving palladium complexes. Furthermore it became clear that it is more difficult to evaluate ligands by mass spectrometric monitoring of the allyl intermediates **202a** and **202b** in this case. If a screening method based on ESI-MS can be established in the future remains open at this stage. Closer mechanistic studies are required beforehand to reveal the exact process for enantioselection in this transformation.

6.2.1 Conclusions and Outlook

After having established a fast and reliable ESI-MS screening method for the evaluation of palladium catalysts in asymmetric allylic substitutions, similar iridium-catalysed transformations were investigated. In this context it was oft special interest if an analogous protocol can be applied to determine the selectivity of chiral ligands in these reactions and preliminary experiments were carried out.

The activation process of a catalyst derived from a phosphoramidite ligand was followed by ESI-MS and all involved species were detected. In addition mass spectrometric analysis of a related allylic amination revealed the existence of a previously postulated allyl-iridium species.

Applying the principle of microscopic reversibility the back reaction of quasienantiomeric products leading to the corresponding mass-labelled allyl-iridium intermediates was monitored. However the selectivities calculated from the signal ratio do not correlate with the enantiomeric excesses determined from product analysis of the respective preparative reaction. In order to obtain a better understanding of the substitution process, the amination of an allylic carbonate with aniline was investigated by a combined ESI-MS and NMR experiment.

In summary, it was found that the mechanism of iridium-catalysed allylic substitutions is quite different from the analogous reactions involving palladium catalysts. The mass spectrometric monitoring of allyl intermediates derived from quasienantiomeric substrates does not allow the evaluation of chiral ligands in an easy way. Before a screening method based on ESI-MS can be developed, further mechanistic studies will be indispensable to reveal the exact process for enantioselection.

CHAPTER 7

EXPERIMENTAL

7 Experimental

7.1 Working Techniques and Reagents

All reactions were performed in flame-dried glassware under argon using Schlenk techniques or under purified nitrogen in a glovebox (MBraun Labmaster 130). Air- or moisture-sensitive reagents were transferred with the help of oven-dried, gas-tight syringes or cannulas and introduced into the apparatus through septa.

Solvents were distilled from calcium hydride (dichloromethane, triethylamine) or sodium (diethyl ether, pentane, tetrahydrofuran, toluene) and stored under nitrogen,[144] or were purchased from Fluka or Aldrich in septum-sealed bottles and kept under an inert atmosphere over molecular sieves. The solvents were degassed by three freeze-pump-thaw cycles, when necessary.

Column chromatographic purifications were performed on Merck silica gel 60 (Darmstadt, particle size 40-63 nm) under 0.1-0.8 bar nitrogen or argon pressure. The eluents were technical grade and purified by distillation prior to use. In the case of air-sensitive compounds the solvents were degassed by a continuous stream of argon and the silica gel by three vacuum-argon cycles.

All reagents were purchased from Acros, Aldrich, Fluka, Strem or Lancaster and used without further purification. Phosphorus trichloride and BzCl were distilled under argon prior to use. *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) was distilled from *n*-butyllithium.[144] Racemic cyclohex-3-enecarboxylic acid was prepared according to a literature procedure.[98]

7.2 Analytical Methods

NMR-Spectroscopy (NMR): NMR spectra were measured either on a Bruker Avance 400 (400 MHz) or a Bruker Avance DRX 500 (500 MHz) spectrometer, equipped with BBO broadband probe heads. 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 THF-d_8 3.58 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 and THF-d_8 67.4 ppm), respectively as internal standards.[145] ^{31}P spectra are calibrated relative to 85% phosphoric acid (δ = 0 ppm) as external standard. The assignment of ^{1}H and ^{13}C signals was accomplished with the help of DEPT experiments or, when needed by two-dimensional correlation experiments (COSY, HMQC and HMBC). Multiplets are assigned as s (singlet), d

(doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), m (multiplet), m_c (centred multiplet) and br (broad).

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 wave numbers ($\tilde{\nu}$ [cm^{-1}]). The peak intensity is described by s (strong), m (medium), w (weak) and br (broad).

Mass Spectrometry (MS): Mass spectra were measured by Dr. H. Nadig (Department of Chemistry, University of Basel) on a VG70-250 spectrometer (electron ionisation (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 Finnigan MAT LCQ or 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 or 100 °C, 75 V capillary voltage, 1500 V detector voltage). Every spectrum consisted of at least 50 averaged scans. 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*). The fragments and relative intensities are given in brackets.

Elemental Analysis: Elemental analyses were measured by Mr. W. Kirsch (Department of Chemistry, University of Basel) on a Leco CHN-900 (C-, H-, N-detection) and Leco RO-478 analysers (O-detection). 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 column (30 m × 0.25 mm × 0.25 μm) and for chiral separations β- and γ-cyclodextrine columns (30 m × 0.25 mm × 0.25 μm) 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. Chiral columns Chiracel OD-H, OJ, or AD-H (4.6 × 250 mm) as well as Chiracel OD or AD (20 × 300 mm) from Daicel Chemical Industries were used.

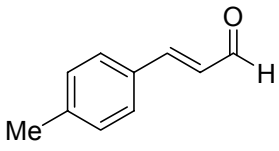
Semipreparative High Performance Liquid Chromatography (HPLC): Separations by semipreparative HPLC were performed on Shimadzu systems with SIL 10 Advp autosampler, CTO 10 Asvp column oven, LC 10 Atvp pump system, FCV 10 Alvp degasser and SPD M10 Avp diode array detector. Chiral columns Chiracel OD or AD (2 × 25 cm) from Daicel Chemical Industries were used in this case.

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, 366 nm), basic permanganate solution or ceric ammonium molybdate solution were used for the visualisation of the respective compounds.

7.3 Quasienantiomeric Substrates

7.3.1 Diarylallyl Substrates

4-Methylcinnamaldehyde (34)[88]



34

To a stirred solution of 4-iodotoluene (4.81 g, 22.3 mmol) in abs. DMF (85 mL) were added acrolein diethyl acetal (8.05 g, 61.8 mmol), [*n*Bu_4N]OAc (13.4 g, 44.5 mmol), K_2CO_3 (4.27 g, 30.9 mmol), KCl (1.64 g, 22.0 mmol) and $Pd(OAc)_2$ (111 mg, 0.500 mmol). The mixture was stirred at 90 °C for 3 h. After cooling the suspension to r.t. 2 M HCl (100 mL) was slowly added and the resulting mixture stirred for 10 min. It was then diluted with Et_2O (250 mL) and ice-cold water (900 mL) and the aqueous phase extracted with Et_2O (2 × 250 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

The residue was purified by column chromatography (silica gel, 5 × 20 cm, hexanes/EtOAc 10:1, F32-60) to give aldehyde **34** as slightly yellow solid (2.57 g, 79%).

$C_{10}H_{10}O$ (146.19 g*mol^{-1}):

m.p. 40-42 °C.

R_f = 0.44 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, CH_3), 6.65 (ddd, *J*(H,H) = 16.0, 7.7, 0.7 Hz, 1 H, ArCHC*H*), 7.22 (d, *J*(H,H) = 8.3 Hz, 2 H, Ar-*m*-H), 7.43 (d, *J*(H,H) = 16.0 Hz, 1 H, ArC*H*CH), 7.45 (d, *J*(H,H) = 7.9 Hz, 2 H, Ar-*o*-H), 9.67 (d, *J*(H,H) = 7.7, 0.9 Hz, 1 H, CHO) ppm.

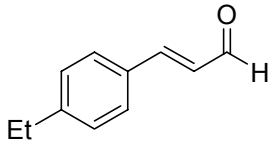
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 21.7 (CH_3), 127.8 (ArCH*C*H), 128.7 (Ar-*o*-CH), 129.9 (Ar-*m*-CH), 131.4 (Ar-*i*-C), 142.1 (Ar-*p*-C), 153.1 (Ar*C*HCH), 194.0 (CHO) ppm.

IR (KBr): $\tilde{\nu}$ = 3028m, 2967m, 2923w, 2841m, 2756w, 1932w, 1678s, 1608s, 1512m, 1417m, 1298m, 1251m, 1181m, 1127s, 1010m, 979m, 805s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 146 (21, M^+), 131 (100, $[M–CH_3]^+$), 117 (29, $[M–CHO]^+$), 115 (34), 103 (21), 91 (30).

Elemental analysis calcd. (%) for $C_{10}H_{10}O$: C 82.16, H 6.89; found: C 82.03, H 6.97.

4-Ethylcinnamaldehyde (35)[88]



35

To a stirred solution of 1-ethyl-4-iodobenzene (4.81 g, 20.7 mmol) in abs. DMF (85 mL) were added acrolein diethyl acetal (8.06 g, 61.9 mmol), [*n*Bu$_4$N]OAc (12.4 g, 41.3 mmol), K_2CO_3 (4.28 g, 31.0 mmol), KCl (1.54 g, 20.7 mmol) and $Pd(OAc)_2$ (139 mg, 0.600 mmol). The mixture was stirred at 90 °C for 15 h. After cooling the reaction mixture to r.t. 2 M HCl (100 mL) was slowly added and the black solution stirred for 10 min. It was then diluted with Et_2O (250 mL) and ice-cold water (900 mL) and the aqueous phase extracted with Et_2O (2 × 250 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 5 × 20 cm,

hexanes/EtOAc 10:1, F23-55) to give 4-ethylcinnamaldehyde (**35**) as yellow solid (2.04 g, 88%).

$C_{11}H_{12}O$ (160.21 g*mol^{-1}):

m.p. 25 °C.

$\boldsymbol{R_f}$ = 0.30 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, *J*(H,H) = 7.7 Hz, 3 H, CH_3), 2.65 (q, *J*(H,H) = 7.7 Hz, 2 H, CH_2), 6.65 (dd, *J*(H,H) = 16.2, 7.9 Hz, 1 H, ArCHC*H*), 7.25 (d, *J*(H,H) = 8.1 Hz, 2 H, Ar-*m*-H), 7.43 (d, *J*(H,H) = 16.2 Hz, 1 H, ArC*H*CH), 7.47 (d, *J*(H,H) = 8.2 Hz, 2 H, Ar-*o*-H), 9.67 (d, *J*(H,H) = 7.9 Hz, 1 H, CHO) ppm.

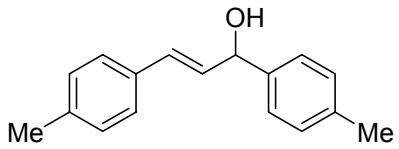
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 15.3 (CH_3), 28.9 (CH_2), 127.8 (ArCH*C*H), 128.7 (Ar-*o*-CH), 128.8 (Ar-*m*-CH), 131.6 (Ar-*i*-C), 148.3 (Ar-*p*-C), 153.1 (Ar*C*HCH), 193.9 (CHO) ppm.

IR (KBr): $\tilde{\nu}$ = 3028m, 2967s, 2932s, 2873m, 2818m, 2736w, 1913w, 1678s, 1621s, 1566m, 1511m, 1456m, 1423m, 1389w, 1297m, 1249m, 1181m, 1056m, 1010m, 907s, 858w, 752w cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 160 (12, M^+), 131 (100, $[M–C_2H_5]^+$), 115 (15), 103 (16), 91 (10).

Elemental analysis calcd. (%) for $C_{11}H_{12}O$: C 82.46, H 7.55; found: C 82.35, H 7.53.

1,3-Di-(4'-tolyl)-prop-2-en-1-ol (37a)



37a

At –78 °C 4-bromotoluene (3.05 g, 17.8 mmol) in abs. THF (36 mL) was treated with *n*BuLi in hexane (2.5 M, 9.70 mL, 24.3 mmol) resulting in the formation of a colourless solid. The mixture was warmed to –25 °C, until all the precipitate had dissolved, re-cooled to –78 °C and treated with a solution of aldehyde **34** (1.81 g, 12.4 mmol) in abs. THF (6.0 mL). The mixture was allowed to warm to r.t. overnight and then quenched with saturated aqueous NH_4Cl solution (75 mL). The THF was removed under reduced pressure, the residue extracted with Et_2O (3 × 80 mL) and the combined organic phases were washed with saturated aqueous

solutions of NH_4Cl (200 mL) and NaCl (200 mL). After drying over $MgSO_4$ the solvent was evaporated. The crude product was purified by column chromatography (silica gel, 5 × 20 cm, hexanes/EtOAc 5:1, F22-56) and **37a** was obtained as a colourless solid (2.78 g, 94%).

$C_{17}H_{18}O$ (238.32 g*mol^{-1}):

m.p. 64 °C.

R_f = 0.30 (hexanes/EtOAc 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (br s, 1 H, OH), 2.35 (s, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 5.34 (d, *J*(H,H) = 6.5 Hz, 1 H, C*H*OH), 6.31 (dd, *J*(H,H) = 15.7, 6.5 Hz, 1 H, ArCHC*H*), 6.67 (d, *J*(H,H) = 15.7 Hz, 1 H, ArC*H*CH), 7.10-7.25 (m, 4 H, Ar-H), 7.27-7.40 (m, 4 H, Ar-H) ppm.

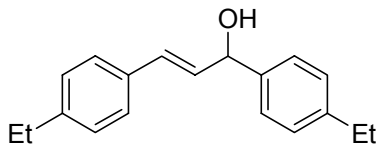
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 21.3 (CH_3), 21.3 (CH_3), 75.2 (CHOH), 126.4 (CH), 126.6 (CH), 129.4 (CH), 129.4 (CH), 130.4 (CH), 130.8 (CH), 133.9 (3-Ar-*i*-C), 137.6 (Ar-*p*-C), 137.8 (Ar-*p*-C), 140.1 (1-Ar-*i*-C) ppm.

IR (KBr): $\tilde{\nu}$ = 3262br, 3022s, 2915s, 1905m, 1801w, 1716w, 1509s, 1417s, 1207m, 1087s, 1021s, 966s, 805s, 743m, 713m, 656m, 512m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 238 (21, M^+), 223 (16, $[M–CH_3]^+$), 119 (100), 105 (20), 91 (21).

Elemental analysis calcd. (%) for $C_{17}H_{18}O$: C 85.67, H 7.61, O 6.71; found: C 85.68, H 7.69, O 6.66.

1,3-Di-(4'-ethylphenyl)-prop-2-en-1-ol (37b)



37b

At –78 °C 1-ethyl-4-iodobenzene (2.70 g, 11.6 mmol) in abs. THF (30 mL) was treated with *n*BuLi in hexane (2.5 M, 6.40 mL, 16.0 mmol). The resulting orange suspension was allowed to warm to –25 °C, re-cooled to –78 °C and treated with a solution of **35** (1.29 g, 8.10 mmol) in abs. THF (4.0 mL). The mixture was warmed to r.t. overnight and then quenched with saturated aqueous NH_4Cl solution (30 mL). The THF was removed under reduced pressure, the residue extracted with Et_2O (3 × 70 mL) and the combined organic phases were washed

with saturated aqueous solutions of NH_4Cl (150 mL) and NaCl (150 mL). After drying over $MgSO_4$ the solvent was evaporated. The crude product was purified by column chromatography (silica gel, 5 × 20 cm, pentanes/Et_2O 5:1, F54-120) and alcohol **37b** was obtained as a colourless solid (1.09 g, 51%).

$C_{19}H_{22}O$ (266.38 g*mol^{-1}):

m.p. 61-63 °C.

R_f = 0.31 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (m_c, 6 H, CH_3), 2.08 (d, J(H,H) = 3.7 Hz, 1 H, OH), 2.68 (m_c, 4 H, CH_2), 5.36 (d, J(H,H) = 6.6 Hz, 1 H, C*H*OH), 6.32 (dd, J(H,H) = 15.8, 6.6 Hz, 1 H, ArCHC*H*), 6.65 (d, J(H,H) = 15.8 Hz, 1 H, ArC*H*CH), 7.13-7.17 (m, 2 H, Ar-H), 7.19-7.23 (m, 2 H, Ar-H), 7.30-7.36 (m, 4 H, Ar-H) ppm.

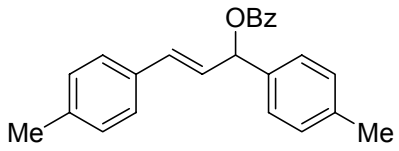
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 15.7 (CH_3), 15.7 (CH_3), 28.7 (CH_2), 28.7 (CH_2), 75.2 (CHOH), 126.5 (Ar-CH), 126.7 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 130.4 (ArCH*C*H), 130.8 (Ar*C*HCH), 134.2 (3-Ar-*i*-C), 140.3 (Ar-*p*-C), 144.0 (Ar-*p*-C), 144.1 (1-Ar-*i*-C) ppm.

IR (KBr): $\tilde{\nu}$ = 3392br, 3021s, 2963s, 2929m, 2871m, 1512s, 1457m, 1419m, 1179w, 1090m, 967s, 832m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 266 (16, M^+), 237 (47, $[M–C_2H_5]^+$), 133 (100), 119 (18, $C_8H_7O^+$), 91 (7).

Elemental analysis calcd. (%) for $C_{19}H_{22}O$: C 85.67, H 8.32; found: C 85.48, H 8.38.

1,3-Di-(4'-tolyl)-prop-2-enyl benzoate (38a)



38a

A solution of alcohol **37a** (1.90 g, 7.90 mmol), abs. NEt_3 (1.75 g, 17.3 mmol) and DMAP (25.0 mg, 0.205 mmol) in abs. CH_2Cl_2 (32 mL) was treated dropwise with BzCl (1.46 g, 10.4 mmol) at –78 °C. The mixture was allowed to warm to r.t. overnight. After quenching the reaction with saturated aqueous NH_4Cl solution (20 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. The

solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 5 × 20 cm, hexanes/EtOAc/NEt_3 18:1:1, F4-34) to yield benzoate **38a** as a colourless solid (2.48 g, 91%).

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

m.p. 58-59 °C.

R_f = 0.56 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, CH_3), 2.36 (s, 3 H, CH_3), 6.40 (dd, *J*(H,H) = 16.0, 6.9 Hz, 1 H, ArCHC*H*), 6.66 (d, *J*(H,H) = 6.9 Hz, 1 H, CHOBz), 6.68 (d, *J*(H,H) = 16.0 Hz, 1 H, ArC*H*CH), 7.11 (d, *J*(H,H) = 7.8 Hz, 2 H, Ar-H), 7.21 (d, *J*(H,H) = 8.1 Hz, 2 H, Ar-H), 7.29 (d, *J*(H,H) = 8.1 Hz, 2 H, Ar-H), 7.39-7.49 (m, 4 H, Ar-H), 7.55 (m_c, 1 H, Bz-*p*-H), 8.12 (d, *J*(H,H) = 7.8 Hz, 2 H, Bz-*o*-H) ppm.

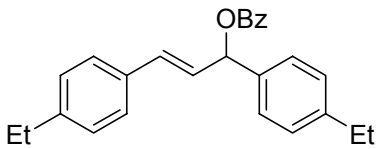
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 21.3 (CH_3), 21.4 (CH_3), 76.8 (CHOBz), 126.8 (CH), 126.8 (CH), 127.2 (CH), 128.4 (CH), 129.4 (CH), 129.5 (CH), 129.9 (CH), 130.3 (Bz-*i*-C), 132.7 (CH), 133.1 (CH), 133.6 (3-*p*Tol-*i*-C), 136.6 (*p*Tol-*p*-C), 138.0 (*p*Tol-*p*-C), 138.1 (1-*p*Tol-*i*-C), 166.8 (CO_2) ppm.

IR (KBr): $\tilde{\nu}$ = 3026s, 2920s, 1907w, 1716s, 1602m, 1512m, 1450m, 1312s, 1264s, 1176m, 1103s, 1066m, 1025m, 968s, 805s, 709s, 578m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 342 (12, M^+), 237 (42, $[M–C_7H_5O]^+$), 221 (61, $[M–C_7H_5O_2]^+$), 220 (100), 205 (44), 129 (15), 105 (75), 77 (21, $C_6H_5^+$).

Elemental analysis calcd. (%) for $C_{24}H_{22}O_2$: C 84.18, H 6.48; found: C 84.40, H 6.60.

1,3-Di-(4'-ethylphenyl)-prop-2-enyl benzoate (38b)



38b

At –78 °C a solution of alcohol **37b** (492 mg, 1.84 mmol), abs. NEt_3 (379 mg, 3.80 mmol) and DMAP (6.00 mg, 49.0 μmol) in abs. CH_2Cl_2 (8.0 mL) was treated dropwise with BzCl (379 mg, 2.40 mmol). The mixture was allowed to warm to r.t. overnight. The reaction was quenched with saturated aqueous NH_4Cl solution (5.0 mL). The aqueous phase was extracted

with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was re-crystallised from hexanes/CH_2Cl_2 to yield benzoate **38b** as a colourless solid (512 mg, 75%).

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

m.p. 79 °C.

R_f = 0.53 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, J(H,H) = 7.5 Hz, 3 H, CH_3), 1.24 (t, J(H,H) = 7.6 Hz, 3 H, CH_3), 2.62 (q, J(H,H) = 7.6 Hz, 2 H, CH_2), 2.66 (q, J(H,H) = 7.5 Hz, 2 H, CH_2), 6.42 (dd, J(H,H) = 15.9, 6.7 Hz, 1 H, ArCHC*H*), 6.66 (d, J(H,H) = 6.7 Hz, 1 H, CHOBz), 6.71 (d, J(H,H) = 15.9 Hz, 1 H, ArC*H*CH), 7.12 (d, J(H,H) = 8.2 Hz, 2 H, Ar-H), 7.21 (d, J(H,H) = 8.2 Hz, 2 H, Ar-H), 7.31 (d, J(H,H) = 8.0 Hz, 2 H, Ar-H), 7.40-7.48 (m, 4 H, Ar-H), 7.54 (m_c, 1 H, Bz-*p*-H), 8.11 (d, J(H,H) = 8.1 Hz, 2 H, Bz-*o*-H) ppm.

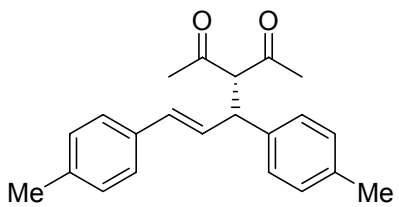
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 15.6 (CH_3), 15.7 (CH_3), 28.7 (CH_2), 28.7 (CH_2), 76.8 (CHOBz), 126.9 (CH), 127.2 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 129.9 (CH), 130.6 (Bz-*i*-C), 132.7 (CH), 133.1 (CH), 133.9 (3-Ar-*i*-C), 136.8 (1-Ar-*i*-C), 144.4 (Ar-*p*-C), 144.5 (Ar-*p*-C), 165.8 (CO_2) ppm.

IR (KBr): $\tilde{\nu}$ = 3027m, 2961s, 2868m, 1915w, 1710s, 1601m, 1512m, 1452s, 1312s, 1266s, 1174m, 1103s, 1065m, 975m, 927m, 824s, 706s, 580m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 370 (16, M^+), 265 (56, $[M–C_7H_5O]^+$), 249 (62, $[M–C_7H_5O_2]^+$), 248 (100), 219 (52), 205 (21), 113 (29), 105 (96, $C_8H_9^+$), 77 (25, $C_6H_5^+$).

Elemental analysis calcd. (%) for $C_{26}H_{26}O_2$: C 84.29, H 7.07; found: C 84.27, H 7.30.

(*R*)-3-[1',3'-Di-(4''-tolyl)-prop-2'-enyl]-pentane-2,4-dione ((*R*)-30a)



(*R*)-**30a**

In a Young tube a solution of $[Pd(C_3H_5)Cl]_2$ (8.00 mg, 21.9 μmol) and ligand (*R*)-**27** (19.3 mg, 51.7 μmol) in CH_2Cl_2 (2.0 mL) was degassed by three freeze-pump-thaw cycles.

The ampoule was sealed at 0.01 mbar and the solution stirred at 50 °C for 2 h. A solution of benzoate **38a** (300 mg, 0.875 mmol) in CH_2Cl_2 (3.5 mL) in a Young tube was treated with acetyl acetone (263 mg, 2.63 mmol), followed by BSA (535 mg, 2.63 mmol) and catalytic amounts of dried KOAc (ca. 5.00 mg). After three freeze-pump-thaw cycles the catalyst solution was added by syringe and the resulting mixture stirred at 0 °C. After 40 h the orange solution was diluted with Et_2O (50 mL) and ice-cold saturated aqueous NH_4Cl solution (30 mL) was added. The aqueous phase was extracted with Et_2O (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc/NEt_3 18:1:1, F16-36) afforded the product (*R*)-**30a** as colourless solid with > 99.5 % *ee* (252 mg, 90%).

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

m.p. 95 °C.

R_f = 0.47 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (s, 3 H, $COCH_3$), 2.24 (s, 3 H, $COCH_3$), 2.30 (s, 6 H, CH_3), 4.24-4.35 (m, 2 H, C*H*CH$(COCH_3)_2$ and CHC*H*$(COCH_3)_2$), 6.09 (dd, *J*(H,H) = 15.8, 7.0 Hz, 1 H, ArCHC*H*), 6.36 (d, *J*(H,H) = 15.8 Hz, 1 H, ArC*H*CH), 7.02-7.21 (m, 8 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 21.2 (CH_3), 21.3 (CH_3), 29.9 (CO*C*H_3), 30.1 (CO*C*H_3), 49.0 (*C*HCH$(COCH_3)_2$), 74.8 (CH*C*H$(COCH_3)_2$), 126.4 (CH), 127.9 (CH), 128.5 (CH), 129.3 (CH), 129.8 (CH), 131.4 (CH), 134.0 (3'-Ar-*i*-C), 137.0 (Ar-C), 137.3 (Ar-C), 137.6 (Ar-C), 203.1 (*C*OCH_3), 203.2 (*C*OCH_3) ppm.

IR (KBr): $\tilde{\nu}$ = 3026m, 2929m, 2863m, 1914w, 1727s, 1512s, 1416s, 1359s, 1276s, 1139s, 1065m, 1038w, 973s, 927m, 820s, 721w, 581w, 527m cm^{-1}.

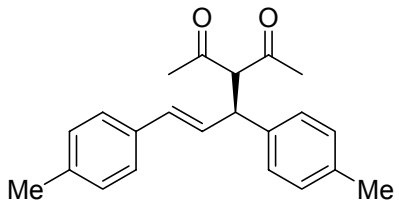
MS (FAB, NBA+KCl): *m/z* (%) = 359 (24, $[M+K]^+$), 302 (29, $[M-C_7H_5O]^+$), 277 (100, $C_{17}H_{17}^+$), 129 (19), 105 (22, $C_8H_9^+$), 43 (36, CH_3CO^+).

$[a]_D^{20}$ = –11.0 (*c* = 1.00, $CHCl_3$).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 97:3, 0.9 mL*min^{-1}, 20 °C, 254 nm): t_R = 16.3 (*R*), 17.8 (*S*) min (> 99.5% *ee*).

Elemental analysis calcd. (%) for $C_{22}H_{24}O_2$: C 82.46, H 7.55; found: C 82.14, H 7.60.

(*S*)-3-[1',3'-Di-(4''-tolyl)-prop-2'-enyl]-pentane-2,4-dione ((*S*)-30a)



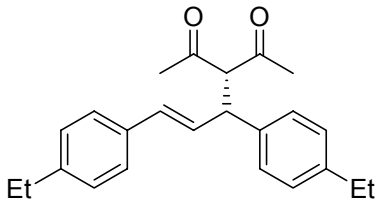
(*S*)-**30a**

The allylic alkylation was carried out in analogy to the preparation of (*R*)-**30a** using $[Pd(C_3H_5)Cl]_2$ (8.01 mg, 21.9 μmol), ligand (*S*)-**27** (19.6 mg, 52.5 μmol), benzoate **38a** (300 mg, 0.875 mmol), acetyl acetone (275 mg, 2.74 mmol), BSA (534 mg, 2.63 mmol), and catalytic amounts of dried KOAc (ca. 5.00 mg) in CH_2Cl_2 (5.5 mL). Compound (*S*)-**30a** was obtained as colourless solid with > 99.5% *ee* (264 mg, 94%).

$[a]_D^{20} = +11.4$ ($c = 1.00$, $CHCl_3$).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 97:3, 0.9 mL*min^{-1}, 20 °C, 254 nm): $t_R = 16.3$ (*R*), 17.8 (*S*) min (> 99.5% *ee*).

(*R*)-3-[1',3'-Di-(4''-ethylphenyl)-prop-2'-enyl]-pentane-2,4-dione ((*R*)-30b)



(*R*)-**30b**

The allylic alkylation was carried out in analogy to the preparation of (*R*)-**30a** using $[Pd(C_3H_5)Cl]_2$ (5.01 mg, 13.7 μmol), ligand (*R*)-**27** (12.2 mg, 32.7 μmol), benzoate **38b** (200 mg, 0.539 mmol), acetyl acetone (162 mg, 1.62 mmol), BSA (330 mg, 1.62 mmol), and catalytic amounts of dried KOAc (ca. 5.00 mg) in CH_2Cl_2 (4.1 mL). The crude product was purified by column chromatography (silica gel, 3 × 25 cm, hexanes/EtOAc/NEt_3 18:1:1, F12-29) and compound (*R*)-**30b** was obtained as colourless solid with > 99% *ee* (305 mg, quant.).

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

m.p. 65 °C.

R_f = 0.48 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, J(H,H) = 7.7 Hz, 3 H, CH_2CH_3), 1.20 (t, J(H,H) = 7.7 Hz, 3 H, CH_2CH_3), 1.93 (s, 3 H, $COCH_3$), 2.24 (s, 3 H, $COCH_3$), 2.58 (q, J(H,H) = 7.7 Hz, 2 H, CH_2), 2.59 (q, J(H,H) = 7.7 Hz, 2 H, CH_2), 4.25-4.35 (m, 2 H, CHCH$(COCH_3)_2$ and CHC$H(COCH_3)_2$), 6.10 (ddd, J(H,H) = 15.8, 7.0, 1.0 Hz, 1 H, ArCHCH), 6.37 (d, J(H,H) = 15.8 Hz, 1 H, ArCHCH), 7.04-7.24 (m, 8 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 15.5 (CH_2CH_3), 15.7 (CH_2CH_3), 28.5 (CH_2), 28.7 (CH_2), 29.9 ($COCH_3$), 30.2 ($COCH_3$), 49.0 (CHCH$(COCH_3)_2$), 74.8 (CHCH$(COCH_3)_2$), 126.5 (CH), 127.9 (CH), 128.1 (CH), 128.6 (CH), 128.7 (CH), 131.4 (CH), 134.4 (3-Ar-*i*-C), 137.5 (Ar-C), 143.3 (Ar-C), 144.0 (Ar-C), 203.1 (COCH_3), 203.2 (COCH_3) ppm.

IR (KBr): $\tilde{\nu}$ = 3008m, 2962s, 2871m, 1914w, 1730s, 1510s, 1456m, 1417s, 1357s, 1277s, 1239s, 1167m, 1140m, 1052w, 1016w, 969s, 821s, 620w, 532w, 491m cm^{-1}.

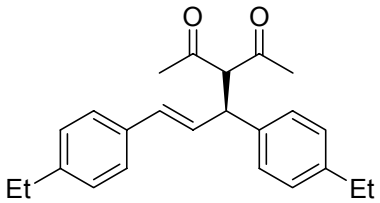
MS (FAB, NBA+KCl): *m/z* (%) = 387 (25, [M+K]$^+$), 330 (26), 305 (22), 249 (100, $C_{19}H_{21}^+$), 119 (22), 57 (17), 43 (36, CH_3CO^+).

$[a]_D^{20}$ = –9.8 (c = 1.00, $CHCl_3$).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 99:1, 0.9 mL*min^{-1}, 30 °C, 254 nm): t_R = 24.4 (*R*), 25.9 (*S*) min (> 99% *ee*).

Elemental analysis calcd. (%) for $C_{24}H_{28}O_2$: C 82.72, H 8.10, O 9.18; found: C 82.40, H 8.05, O 9.35.

(*S*)-3-[1',3'-Di-(4''-ethylphenyl)-prop-2'-enyl]-pentane-2,4-dione ((*S*)-30b)



(*S*)-**30b**

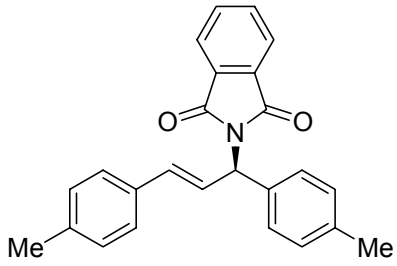
The allylic alkylation was carried out in analogy to the preparation of (*R*)-**30a** using $[Pd(C_3H_5)Cl]_2$ (4.00 mg, 10.9 µmol), ligand (*S*)-**27** (9.20 mg, 24.6 µmol), benzoate **38b** (150 mg, 0.405 mmol), acetyl acetone (127 mg, 1.28 mmol), BSA (259 mg, 1.27 mmol), and

catalytic amounts of dried KOAc (ca. 5.00 mg) in CH_2Cl_2 (2.7 mL). Compound (*S*)-**30b** was obtained as colourless solid with > 99% *ee* (131 mg, 93%).

$[a]_D^{20} = +10.1$ (c = 1.00, $CHCl_3$).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 99:1, 0.9 mL*min^{-1}, 30 °C, 254 nm): t_R = 24.4 (*R*), 25.9 (*S*) min (> 99% *ee*).

(*R*)-*N*-[1,3-Di-(4'-tolyl)-prop-2-enyl]-phthalimide ((*R*)-58a)



(*R*)-**58a**

In a Young tube a solution of $[Pd(C_3H_5)Cl]_2$ (8.00 mg, 21.9 µmol) and ligand (*S*)-**27** (19.3 mg, 51.7 µmol) in CH_2Cl_2 (2.0 mL) was degassed by three freeze-pump-thaw cycles. The ampoule was sealed at 0.01 mbar and the solution stirred at 50 °C for 2 h. After the mixture had been cooled to r.t. it was added to a degassed solution of benzoate **38a** (301 mg, 0.875 µmol) and potassium phthalimide (194 mg, 1.05 mmol) in CH_2Cl_2 (4.0 mL) in a Young tube and the resulting yellow suspension was stirred at r.t. under argon. After 3 d the reaction was diluted with Et_2O (50 mL) and ice-cold saturated aqueous NH_4Cl solution (40 mL) was added. The organic phase was extracted with Et_2O (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc/NEt_3 18:1:1, F20-34) afforded the product (*R*)-**58a** as colourless oil with 97% *ee* (322 mg, quant.).

$C_{25}H_{21}NO_2$ (367.44 g*mol^{-1}):

R_f = 0.27 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 6.07 (d, J(H,H) = 8.7 Hz, 1 H, CHN), 6.65 (d, J(H,H) = 15.8 Hz, 1 H, ArC*H*CH), 6.97 (dd,

J(H,H) = 15.8, 8.7 Hz, 1 H, ArCHC*H*), 7.17 (m_c, 4 H, Ar-H), 7.39 (m_c, 4 H, Ar-H), 7.68-7.73 (m, 2 H, Ar-H), 7.81-7.85 (m, 2 H, Ar-H) ppm.

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 21.2 (CH_3), 21.4 (CH_3), 56.5 (CHN), 123.5 (CH), 124.5 (CH), 126.8 (CH), 127.5 (CH), 129.4 (CH), 132.2 (Ar-C), 133.7 (Ar-C), 134.1 (CH), 134.2 (CH), 136.2 (Ar-C), 137.6 (Ar-C), 138.0 (Ar-C), 168.0 (NCO) ppm.

IR (KBr): $\tilde{\nu}$ = 3024m, 2923s, 1773m, 1712s, 1612s, 1513m, 1467m, 1381s, 1328m, 1232w, 1180w, 1107m, 1080m, 971m, 802m, 718s, 630m cm^{-1}.

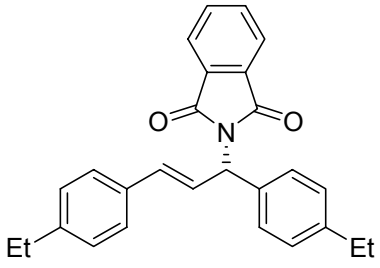
MS (EI, 70 eV): *m/z* (%) = 367 (10, M^+), 352 (6, $[M-CH_3]^+$), 349 (5), 221 (21, $[M-C_8H_4NO_2]^+$), 220 (100), 205 (22), 129 (7).

$[a]_D^{20} = -11.2$ (*c* = 0.500, $CHCl_3$).

HPLC (Daicel Chiracel OD-H, heptane/isopropanol 99:1, 0.5 mL*min^{-1}, 20 °C, 254 nm): t_R = 16.9 (*R*), 18.5 (*S*) min (97% *ee*).

HRMS (EI) *m/z* calcd. (%) for $C_{25}H_{21}NO_2$: 367.1560; found: 367.1572.

(*S*)-*N*-[1,3-Di-(4'-ethylphenyl)-prop-2-enyl]-phthalimide ((*S*)-58b)



(*S*)-**58b**

The allylic amination was carried out in analogy to the preparation of (*R*)-**58a** using $[Pd(C_3H_5)Cl]_2$ (11.4 mg, 31.2 µmol), ligand (*R*)-**27** (28.0 mg, 75.0 µmol), benzoate **38b** (465 mg, 1.24 mmol), and potassium phthalimide (277 mg, 1.49 mmol) in CH_2Cl_2 (8.5 mL). The crude product was purified by column chromatography (silica gel, 3 × 25 cm, hexanes/EtOAc/NEt_3 18:1:1, F11-30) and (*S*)-**58b** was obtained as colourless oil with 97% *ee* (475 mg, 97%).

$C_{27}H_{25}NO_2$ (395.49 g*mol^{-1}):

R_f = 0.30 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, J(H,H) = 7.6 Hz, 3 H, CH_3), 1.20 (t, J(H,H) = 7.6 Hz, 3 H, CH_3), 2.61 (q, J(H,H) = 7.6 Hz, 2 H, CH_2), 2.62 (q, J(H,H) = 7.6 Hz, 2 H, CH_2), 6.08 (d, J(H,H) = 8.5 Hz, 1 H, CHN), 6.66 (d, J(H,H) = 15.9 Hz, 1 H, ArC*H*CH), 6.99 (dd, J(H,H) = 15.9, 8.5 Hz, 1 H, ArCHC*H*), 7.12 (m_c, 4 H, Ar-H), 7.42 (m_c, 4 H, Ar-H), 7.68-7.72 (m, 2 H, Ar-H), 7.82-7.86 (m, 2 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 15.6 (CH_3), 15.7 (CH_3), 28.6 (CH_2), 28.8 (CH_2), 56.5 (CHN), 123.5 (CH), 124.7 (CH), 126.9 (CH), 127.6 (CH), 128.2 (CH), 128.2 (CH), 132.2 (Ar-C), 133.9 (Ar-C), 134.1 (CH), 134.2 (CH), 136.4 (Ar-C), 143.9 (Ar-C), 144.5 (Ar-C), 168.0 (NCO) ppm.

IR (KBr): $\tilde{\nu}$ = 2965s, 1772m, 1713s, 1611m, 1512m, 1466m, 1383s, 1326m, 1226w, 1181w, 1121m, 973m cm^{-1}.

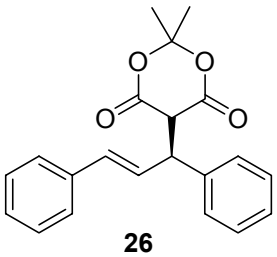
MS (EI, 70 eV): *m/z* (%) = 395 (10, M^+), 366 (53, $[M–C_2H_5]^+$), 249 (23, $[M–C_8H_4NO_2]^+$), 248 (100), 219 (43), 104 (9).

$[a]_D^{20}$ = +10.8 (c = 0.500, $CHCl_3$).

HPLC (Daicel Chiracel OD-H, heptane/isopropanol 99:1, 0.5 mL*min^{-1}, 25 °C, 254 nm): t_R = 16.8 (*S*), 18.3 (*R*) min (97% *ee*).

HRMS (EI) *m/z* calcd. (%) for $C_{27}H_{25}NO_2$: 395.1897; found: 395.1885.

(*S*)-2,2-Dimethyl-5-(1',3'-diphenylprop-2'-enyl)-1,3-dioxane-4,6-dione (26)



26

In a Young tube a solution of $[Pd(C_3H_5)Cl]_2$ (8.10 mg, 22.2 µmol) and ligand (*S*)-**27** (16.6 mg, 44.4 µmol) in CH_2Cl_2 (2.5 mL) was degassed by three freeze-pump-thaw cycles. The ampoule was sealed at 0.01 mbar and the solution stirred at 50 °C for 2 h. After the mixture had been cooled to r.t. it was added to a degassed solution of benzoate **21** (349 mg, 1.11 mmol), Meldrum's acid (240 mg, 1.67 mmol) and DBU (338 mg, 1.67 mmol) in CH_2Cl_2 (4.0 mL) in a Young tube. The resulting yellow mixture was stirred at 50 °C for 6 d. After cooling the solution to r.t. it was diluted with Et_2O (30 mL) and ice-cold saturated aqueous

NH_4Cl solution (50 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (3 × 20 cm, silica gel, hexanes/EtOAc 4:1) afforded product **26** as colourless solid with 81% *ee* (116 mg, 31%).

$C_{21}H_{20}O_4$ (336.38 g*mol^{-1}):

m.p. 141 °C.

R_f = 0.32 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3), 3.97 (d, *J*(H,H) = 2.7 Hz, 1 H, CHC*H*$(CO_2)_2$), 4.74 (dd, *J*(H,H) = 9.3, 2.7 Hz, 1 H, C*H*CH$(CO_2)_2$), 6.66 (d, *J*(H,H) = 15.8 Hz, 1 H, ArC*H*CH), 6.92 (dd, *J*(H,H) = 15.8, 9.3 Hz, 1 H, ArCHC*H*), 7.20-7.50 (m, 10 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 27.8 (CH_3), 28.4 (CH_3), 47.6 (*C*HCH$(CO_2)_2$), 52.6 (CH*C*H$(CO_2)_2$), 52.6 (*C*$(CH_3)_2$), 126.7 (Ar-CH), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.6 (Ar-CH), 128.7 (Ar-CH), 128.8 (Ar-CH), 133.5 (CH), 136.8 (3-Ar-*i*-C), 139.9 (1-Ar-*i*-C), 164.6 (CO_2), 164.6 (CO_2) ppm.

IR (KBr): $\tilde{\nu}$ = 2895m, 1785s, 1744s, 1643s, 1495m, 1450m, 1385m, 1315s, 1270s, 1232m, 1198m, 1118m, 1056m, 1011m, 975w, 926w, 897w, 852w, 797w, 752m, 700s cm^{-1}.

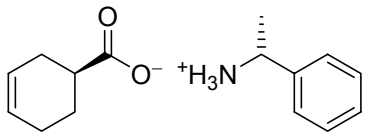
MS (FAB, NBA): *m/z* (%) = 250 (6), 221 (100), 193 (55, $[M–C_6H_3O_4]^+$), 115 (32).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 81:19, 0.5 mL*min^{-1}, 20 °C, 254 nm): t_R = 16.2 (*R*), 21.5 (*S*) min (81% *ee*).

Elemental analysis calcd. (%) for $C_{21}H_{20}O_4$: C 74.98, H 5.99; found: C 74.76, H 6.14.

7.3.2 Carbocyclic Substrates

(*R*)-α-Phenylethylammonium (*S*)-cyclohex-3-enylcarboxylate (207a)[99, 100]



207a

A solution of cyclohex-3-enecarboxylic acid **66** (21.3 g, 169 mmol) in acetone (100 mL) was treated with (*R*)-α-phenylethylamine (23.6 g, 194 mmol) and the mixture was gently heated at 70 °C. After all solids had been dissolved, the mixture was allowed to cool to r.t. and then kept in the refridgerator overnight. The precipitate was collected and seven further re-crystallisations, carried out in the same manner as the first, gave the enantiomerically enriched salt **207a** as colourless needles (7.41 g, 18%).

$C_{15}H_{21}NO_2$ (247.33 g*mol^{-1}):

m.p. 119-120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (br s, 1 H, CH_2), 1.52 (d, *J*(H,H) = 6.5 Hz, 3 H, CH_3), 1.69 (br s, 1 H, CH_2), 1.93 (br s, 4 H, CH_2), 2.04 (br s, 1 H, CH), 4.2 (q, *J*(H,H) = 6.5 Hz, 1 H, CHN), 5.56 (br s, 2 H, C*H*CH and CHC*H*), 7.22-7.34 (m, 3 H, Ar-H), 7.36-7.44 (m, 2 H, Ar-H), 8.30 (br s, 3 H, NH_3) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 22.3 (CH_3), 25.1 (CH_2), 25.9 (CH_2), 28.5 (CH_2), 41.8 ($CHCO_2^-$), 51.1 (CHN), 126.2 (*C*HCH), 126.5 (Ph-*o*-CH), 126.8 (CH*C*H), 128.1 (Ph-*p*-CH), 128.8 (Ph-*m*-CH), 141.0 (Ph-*i*-C), 183.0 (CO_2^-) ppm.

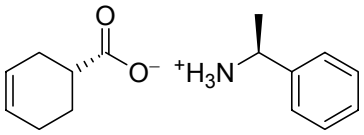
IR (KBr): $\tilde{\nu}$ = 2909s, 2687s, 1573s, 1530s, 1452m, 1397s, 1338s, 1264s, 1196m, 1154m, 1087w, 1023w, 920w, 822w, 764m, 696s, 675s, 646m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 126 (8, $C_7H_{10}O_2^+$), 120 (6), 106 (100, $C_8H_{10}N^+$), 81 (35, $C_6H_9^+$), 53 (11).

$[a]_D^{20}$ = –40.4 (*c* = 1.00, $CHCl_3$); Lit.: –40.2 (*c* = 1.00, $CHCl_3$).[99]

Elemental analysis calcd. (%) for $C_{15}H_{21}NO_2$: C 72.84, H 8.56, N 5.66; found: C 72.70, H 7.97, N 4.42.

(*S*)-α-Phenylethylammonium (*R*)-cyclohex-3-enylcarboxylate (207b)[99, 100]

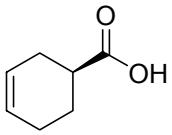


207b

In analogy to the preparation of **207a** resolution of cyclohex-3-enecarboxylic acid **66** (8.79 g, 69.7 mmol) was effected by six re-crystallisations of the corresponding salt, from (*S*)-α-phenylethylamine (10.1 g, 83.3 mmol). The product **207b** was obtained as colourless needles (2.00 g, 12%).

$[a]_D^{20}$ = +40.2 (*c* = 1.00, $CHCl_3$); Lit.: +40.5 (*c* = 1.00, $CHCl_3$).[99]

(*S*)-Cyclohex-3-enecarboxylic acid ((*S*)-66)[99, 100]



(*S*)-**66**

(*R*)-α-Phenylethylammonium (*S*)-cyclohex-3-enylcarboxylate (**207a**, 988 mg, 3.99 mmol) was dissolved in ice water (100 mL) and treated with 1 M aqueous HCl (10 mL). The mixture was stirred for 5 min and then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The free carboxylic acid (*S*)-**66** was isolated as colourless liquid with 96.5% *ee* (511 mg, quant.).

$C_7H_{10}O_2$ (126.15 g*mol^{-1}):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71 (m_c, 1 H, 6-H), 1.99-2.16 (m, 3 H, 6-H and 5-H), 2.27 (m_c, 2 H, 2-H), 2.60 (m_c, 1 H, 1-H), 5.66 (s, 2 H, 3-H and 4-H), 11.44 (br s, 1 H, CO_2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 24.4 (5-CH_2), 24.9 (6-CH_2), 27.3 (2-CH_2), 39.3 (1-CH), 125.1 (*C*HCH), 126.8 (CH*C*H), 182.8 (CO_2H) ppm.

IR (KBr): $\tilde{\nu}$ = 2928br, 1705s, 1423m, 1302m, 1238m, 1193m, 1089w, 1044w, 920m, 818w, 747w, 651m cm^{-1}.

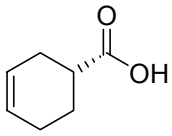
MS (EI, 70 eV): *m/z* (%) = 126 (22, M^+), 108 (29), 81 (100, $C_6H_9^+$), 54 (29).

$[a]_D^{20}$ = –89.8 (*c* = 1.14, MeOH); Lit.: –95.9 (*c* = 1.00, $CHCl_3$).[99]

GC (γ-CD, DetTBuSil SE 54, 75/0/2/150/0/20/180): t_R = 26.0 (*S*), 27.0 (*R*) min (96.5 % *ee*).

Elemental analysis calcd. (%) for $C_7H_{10}O_2$: C 66.65, H 7.99; found: C 66.38, H 7.97.

(*R*)-Cyclohex-3-enecarboxylic acid ((*R*)-66)[99, 100]



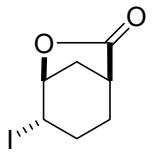
(*R*)-**66**

The synthesis of (*R*)-**66** was accomplished in analogy to the preparation of (*S*)-**66** starting from (*S*)-α-phenylethylammonium (*R*)-cyclohex-3-enylcarboxylate (**207b**, 696 mg, 2.81 mmol) with 1 M aqueous HCl (10 mL). The free carboxylic acid (*R*)-**66** was isolated as colourless liquid with 95.5% *ee* (410 mg, quant.).

$[a]_D^{20}$ = +95.6 (*c* = 1.00, CH_3Cl); Lit.: +95.3 (*c* = 1.00, $CHCl_3$).[99]

GC (γ-CD, DetTBuSil SE 54, 75/0/2/150/0/20/180): t_R = 26.0 (*S*), 27.0 (*R*) min (> 95.5% *ee*).

4-Iodo-6-oxa-bicyclo[3.2.1]octan-7-one (67)[101]



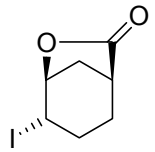
67

Cyclohex-3-enecarboxylic acid (**66**, 1.01 g, 8.43 mmol) was added to a solution of $NaHCO_3$ (2.02 g, 24.0 mmol) in water (20 mL) and the resulting mixture was stirred, until it was homogeneous. The flask was then protected from light and the mixture treated with a solution of KI (8.40 g, 50.6 mmol) and iodine (2.14 g, 8.41 mmol) in water (20 mL). The reaction mixture was stirred at r.t. for 20 h and then extracted with $CHCl_3$ (3 × 50 mL). The organic

phases were combined, washed with 10% aqueous $Na_2S_2O_3$, 10% aqueous $NaHCO_3$ and water and then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave **67** as off-white solid (1.91 g, 95%).

$C_7H_9IO_2$ (252.0 g*mol^{-1}):
m.p. 138 °C.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75-1.92 (m, 2 H), 2.03 (dd, *J*(H,H) = 16.6, 5.0 Hz, 1 H), 2.34-2.49 (m, 2 H), 2.64-2.70 (m, 1 H), 2.77 (d, *J*(H,H) = 12.3 Hz, 1 H, 1-H), 4.49 (br t, *J*(H,H) = 4.6 Hz, 1 H, 4-H), 4.82 (br t, *J*(H,H) = 5.2 Hz, 1 H, 3-H) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 22.2 (2-CH_2), 23.9 (4-CH), 29.8 (3-CH_2), 34.6 (6-CH_2), 38.7 (1-CH), 80.3 (5-CH), 177.9 (7-CO) ppm.
IR (KBr): $\tilde{\nu}$ = 2932m, 2853m, 1772s, 1442m, 1348m, 314m, 1269m, 1162s, 1076m, 1002s, 953s, 897m, 830m cm^{-1}.
MS (EI, 70 eV): *m/z* (%) = 252 (3, M^+), 125 (50, $[M–I]^+$), 81 (100), 41 (29).
Elemental analysis calcd. (%) for $C_7H_9IO_2$: C 33.36, H 3.60; found: C 33.39, H 3.45.

(1*S*,4*S*,5*S*)-4-Iodo-6-oxa-bicyclo[3.2.1]octan-7-one ((*S*,*S*,*S*)-67)[101]

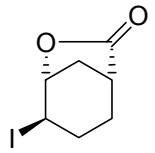


(*S*,*S*,*S*)-**67**

The iodolactonisation was carried out in analogy to the preparation of **67** using (*S*)-cyclohex-3-enecarboxylic acid ((*S*)-**66**, 333 mg, 2.64 mmol), $NaHCO_3$ (665 mg, 7.91 mmol), KI (2.62 g, 15.8 mmol) and iodine (701 mg, 2.77 mmol) in water (14 mL). Lactone (*S*,*S*,*S*)-**67** was isolated as off-white solid (594 mg, 90%).

$[a]_D^{20}$ = –41.3 (*c* = 2.00, $CHCl_3$); Lit.: –43.2 (*c* = 2.00, $CHCl_3$).[146]

(1*R*,4*R*,5*R*)-4-Iodo-6-oxa-bicyclo[3.2.1]octan-7-one ((*R*,*R*,*R*)-67)[101]

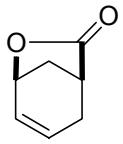


(*R*,*R*,*R*)-**67**

The iodolactonisation was accomplished in analogy to the preparation of **67** using (*R*)-cyclohex-3-enecarboxylic acid ((*R*)-**66**, 533 g, 4.22 mmol), $NaHCO_3$ (1.06 g, 12.7 mmol), KI (4.21 g, 25.4 mmol) and iodine (1.13 g, 4.47 mmol) in water (20 mL). The lactone (*R*,*R*,*R*)-**67** was obtained as off-white solid (946 mg, 89%).

$[a]_D^{20}$ = +36.9 (*c* = 1.92, $CHCl_3$); Lit.: +37.6 (*c* = 2.03, $CHCl_3$).[147]

6-Oxa-bicyclo[3.2.1]oct-3-en-7-one (68)[102]



68

To a solution of iodolactone **67** (5.53 g, 21.9 mmol) in abs. THF (120 mL) DBU (4.90 mL, 32.8 mmol) was added and the mixture was stirred at reflux for 8 h. After being cooled to r.t. the mixture was poured into 0.5 M HCl and the resulting emulsion extracted with Et_2O (3 × 50mL). The combined organic phases were washed with brine, dried over Mg_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 5 × 20 cm, hexanes/EtOAc 2:1, F37-62) to give alkene **68** as a colourless oil (2.60 g, 96%).

$C_7H_8O_2$ (124.14 g*mol^{-1}):

$\boldsymbol{R_f}$ = 0.23 (hexanes/EtOAc 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (d, J(H,H) =11.2 Hz, 1 H), 2.37-2.54 (m, 3 H), 2.89 (br s, 1 H), 4.72 (t, J(H,H) = 5.4 Hz, 1 H, 5-CH), 5.82 (m_c, 1 H, C*H*CH), 6.20 (m_c, 1 H, CHC*H*) ppm.

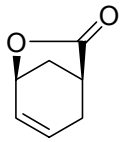
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 29.2 (2-CH_2), 34.5 (6-CH_2), 38.1 (1-CH), 73.4 (5-CH), 129.4 (*C*HCH), 130.4 (CH*C*H), 179.5 (7-CO) ppm.

IR (NaCl): $\tilde{\nu}$ = 2986m, 2908m, 1774s, 1632w, 1448m, 1382m, 1238m, 1244m, 1137s, 1055m, 981m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 124 (3, M^+), 95 (5), 80 (100), 79 (95, $C_6H_7^+$), 39 (22).

Elemental analysis calcd. (%) for $C_7H_8O_2$: C 67.73, H 6.50; found: C 67.43. H 6.75.

(1*S*,5*S*)-6-Oxa-bicyclo[3.2.1]oct-3-en-7-one ((*S*,*S*)-68)[102]

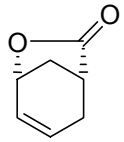


(*S*,*S*)-**68**

The synthesis was accomplished in analogy to the preparation of **68** using iodolactone (*S*,*S*,*S*)-**67** (507 mg, 2.01 mmol) and DBU (450 µL, 3.01 mmol) in abs. THF (12 mL). Alkene (*S*,*S*)-**68** was isolated as colourless oil (215 mg, 86%).

$[a]_D^{20}$ = –197.0 (*c* = 1.08, $CHCl_3$); Lit.: –201.2 (*c* = 4.00, $CHCl_3$).[146]

(1*R*,5*R*)-6-Oxa-bicyclo[3.2.1]oct-3-en-7-one ((*R*,*R*)-68)[102]

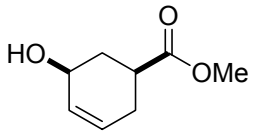


(*R*,*R*)-**68**

The synthesis was accomplished in analogy to the preparation of **68** using iodolactone (*R*,*R*,*R*)-**67** (624 mg, 2.47 mmol) and DBU (554 µL, 3.70 mmol) in abs. THF (15 mL). The alkene (*R*,*R*)-**68** was obtained as colourless oil (245 mg, 80%).

$[a]_D^{20}$ = +253.0 (*c* = 1.50, $CHCl_3$); Lit.: +179.2 (*c* = 9.76, $CHCl_3$).[147]

cis-Methyl 5-hydroxycyclohex-3-enecarboxylate (69a)[102]



69a

To a solution of lactone **68** (497 mg, 4.00 mmol) in anhydrous MeOH (20 mL) was added $NaHCO_3$ (347 mg, 4.13 mmol). The mixture was stirred at r.t. for 7 h and the solvent was removed under reduced pressure. The residue was re-dissolved in water (15 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel, 3 × 10 cm, hexanes/EtOAc 9:1, F4-13) afforded hydroxy ester **69a** as a colourless oil (556 mg, 89%).

$C_8H_{12}O_2$ (156.18 g*mol^{-1}):

$\boldsymbol{R_f}$ = 0.24 (Et_2O/hexanes 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (ddd, *J*(H,H) = 12.8, 11.0, 8.1 Hz, 1 H), 2.17 (m_c, 1 H), 2.25-2.32 (m, 3 H), 2.67 (m_c, 1 H), 3.69 (s, 3 H, CH_3), 4.27 (br d, *J*(H,H) = 7.1 Hz, 1 H, 5-H), 5.70-5.79 (m, 2 H, 3-H and 4-H) ppm.

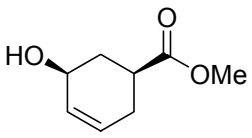
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 27.5 (2-CH_2), 34.3 (6-CH_2), 37.8 (1-CH), 52.1 (CH_3), 66.1 (5-CH), 127.0 (*C*HCH), 130.9 (CH*C*H), 175.8 (CO_2) ppm.

IR (NaCl): $\tilde{\nu}$ = 3403br, 3028s, 2952s, 1734s, 1653m, 1437s, 1379m, 1245s, 1200s, 1115m, 1045s, 1003s, 939w, 917m, 888w, 767m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 156 (2, M^+), 139 (63, $[M–OH]^+$), 97 (29, $[M–CO_2CH_3]^+$), 79 (100, $C_6H_7^+$), 41 (9).

Elemental analysis calcd. (%) for $C_8H_{12}O_2$: C 61.52, H 7.74; found: C 61.18, H 7.84.

(1S,5S)-Methyl 5-hydroxycyclohex-3-enecarboxylate ((S,S)-69a)[102]

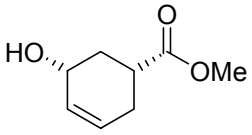


(*S*,*S*)-**69a**

The synthesis in analogy to the preparation of **69a** using lactone (*S*,*S*)-**68** (225 mg, 1.81 mmol) and $NaHCO_3$ (152 mg, 1.81 mmol) in anhydrous MeOH (9.0 mL) gave (*S*,*S*)-**69a** as colourless oil (246 mg, 87%).

$[a]_D^{20}$ = +3.5 (*c* = 1.46, $CHCl_3$).

(1*R*,5*R*)-Methyl 5-hydroxycyclohex-3-enecarboxylate ((*R*,*R*)-69a)[102]

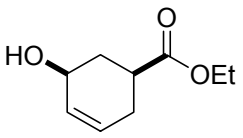


(*R*,*R*)-**69a**

The synthesis in analogy to the preparation of **69a** using lactone (*R*,*R*)-**68** (300 mg, 2.41 mmol) and $NaHCO_3$ (206 mg, 2.45 mmol) in anhydrous MeOH (12 mL) gave (*R*,*R*)-**69a** as colourless oil (339 mg, 90%).

$[a]_D^{20}$ = –4.5 (*c* = 2.20, $CHCl_3$); Lit.: –4.6 (*c* = 2.25, $CHCl_3$).[102]

cis-Ethyl 5-hydroxycyclohex-3-enecarboxylate (69b)[102]

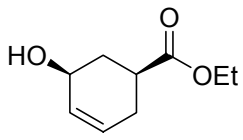


69b

Lactone **68** (820 mg, 6.61 mmol) and $NaHCO_3$ (610 mg, 7.27 mmol) were stirred in anhydrous EtOH (20 mL) at r.t. for 5 h. The solvent was removed under reduced pressure and the residue partitioned between Et_2O (10 mL) and 1 M aqueous hydrochloric acid (10 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined organic phases were washed with saturated aqueous solutions of $NaHCO_3$ (40 mL) and NaCl (40 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 1:1, F17-28) afforded hydroxy ester **69b** as a colourless oil (864 mg, 77%).

$C_9H_{14}O_3$ (170.21 g*mol^{-1}):
R_f = 0.24 (Et_2O/hexanes 9:1).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, J(H,H) = 7.2 Hz, 3 H, CH_3), 1.69 (J(H,H) = 12.8, 11.1, 7.9 Hz, 1 H), 2.18 (br s, 1 H), 2.24-2.34 (m, 3 H), 2.66 (m_c, 1 H), 4.12 (q, J(H,H) = 7.2 Hz, 2 H, CH_2CH$_3$), 4.27 (m_c, 1 H), 5.71-5.80 (m, 2 H, 3-H and 4-H) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 14.3 (CH_3), 27.6 (2-CH_2), 34.3 (6-CH_2), 38.0 (1-CH), 60.9 (CH_2CH_3), 66.1 (5-CH), 127.1 (*C*HCH), 131.0 (CH*C*H), 175.4 (CO_2) ppm.
IR (NaCl): $\tilde{\nu}$ = 3035m, 2979m, 2936m, 1718s, 1653w, 1601m, 1584w, 1451s, 1378w, 1273s, 1178s, 1111s, 1069s, 1026s, 998m, 955w, 927m, 858w, 806w cm^{-1}.
MS (EI, 70 eV): *m/z* (%) = 170 (1, M^+), 153 (36, $[M–OH]^+$), 97 (67, $[M–CO_2CH_2CH_3]^+$), 79 (100, $C_6H_7^+$), 41 (24).

(1*S*,5*S*)-Ethyl 5-hydroxycyclohex-3-enecarboxylate ((*S*,*S*)-69b)[102]

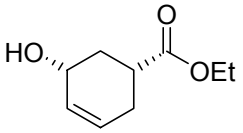


(*S*,*S*)-**69b**

The synthesis in analogy to the preparation of **69b** using lactone (*S*,*S*)-**68** (209 mg, 1.68 mmol) and $NaHCO_3$ (161 mg, 1.92 mmol) in anhydrous EtOH (9.0 mL) gave (*S*,*S*)-**69b** as colourless oil (234 mg, 82%).

$[a]_D^{20}$ = –2.5 (*c* = 1.20, $CHCl_3$).

(1*R*,5*R*)-Ethyl 5-hydroxycyclohex-3-enecarboxylate ((*R*,*R*)-69b)[102]

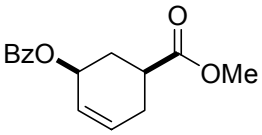


(*R*,*R*)-**69b**

The synthesis in analogy to the preparation of **69b** using lactone (*R*,*R*)-**68** (567 mg, 4.64 mmol) and $NaHCO_3$ (393 mg, 4.68 mmol) in anhydrous EtOH (30 mL) gave (*R*,*R*)-**69b** as colourless oil (749 mg, 95%).

$[a]_D^{20} = +2.8$ (c = 1.20, $CHCl_3$).

cis-5-(Methoxycarbonyl)-cyclohex-2-enyl benzoate (65a)



65a

A solution of alcohol **69a** (745 mg, 4.78 mmol), abs. NEt_3 (1.33 mL, 9.55 mmol) and a spatula tip of DMAP (ca. 10 mg) in abs. CH_2Cl_2 (20 mL) was treated dropwise with BzCl (815 mg, 5.80 mmol) at –78 °C. The mixture was allowed to warm to r.t. overnight. After the reaction had been quenched with saturated aqueous NH_4Cl solution (20 mL), the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc/NEt_3 18:1:1, F7-16) to yield benzoate **65a** as a colourless solid (1.14 g, 92%).

$C_{15}H_{16}O_4$ (260.29 g*mol^{-1}):
m.p. 35 °C.
R_f = 0.43 (hexanes/EtOAc 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (ddd, *J*(H,H) = 12.7, 10.8, 8.8 Hz, 1 H), 2.31-2.44 (m, 2 H), 2.49 (m_c, 1 H), 2.80 (m_c, 1 H), 3.66 (s, 3 H, CH_3), 5.64 (m_c, 1 H, 1-H), 5.78 (m_c, 1 H, C*H*CH), 5.93 (m_c, 1 H, CHC*H*), 7.43 (t, *J*(H,H) = 7.6 Hz, 2 H, Bz-*m*-H), 7.55 (t, *J*(H,H) = 7.6 Hz, 1 H, Bz-*p*-H), 8.03 (m_c, 2 H, Bz-*o*-H) ppm.

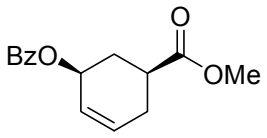
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 27.3 (4-CH_2), 30.7 (6-CH_2), 37.8 (5-CH), 52.0 (CH_3), 69.6 (1-CH), 126.8 (3-CH), 128.4 (Bz-*m*-CH), 129.6 (Bz-*o*-CH), 129.8 (2-CH), 130.4 (Bz-*i*-C), 133.1 (Bz-*p*-CH), 166.3 (CO_2Ph), 174.8 (CO_2CH_3) ppm.

IR (KBr): $\tilde{\nu}$ = 3030w, 2981m, 2940m, 1734s, 1686s, 1653m, 1617m, 1559m, 1507m, 1457m, 1274m, 999m, 860w, 668m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 260 (2, M^+), 105 (100, $C_7H_5O^+$), 77 (21, $C_6H_5^+$).

Elemental analysis calcd. (%) for $C_{15}H_{16}O_4$: C 69.22, H 6.20; found: C 69.31, H 6.29.

(1*S*,5*S*)-5-(Methoxycarbonyl)-cyclohex-2-enyl benzoate ((*S*,*S*)-65a)



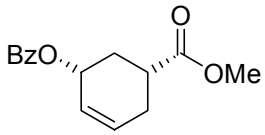
(*S*,*S*)-**65a**

The synthesis in analogy to the preparation of **65a** using alcohol (*S*,*S*)-**69a** (2.07 g, 21.1 mmol), abs. NEt_3 (5.90 mL, 42.4 mmol), DMAP (ca. 20 mg) and BzCl (468 mg, 3.33 mmol) in abs. CH_2Cl_2 (12 mL) gave (*S*,*S*)-**65a** as colourless oil with 98% *ee* (632 mg, 91%).

$[a]_D^{20}$ = –89.0 (*c* = 1.00, $CHCl_3$).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 99.6:0.4, 0.9 mL*min^{-1}, 35 °C, 220 nm): t_R = 33.3 (*S*), 39.6 (*R*) min (98% *ee*).

(1*R*,5*R*)-5-(Methoxycarbonyl)-cyclohex-2-enyl benzoate ((*R*,*R*)-65a)



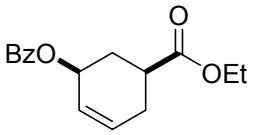
(*R*,*R*)-**65a**

The synthesis in analogy to the preparation of **65a** using alcohol (*R*,*R*)-**69a** (235 mg, 1.51 mmol), abs. NEt_3 (420 µL, 3.01 mmol), DMAP (ca. 10 mg) and BzCl (253 mg, 1.81 mmol) in abs. CH_2Cl_2 (7.0 mL) gave (*R*,*R*)-**65a** as colourless oil with 97% *ee* (350 mg, 89%).

$[a]_D^{20} = +137.0$ ($c = 0.60$, $CHCl_3$).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 99.6:0.4, 0.9 mL*min^{-1}, 35 °C, 220 nm): $t_R = 33.3$ (*S*), 39.6 (*R*) min (97% *ee*).

5-(Ethoxycarbonyl)-cyclohex-2-enyl benzoate (65b)



65b

A solution of alcohol **69b** (500 mg, 2.94 mmol), abs. NEt_3 (820 µL, 5.88 mmol) and a spatula tip of DMAP (ca. 10 mg) in abs. CH_2Cl_2 (13 mL) was treated dropwise with BzCl (500 mg, 3.56 mmol) at –78 °C. The mixture was allowed to warm to r.t. overnight. After the reaction had been quenched with saturated aqueous NH_4Cl solution (15 mL), the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc/NEt_3 18:1:1, F5-16) to yield benzoate **65b** as a colourless oil (661 mg, 82%).

$C_{16}H_{18}O_4$ (274.31 g*mol^{-1}):

R_f = 0.32 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, J(H,H) = 7.1 Hz, 3 H, CH_3), 1.93 (ddd, J(H,H) = 12.3, 9.3 Hz, 1 H), 2.30-2.42 (m, 2 H), 2.48 (m_c, 1 H), 2.78 (m_c, 1 H), 4.12 (m_c, 2 H), 5.65 (m_c, 1 H, 1-H), 5.77 (d, J(H,H) = 10.4 Hz, 1 H, C*H*CH), 5.93 (d, J(H,H) = 10.4 Hz, 1 H, CHC*H*), 7.43 (t, J(H,H) = 7.8 Hz, 2 H, Bz-*m*-H), 7.55 (t, J(H,H) = 7.7 Hz, 1 H, Bz-*p*-H), 8.03 (d, J(H,H) = 7.7 Hz, 2 H, Bz-*o*-H) ppm.

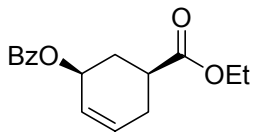
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 14.3 (CH_3), 27.3 (4-CH_2), 30.7 (6-CH_2), 38.0 (5-CH), 60.7 (CH_2CH_3), 69.8 (1-CH), 126.9 (3-CH), 128.4 (Bz-*m*-CH), 129.6 (Bz-*o*-CH), 129.8 (2-CH), 130.4 (Bz-*i*-C), 133.1 (Bz-*p*-CH), 166.3 (CO_2Ph), 174.8 ($CO_2CH_2CH_3$) ppm.

IR (KBr): $\tilde{\nu}$ = 3035w, 2979m, 2936m, 1715s, 1601m, 1451s, 1378m, 1275s, 1178s, 1111s, 1026s, 998m, 955m, 927m, 858w, 712s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 274 (3, M^+), 105 (100, $C_7H_5O^+$), 77 (18, $C_6H_5^+$).

Elemental analysis calcd. (%) for $C_{16}H_{18}O_4$: C 70.06, H 6.61; found: C 69.94, H 6.80.

(1*S*,5*S*)-5-(Ethoxycarbonyl)-cyclohex-2-enyl benzoate ((*S*,*S*)-65b)



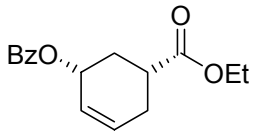
(*S*,*S*)-**65b**

The synthesis in analogy to the preparation of **65b** using alcohol (*S*,*S*)-**69b** (234 mg, 1.38 mmol), abs. NEt_3 (395 µL, 2.84 mmol), DMAP (ca. 5 mg) and BzCl (235 mg, 1.67 mmol) in abs. CH_2Cl_2 (6.0 mL) gave (*S*,*S*)-**65b** as colourless oil with 97% *ee* (302 mg, 80%).

$[a]_D^{20}$ = –87.0 (*c* = 1.00, $CHCl_3$).

HPLC (Daicel Chiracel OD, heptane/isopropanol 99:1, 0.5 mL*min^{-1}, 20 °C, 220 nm): t_R = 19.3 (*S*), 20.8 (*R*) min (97% *ee*).

(1*R*,5*R*)-5-(Ethoxycarbonyl)-cyclohex-2-enyl benzoate ((*R*,*R*)-65b)



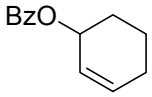
(*R*,*R*)-**65b**

The synthesis in analogy to the preparation of **65b** using alcohol (*R*,*R*)-**69b** (532 mg, 3.13 mmol), abs. NEt_3 (870 µL, 6.26 mmol), DMAP (ca. 10 mg) and BzCl (541 mg, 3.86 mmol) in abs. CH_2Cl_2 (14 mL) gave (*R*,*R*)-**65b** as colourless oil with 97% *ee* (712 mg, 83%).

$[a]_D^{20} = +90.3$ ($c = 1.00$, $CHCl_3$).

HPLC (Daicel Chiracel OD, heptane/isopropanol 99:1, 0.5 mL*min^{-1}, 20 °C, 220 nm): $t_R = 19.3$ (*S*), 20.8 (*R*) min (97% *ee*).

Cyclohex-2-enyl benzoate (77)



77

The synthesis in analogy to the preparation of **65a** using cyclohex-2-enol (2.07 g, 21.1 mmol), abs. NEt_3 (5.90 mL, 42.4 mmol), DMAP (ca. 10 mg) and BzCl (3.55 g, 25.3 mmol) in abs. CH_2Cl_2 (30 mL) gave benzoate **77** after column chromatography (silica gel, 5 × 20 cm, hexanes/EtOAc/NEt_3 18:1:1, F8-19) as colourless oil (3.86 g, 90%).

$C_{13}H_{14}O_2$ (202.24 g*mol^{-1}):

$R_f = 0.50$ (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.64$-1.74 (m, 1 H, CH_2), 1.78-1.93 (m, 2 H, CH_2), 1.93-2.21 (m, 3 H, CH_2), 5.51 (m_c, 1 H, 1-H), 5.84 (m_c, 1 H, C*H*CH), 6.00 (m_c, 1 H, CHC*H*), 7.43 (m_c, 2 H, Bz-*m*-H), 7.54 (m_c, 1 H, Bz-*p*-H), 8.06 (m_c, 2 H, Bz-*o*-H) ppm.

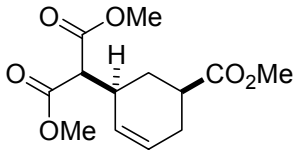
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 19.1 (CH_2), 25.1 (CH_2), 28.5 (CH_2), 68.7 (1-CH), 125.8 (CH), 128.4 (Bz-CH), 129.2 (Bz-CH), 130.9 (Bz-*i*-C), 132.9 (CH), 133.0 (CH), 166.3 (CO_2) ppm.

IR (KBr): $\tilde{\nu}$ = 3033m, 2939m, 2869m, 1965w, 1915w, 1712s, 1602m, 1491w, 1450s, 1395w, 1271s, 1171m, 1110s, 1062m, 1010m, 918s, 851w, 713s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 202 (17, M^+), 105 (100, $C_7H_5O^+$), 81 (25, $C_6H_9^+$), 41 (13).

Elemental analysis calcd. (%) for $C_{13}H_{14}O_2$: C 77.20, H 6.98; found: C 77.29, H 7.13.

cis-Methyl 5-[di-(methoxycarbonyl)-methyl]-cyclohex-3-enecarboxylate (79a)[148]



79a

In a Young tube benzoate **65a** (53.4 mg, 0.205 mmol), $Pd(PPh_3)_4$ (8.30 mg, 7.18 µmol) and PPh_3 (19.0 mg, 7.24 µmol) were stirred in abs. THF (1.0 mL) at r.t. After 20 min the solution was treated with the nucleophile, freshly prepared from NaH (12.8 mg, 0.535 mmol) and dimethyl malonate (98.7 mg, 0.747 mmol) in abs. THF (1.5 mL). The reaction mixture was heated under reflux for 15 h, cooled to r.t. and then partitioned between Et_2O (10 mL) and saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc 5:2, F9-13) afforded **79a** as colourless oil (55.4 mg, quant.).

$C_{13}H_{18}O_6$ (270.28 g*mol^{-1}):

$\boldsymbol{R_f}$ = 0.19 (hexanes/EtOAc 4:1).

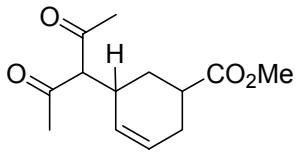
^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (q, *J*(H,H) = 12.1 Hz, 1 H, CH_2), 2.07 (d, *J*(H,H) = 9.7 Hz, 1 H, CH_2), 2.17 (m_c, 1 H, CH_2), 2.27 (m_c, 1 H, CH_2), 2.62 (m_c, 1 H, 2-H), 2.69 (m_c, 1 H, C*H*(CO_2CH_3)$_2$), 3.26 (d, *J*(H,H) = 8.6 Hz, 1 H, 5-H), 3.37 (s, 3 H, CO_2CH_3), 3.71 (s, 6 H, CH(CO_2CH_3)$_2$), 5.51 (d, *J*(H,H) = 10.4 Hz, 1 H, C*H*CH), 5.76 (m_c, 1 H, CHC*H*) ppm.

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 27.7 (2-CH_2), 29.4 (6-CH_2), 36.1 (5-CH), 39.4 (1-CH), 51.6 (CO_2CH_3), 52.4 ($CH(CO_2CH_3)_2$), 52.4 ($CH(CO_2CH_3)_2$), 55.4 ($CH(CO_2CH_3)_2$), 127.3 (*C*HCH), 127.4 (CH*C*H), 167.0 (CO_2), 168.5 (CO_2), 175.4 (CO_2) ppm.

IR (KBr): $\tilde{\nu}$ = 3004w, 2955w, 2849w, 1739s, 1439m, 1339m, 1255m, 1165m, 1023m, 850w, 706w, 461s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 270 (5, M^+), 239 (21, $[M-OCH_3]^+$), 238 (24), 210 (90, $C_{11}H_{14}O_4^+$), 148 (51), 178 (93), 150 (72), 119 (62), 91 (64), 79 (100).

Methyl 5-(2',4'-dioxopentan-3'-yl)-cyclohex-3-enecarboxylate (80a)



80a

A suspension of NaH (69.0 mg, 2.88 mmol) in abs. THF (4.0 mL) was carefully treated with acetyl acetone (671 mg, 6.64 mmol) at 0 °C. A solution of benzoate **65a** (480 mg, 1.85 mmol), $Pd(PPh_3)_4$ (70.0 mg, 60.5 µmol) and PPh_3 (150 mg, 0.572 mmol) in abs. THF (6.0 mL) was stirred for 15 min at r.t. and then added to the sodium salt of acetyl acetone. The reaction mixture was stirred at r.t. for 26 h. The thick yellow slurry was partitioned between Et_2O (20 mL) and saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 3:1, F25-45) afforded the product **80a** as light-yellow solid (420 mg, 96%). This consisted of a mixture of the *cis*-diastereomer (major) and the *trans*-diastereomer (minor) with a ratio of 73:27 according to ^1H NMR spectroscopy.

$C_{13}H_{18}O_4$ (238.28 g*mol^{-1}):

R_f = 0.54 (hexanes/EtOAc 2:1).

^1H NMR (400 MHz, $CDCl_3$, major *cis*-diastereomer): δ = 1.23 (q, *J*(H,H) = 12.3 Hz, 1 H, CH_2), 1.99 (m_c, 1 H, CH_2), 2.10-2.16 (m, 1 H, CH_2), 2.16 (s, 6 H, $COCH_3$), 2.25 (m_c, 1 H, CH_2), 2.61 (m_c, 1 H, 5-H), 3.08 (m_c, 1 H, 1-H), 3.57 (d, *J*(H,H) = 9.7 Hz, 1 H, 3'-H), 3.64 (s, 3 H, OCH_3), 5.35 (d, *J*(H,H) = 10.6 Hz, 1 H, C*H*CH), 5.76 (m_c, 1 H, CHC*H*) ppm.

^{1}H NMR (400 MHz, $CDCl_3$, characteristic signals of the minor *trans*-diastereomer): δ = 2.17 (s, 6 H, $COCH_3$), 3.65 (s, 3 H, OCH_3), 5.46 (m_c, 1 H, C*H*CH) ppm.

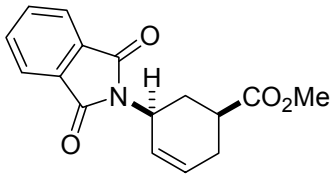
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, major *cis*-diastereomer): δ = 27.7 (CH_2), 29.6 (CH_2), 30.0 ($COCH_3$), 30.2 ($COCH_3$), 36.1 (5-CH), 39.3 (1-CH), 51.6 (OCH_3), 73.9 (3'-CH), 127.3 (*C*HCH), 127.7 (CH*C*H), 175.3 (CO_2), 203.1 (*C*OCH_3), 203.3 (*C*OCH_3) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, minor *trans*-diastereomer): δ = 27.2 (CH_2), 28.1 (CH_2), 29.5 ($COCH_3$), 30.5 ($COCH_3$), 33.7 (5-CH), 35.7 (1-CH), 51.7 (OCH_3), 73.6 (3'-CH), 126.7 (*C*HCH), 127.9 (CH*C*H), 175.2 (CO_2), 202.9 (*C*OCH_3), 203.1 (*C*OCH_3) ppm.

IR (KBr): $\tilde{\nu}$ = 2950m, 1731s, 1434m, 1360s, 1252s, 1168s, 1060w, 1002w, 960w, 888w, 701m, 624m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 238 (2, M^+), 195 (100, $[M–COCH_3]^+$), 135 (74), 117 (55), 79 (47).

cis-Methyl 5-(1',3'-dioxoisoindolin-2'-yl)-cyclohex-3-enecarboxylate (81a)



81a

In a Young tube benzoate **65a** (75.0 mg, 0.288 mmol), $Pd(PPh_3)_4$ (7.00 mg, 6.06 μmol) and PPh_3 (23.0 mg, 8.76 μmol) were stirred in abs. THF (2.0 mL) at r.t. After 20 min potassium phthalimide (152 mg, 0.820 mmol) was added and the mixture heated under reflux for 8 h. The thick yellow reaction mixture was cooled to r.t. and partitioned between Et_2O (10 mL) and saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 4:1, F24-36) afforded **81a** as colourless solid (82.2 mg, quant.).

$C_{16}H_{15}NO_4$ (285.29 g*mol^{-1}):

m.p. 108-110 °C.

R_f = 0.15 (hexanes/EtOAc 4:1).

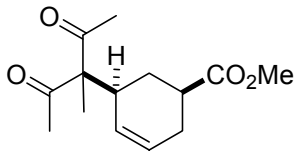
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15-2.24 (m, 1 H, 6-H), 2.34 (t, *J*(H,H) = 12.4 Hz, 1 H, 2-H), 2.38-2.45 (m, 2 H, 2-H and 6-H), 2.81 (m_c, 1 H, 1-H), 3.69 (s, 3 H, CH_3), 4.98 (m_c, 1 H, 5-H), 5.59 (dt, *J*(H,H) = 10.1, 1.8 Hz, 1 H, C*H*CH), 5.80 (m_c, 1 H, CHC*H*), 7.71 (dd, *J*(H,H) = 5.6, 3.0 Hz, 2 H, Ar-H), 7.83 (dd, *J*(H,H) = 5.5, 3.0 Hz, 2 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 27.3 (2-CH_2), 29.2 (6-CH_2), 39.5 (1-CH), 47.5 (5-CH), 52.0 (CH_3), 123.4 (4-CH), 125.8 (CH), 128.1 (CH), 132.1 (Ar-C), 134.1 (CH), 168.0 (CON), 174.8 (CO_2) ppm.

IR (KBr): $\tilde{\nu}$ = 3195w, 3040w, 2995w, 1712s, 1462m, 1385s, 1306s, 1214s, 1136m, 1109m, 1056m, 1006m, 934m, 864w, 797w, 718s, 642m, 528m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 285 (5, M^+), 254 (15, $[M–OCH_3]^+$), 226 (32, $[M–COCH_3]^+$), 225 (90), 148 (51), 138 (100, $[M–C_8H_4NO_2]^+$), 104 (53), 78 (62).

cis-Methyl 5-(3'-methyl-2',4'-dioxopentan-3'-yl)-cyclohex-3-enecarboxylate (83a)



83a

In a Young tube NaH (78.8 mg, 3.29 mmol) in abs. THF (5.0 mL) was treated with 3-methylpentane-2,4-dione (520 mg, 4.56 mmol) resulting in a thick colourless suspension. A solution of benzoate **65a** (329 mg, 1.27 mmol), $Pd(PPh_3)_4$ (43.9 mg, 37.9 μmol) and PPh_3 (99.5 mg, 37.9 μmol) in abs. THF (5.0 mL) was stirred for 15 min at r.t. and then added to the sodium salt of 3-methylpentane-2,4-dione. The resulting mixture was heated at 75 °C for 17 h. After the reaction had been cooled to r.t., the thick yellow slurry was partitioned between Et_2O (20 mL) and saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 4:1, F15-25) afforded the product **83a** as light-yellow solid (320 mg, quant.).

$C_{14}H_{20}O_4$ (252.31 g*mol^{-1}):

m.p. 54-55 °C.

R_f = 0.16 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3 H, 3'-CH_3), 1.75-1.84 (m, 1 H), 2.08 (s, 3 H, $COCH_3$), 2.06-2.19 (m, 2 H), 2.10 (s, 3 H, $COCH_3$), 2.22-2.32 (m, 1 H), 2.60 (m_c, 1 H), 3.40 (m_c, 1 H), 3.66 (s, 3 H, OCH_3), 5.22 (d, *J*(H,H) = 11.1 Hz, 1 H, C*H*CH), 5.77 (m_c, 1 H, CHC*H*) ppm.

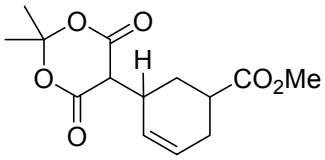
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 13.7 (3'-CH_3), 26.8 (CH_2), 27.0 (CO*C*H_3), 27.0 (CO*C*H_3), 27.8 (CH_2), 39.4 (CH), 39.7 (CH), 51.9 (OCH_3), 70.7 (3'-C), 127.1 (*C*HCH), 128.3 (CH*C*H), 175.7 (CO_2), 206.2 (*C*OCH_3), 206.6 (*C*OCH_3) ppm.

IR (KBr): $\tilde{\nu}$ = 3031s, 2939s, 2856s, 1737s, 1694s, 1445s, 1317m, 1221s, 1129s, 1092m, 956m, 892w, 835m, 776w, 738m, 650m cm^{-1}.

MS (FAB, NBA): *m/z* (%) = 307 (24, $[M+H]^+$), 209 (18, $[M-COCH_3]^+$), 154 (100), 79 (38, $C_6H_7^+$).

Elemental analysis calcd. (%) for $C_{14}H_{20}O_4$: C 66.65, H 7.99; found: C 66.41, H 8.00.

Methyl 5-(2',2'-dimethyl-4',6'-dioxo-1',3'-dioxan-5'-yl)-cyclohex-3-enecarboxylate (88a)



88a

In a Young tube benzoate **65a** (72.8 mg, 0.280 mmol), $Pd(PPh_3)_4$ (9.60 mg, 8.31 μmol) and PPh_3 (34.0 mg, 0.129 mmol) in abs. DMF (4.0 mL) were stirred for 15 min at r.t. The solution was treated with the sodium salt of Meldrum's acid in DMF (3.0 mL), which had been freshly prepared from NaH (20.0 mg, 0.835 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (144 mg, 0.998 mmol) at 0 °C. The resulting mixture was stirred for 20 h at 70 °C. The thick yellow reaction mixture was cooled to r.t. and then partitioned between Et_2O (15 mL) and saturated aqueous NH_4Cl solution (15 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent purification of the crude product by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 2:1, F19-30) afforded **88a** as off-white solid (26.0 mg, 33%). This consisted of a mixture of the *cis*-diastereomer (major) and the *trans*-diastereomer (minor) in a ratio of 75:25 according to ^{1}H NMR spectroscopy.

$C_{14}H_{18}O_6$ (282.29 g*mol^{-1}):

m.p. 111-112 °C.

R_f = 0.22 (hexanes/EtOAc 2:1).

^{1}H NMR (500 MHz, $CDCl_3$, major *cis*-diastereomer): δ = 1.76 (s, 3 H, C(C*H*$_3$)(CH$_3$)), 1.78 (s, 3 H, C(CH$_3$)(C*H*$_3$)), 1.96 (q, *J*(H,H) = 12.1 Hz, 1 H, CH$_2$), 2.09 (m$_c$, 1 H, CH$_2$), 2.30-2.35 (m, 2 H, CH$_2$), 2.68 (m$_c$, 1 H, 1-H), 3.38 (m$_c$, 1 H, 5-H), 3.56 (d, *J*(H,H) = 3.2 Hz, 1 H, 5'-H), 3.67 (s, 3 H, OCH$_3$), 5.52 (d, *J*(H,H) = 10.3 Hz, 1 H, C*H*CH), 5.83 (m$_c$, 1 H, CHC*H*) ppm.

^{1}H NMR (500 MHz, $CDCl_3$, characteristic signals of the minor *trans*-diastereomer): δ = 1.73 (s, 6 H, C(CH$_3$)$_2$), 2.92 (m$_c$, 1 H, 5-H), 3.51 (d, *J*(H,H) = 3.6 Hz, 1 H, 5'-H), 3.71 (s, 3 H, OCH$_3$) ppm.

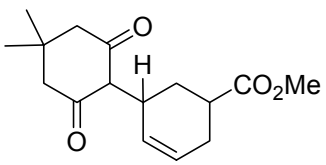
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, major *cis*-diastereomer): δ = 27.4 (C(*C*H$_3$)(CH$_3$)), 27.5 (CH$_2$), 28.0 (CH$_2$), 28.4 (C(CH$_3$)(*C*H$_3$)), 36.4 (5-CH), 39.7 (1-CH), 50.0 (5'-CH), 51.9 (OCH$_3$), 105.0 (*C*(CH$_3$)$_2$), 127.1 (*C*HCH), 127.5 (CH*C*H), 164.3 (CO$_2$), 164.3 (CO$_2$), 175.4 (*C*O$_2$CH$_3$) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, characteristic signals of the minor *trans*-diastereomer): δ = 26.1 (CH$_2$), 27.4 (CH$_2$), 27.8 (C(*C*H$_3$)(CH$_3$)), 28.5 (C(CH$_3$)(*C*H$_3$)), 37.1 (1-CH), 50.3 (5'-CH), 52.1 (OCH$_3$), 126.3 (*C*HCH), 127.9 (CH*C*H) ppm.

IR (KBr): $\tilde{\nu}$ = 3007m, 2950m, 2875m, 1778s, 1735s, 1604w, 1429m, 1388m, 1301s, 1167s, 1068m, 994m, 933m, 863m, 807w, 706s cm^{-1}.

MS (FAB, NBA): *m/z* (%) = 283 (33, [M+H]$^+$), 225 (100), 137 (71), 79 (51, $C_6H_7^+$), 39 (28).

Methyl 5-(4',4'-dimethyl-2',6'-dioxocyclohexyl)-cyclohex-3-enecarboxylate (89a)



89a

In a Young tube a suspension of NaH (74.0 mg, 3.09 mmol) in DMF (12 mL) was treated with 5,5-dimethylcyclohexane-1,3-dione (490 mg, 4.29 mmol) at r.t. To the resulting turbid mixture a solution of benzoate **65a** (307 mg, 1.18 mmol), Pd(PPh$_3$)$_4$ (43.0 mg, 37.2 μmol) and PPh$_3$ (93.0 mg, 35.5 μmol) in abs. DMF (10 mL) was added. The reaction mixture was stirred 30 min at r.t. and then 20 h at 70 °C. The thick yellow reaction mixture was cooled to r.t. and

partitioned between Et_2O (20 mL) and saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (silica gel, 3 × 25 cm, hexanes/EtOAc 1:1, F8-18) gave **89a** as off-white solid (325 mg, 98%). This consisted of a mixture of the *cis*-diastereomer (major) and the *trans*-diastereomer (minor) in a ratio of 75:25 according to ^{1}H NMR spectroscopy.

$C_{16}H_{22}O_4$ (278.34 g*mol^{-1}):

m.p. 154-155 °C.

R_f = 0.36 (hexanes/EtOAc 1:1).

^{1}H NMR (500 MHz, $CDCl_3$, major *cis*-diastereomer): δ = 1.05 (s, 3 H, C(CH_3)(CH_3)), 1.07 (s, 3 H, C(CH_3)(CH_3)), 1.50 (q, *J*(H,H) = 12.5 Hz, 1 H, CH_2), 1.97 (m_c, 1 H), 2.19 (m_c, 1 H, CH_2), 2.26 (br s, 2 H), 2.30 (m_c, 1 H), 2.34 (br s, 1 H, CH_2), 2.37 (m_c, 1 H, CH_2), 2.64-2.78 (m, 2 H, CH_2), 3.69 (s, 3 H, OCH_3), 3.85 (m_c, 1 H, 5-H), 5.78 (d, *J*(H,H) = 10.3 Hz, 1 H, C*H*CH), 6.08 (m_c, 1 H, CHC*H*) ppm.

^{1}H NMR (500 MHz, $CDCl_3$, minor *trans*-diastereomer): δ = 0.99 (d, *J*(H,H) = 9.4 Hz, 1 H), 1.09 (s, 3 H, C(CH_3)(CH_3)), 1.09 (s, 3 H, C(CH_3)(CH_3)), 1.85 (m_c, 1 H, CH_2), 2.26 (br s, 2 H), 2.31 (m_c, 1 H), 2.32 (br s, 1 H, CH_2), 2.39 (m_c, 1 H, CH_2), 2.42 (m_c, 1 H, CH_2), 2.47 (m_c, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 3.77 (m_c, 1 H, 5-H), 6.08 (m_c, 1 H, C*H*CH), 6.19 (m_c, 1 H, CHC*H*) ppm.

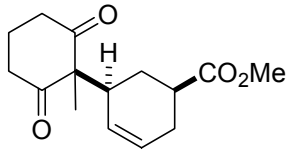
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, major *cis*-diastereomer): δ = 27.6 (CH_2), 27.9 (C(*C*H_3)(CH_3)), 28.7 (C(CH_3)(*C*H_3)), 30.5 (CH_2), 30.7 (5-CH), 31.9 (*C*(CH_3)$_2$), 39.5 (CH), 43.0 (CH_2), 50.4 (CH_2), 51.9 (OCH_3), 130.4 (*C*HCH), 130.5 (CH*C*H), 171.0 (CO), 197.4 (CO) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, minor *trans*-diastereomer): δ = 27.5 (CH_2), 27.9 (C(*C*H_3)CH_3), 28.7 (C(CH_3)(*C*H_3)), 29.6 (5-CH), 31.2 (CH_2), 31.8 (*C*(CH_3)$_2$), 36.4 (CH), 43.4 (CH_2), 50.6 (CH_2), 52.0 (OCH_3), 130.3 (*C*HCH), 131.8 (CH*C*H), 171.9 (CO_2), 197.7 (CO) ppm.

IR (KBr): $\tilde{\nu}$ = 2955m, 2612m, 1728s, 1564s, 1376s, 1342s, 1254m, 1169s, 1062m, 1023m, 947w, 886w, 812w, 755w cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 278 (34, M^+), 237 (7, [M–OCH_3]$^+$), 217 (100), 194 (17), 134 (21), 117 (8), 79 (17).

cis-Methyl 5-(1'-methyl-2',6'-dioxocyclohexyl)-cyclohex-3-enecarboxylate (90a)[105]



90a

In a Young tube benzoate **65a** (295 mg, 1.13 mmol), $Pd(PPh_3)_4$ (40.0 mg, 34.6 μmol) and PPh_3 (90.0 mg, 34.3 μmol) in abs. DMF (10 mL) were stirred for 15 min at r.t. A solution of the sodium salt of 2-methylcyclohexane-1,3-dione in DMF (8.0 mL), which had freshly been prepared from NaH (70.8 mg, 2.96 mmol) and 2-methylcyclohexane-1,3-dione (515 mg, 4.08 mmol) at 0 °C, was added and the resulting mixture stirred at 70 °C for 21 h. The thick yellow reaction mixture was cooled to r.t. and partitioned between Et_2O (20 mL) and saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 1:1, F8-18) afforded **90a** as light-yellow oil, which solidified at 4 °C (287 mg, 96%).

$C_{15}H_{20}O_4$ (264.32 g*mol^{-1}):

m.p. 84-86 °C.

R_f = 0.36 (hexanes/EtOAc 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (s, 3 H, 1'-CH_3), 1.44 (m_c, 1 H, 6-H), 1.71-1.79 (m, 2 H, 6-H and 4'-H), 2.09-2.16 (m, 1 H, 4'-H), 2.16-2.31 (m, 2 H, 2-H), 2.54-2.59 (m, 1 H, 1-H), 2.61-2.66 (m, 2 H, 3'-H and 5'-H), 2.70-2.93 (m, 2 H, 3'-H and 5'-H), 3.01-3.12 (m, 1 H, 5-H), 3.67 (s, 3 H, OCH_3), 5.29 (d, J(H,H) = 9.8 Hz, 1 H, 4-H), 5.80 (m_c, 1 H, 3-H) ppm.

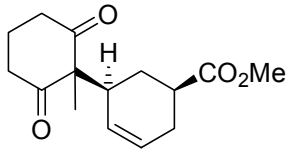
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 11.2 (1'-CH_3), 18.3 (4'-CH_2), 27.0 (6-CH_2), 27.5 (2-CH_2), 37.8 (5'-CH_2), 38.2 (3'-CH_2), 39.9 (1-CH), 42.2 (5-CH), 52.0 (OCH_3), 77.4 (1'-C), 124.8 (4-CH), 128.6 (3-CH), 175.2 (CO_2), 208.6 (CO), 209.2 (CO) ppm.

IR (KBr): $\tilde{\nu}$ = 3010m, 2961s, 2844m, 1724s, 1436s, 1370m, 1319s, 1254s, 1209s, 1092m, 961m, 889m, 825m, 738w, 683m cm^{-1}.

MS (FAB, NBA): *m/z* (%) = 265 (62, $[M+H]^+$), 233 (15, $[M-OCH_3]^+$), 208 (18), 139 (78, $[M-C_7H_9O_2]^+$), 127 (94), 79 (100, $C_6H_7^+$), 39 (71).

Elemental analysis calcd. (%) for $C_{15}H_{20}O_4$: C 68.16, H 7.63; found: C 68.07, H 7.40.

(1*S*,5*S*)-Methyl 5-(1'-methyl-2',6'-dioxocyclohexyl)-cyclohex-3-enecarboxylate ((*S*,*S*)-90a))[97]



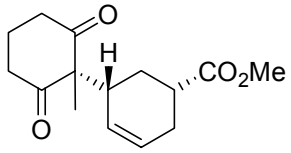
(*S*,*S*)-**90a**

$[Pd(C_3H_5)Cl]_2$ (2.10 mg, 5.47 μmol) and ligand (*S*,*S*)-**93** (811 mg, 16.4 μmol) were stirred in CH_2Cl_2 (1.0 mL) at r.t. for 30 min. 2-Methylcyclohexane-1,3-dione (109 mg, 0.863 mmol) was added to a suspension of NaH (18.0 mg, 0.769 mmol) and tetrahexylammonium bromide (334 mg, 0.769 mmol) in abs. CH_2Cl_2 (2.0 mL) and DMF (0.5 mL) and the resulting mixture was treated with the catalyst solution. After 15 min at r.t. benzoate **65a** (60.0 mg, 0.231 mmol) was added. The thick yellow solution was stirred at r.t. for 24 h, diluted with Et_2O (10 mL) and ice-cold saturated aqueous NH_4Cl solution (20 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 3:1, F15-27) to give (*S*,*S*)-**90a** as light-yellow oil with 96% *ee* (39.7 mg, 65%).

$[a]_D^{20} = -30.0$ (c = 1.00, $CHCl_3$).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 98:2, 0.5 mL*min^{-1}, 30 °C, 220 nm): t_R = 51.7 (*S*), 56.3 (*R*) min (96% *ee*).

(1*R*,5*R*)-Methyl 5-(1'-methyl-2',6'-dioxocyclohexyl)-cyclohex-3-enecarboxylate ((*R*,*R*)-90a))



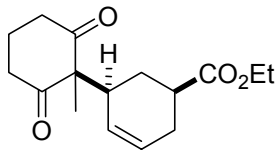
(*R*,*R*)-**90a**

In analogy to the preparation of (*S*,*S*)-**90a** the reaction of benzoate **65a** using ligand (*R*,*R*)-**93** gave (*R*,*R*)-**90a** as light-yellow oil with 96% *ee* (42.8 mg, 70%).

$[a]_D^{20}$ = +30.0 (*c* = 1.00, $CHCl_3$).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 98:2, 0.5 mL*min^{-1}, 30 °C, 220 nm): t_R = 51.7 (*S*), 56.3 (*R*) min (96% *ee*).

cis-Ethyl 5-(1'-methyl-2',6'-dioxocyclohexyl)-cyclohex-3-enecarboxylate (90b)



90b

In analogy to the preparation of **90a** a solution of benzoate **65b** (149 mg, 0.543 mmol), $Pd(PPh_3)_4$ (20.0 mg, 17.3 μmol) and PPh_3 (40.0 mg, 152 μmol) in abs. DMF (7.0 mL) was treated with the sodium salt of 2-methylcyclohexane-1,3-dione in DMF (5.0 mL), freshly prepared from NaH (33.8 mg, 1.41 mmol) and 2-methylcyclohexane-1,3-dione (247 mg, 1.95 mmol). Purification of the crude product by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 2:1, F19-30) afforded the product **90b** as yellow oil (123 mg, 81%).

$C_{16}H_{22}O_4$ (278.34 g*mol^{-1}):

R_f = 0.63 (hexanes/EtOAc 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, 1'-CH_3), 1.24 (t, *J*(H,H) = 7.2 Hz, 3 H, CH_2CH_3), 1.38 (m_c, 1 H, 6-H), 1.61-1.79 (m, 2 H, 6-H and 4'-H), 2.09-2.31 (m, 3 H, 2-H and 4'-H), 2.50-2.66 (m, 3 H, 1-H, 3'-H and 5'-H), 2.71-2.93 (m, 2 H, 3'-H and 5'-H), 3.01-3.12 (m, 1 H, 5-H), 4.07 (q, *J*(H,H) = 7.2 Hz, 2 H, CH_2CH_3), 5.28 (d, *J*(H,H) = 10.8 Hz, 1 H, 4-H), 5.79 (m_c, 1 H, 3-H) ppm.

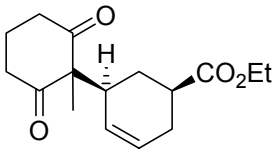
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 11.5 (1'-CH_3), 14.3 (CH_2CH_3), 18.3 (4'-CH_2), 27.0 (6-CH_2), 27.5 (2-CH_2), 37.8 (5'-CH_2), 38.2 (3'-CH_2), 40.0 (1-CH), 42.3 (5-CH), 60.8 (CH_2CH_3), 70.1 (1'-C), 124.8 (4-CH), 128.7 (3-CH), 174.8 (CO_2), 208.6 (CO), 209.2 (CO) ppm.

IR (KBr): $\tilde{\nu}$ = 3032m, 2945s, 1726s, 1693s, 1441m, 1381m, 1258m, 1223m, 1186s, 1102m, 1062m, 1022s, 895m, 858m, 743w, 684m, 632m cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 317 (49, $[M+K]^+$), 279 (85, $[M+H]^+$), 233 (17, $[M-OCH_2CH_3]^+$), 153 (78, $[M-C_7H_9O_2]^+$), 79 (48, $C_6H_7^+$), 38 (100).

Elemental analysis calcd. (%) for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 68.87, H 7.97.

(1*S*,5*S*)-Ethyl 5-(1'-methyl-2',6'-dioxocyclohexyl)-cyclohex-3-enecarboxylate ((*S*,*S*)-90b)



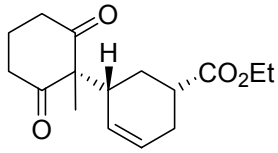
(*S*,*S*)-**90b**

In analogy to the preparation of (*S*,*S*)-**90a** benzoate **65b** (200 mg, 0.719 mmol) was reacted with $[Pd(C_3H_5)Cl]_2$ (6.60 mg, 18.1 μmol), ligand (*S*,*S*)-**93** (37.0 mg, 53.6 μmol), 2-methylcyclohexane-1,3-dione (326 mg, 2.58 mmol), NaH (45.0 mg, 1.88 mmol) and tetrahexylammonium bromide (811 mg, 1.86 mmol) in abs. CH_2Cl_2 (10 mL) and DMF (0.5 mL). The crude product was purified by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 2:1, F10-18) to give (*S*,*S*)-**90b** as light-yellow oil with 96% *ee* (167 mg, 83%).

$[a]_D^{20} = -30.4$ ($c = 1.00$, $CHCl_3$).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 98:2, 0.8 mL*min^{-1}, 30 °C, 220 nm): t_R = 28.1 (*S*) , 34.8 (*R*) min (96% *ee*).

(1*R*,5*R*)-Ethyl 5-(1'-methyl-2',6'-dioxocyclohexyl)-cyclohex-3-enecarboxylate ((*R*,*R*)-90b)



(*R*,*R*)-**90b**

In analogy to the preparation of (*S*,*S*)-**90a** benzoate **65b** (350 mg, 1.28 mmol) was reacted with $[Pd(C_3H_5)Cl]_2$ (11.4 mg, 31.2 μmol), ligand (*R*,*R*)-**93** (64.0 mg, 92.7 μmol), 2-methylcyclohexane-1,3-dione (575 mg, 4.56 mmol), NaH (78.0 mg, 3.26 mmol) and tetrahexylammonium bromide (1.42 g, 3.27 mmol) in abs. CH_2Cl_2 (15 mL) and DMF (0.6 mL). The crude product was purified by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 2:1, F11-18) to give (*R*,*R*)-**90b** as light-yellow oil with 96% *ee* (310 mg, 87%).

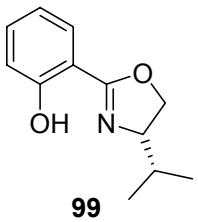
$[a]_D^{20} = +33.5$ ($c = 1.00$, $CHCl_3$).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 98:2, 0.8 mL*min^{-1}, 30 °C, 220 nm): $t_R = 28.1$ (*S*), 34.8 (*R*) min (96% *ee*).

7.4 Bis(*N*-sulfonylamino)phosphine-Oxazoline Ligands

7.4.1 Oxazolines

(S)-2-(4'-Isopropyl-4',5'-dihydrooxazol-2'-yl)-phenol (99)[110]



99

(*S*)-Valinol (**103**, 2.10 g, 20.4 mmol), 2-hydroxybenzonitrile (**102**, 2.02 g, 17.0 mmol) and $ZnCl_2$ (28.5 mg, 0.210 mmol) were dissolved in abs. toluene (30 mL) and refluxed for 72 h. After the reaction mixture had been cooled to r.t. it was filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography

(silica gel, 3 × 20 cm, hexanes/EtOAc 7:1, F16-27) afforded **99** as colourless oil (3.25 g, 93%).

$C_{12}H_{15}NO_2$ (205.35 g*mol^{-1}):

$\boldsymbol{R_f}$ = 0.70 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.95 (d, J(H,H) = 6.8 Hz, 3 H, CH(CH_3)(CH$_3$)), 1.02 (d, J(H,H) = 6.8 Hz, 3 H, CH(CH$_3$)(CH_3)), 1.81 (q, J(H,H) = 6.8 Hz, 1 H, CH(CH$_3$)$_2$), 4.14 (m$_c$, 2 H, Ox-5'-H), 4.44 (m$_c$, 1 H, Ox-4'-H), 6.87 (td, J(H,H) = 7.6, 1.1 Hz, 1 H, Ar-6-H), 6.97 (d, J(H,H) = 7.9 Hz, 1 H, Ar-4-H), 7.37 (td, J(H,H) = 7.9, 1.7 Hz, 1 H, Ar-5-H), 7.64 (dd, J(H,H) = 7.8, 1.6 Hz, 1 H, Ar-3-H), 12.31 (s, 1 H, OH) ppm.

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ=18.4 (CH(CH_3)(CH$_3$)), 18.5 (CH(CH$_3$)(CH_3)), 33.1 (CH(CH$_3$)$_2$), 70.0 (Ox-5'-CH$_2$), 71.6 (Ox-4'-CH), 110.8 (Ar-2-C), 116.6 (Ar-6-CH), 118.5 (Ar-4-CH), 128.0 (Ar-3-CH), 133.2 (Ar-5-CH), 160.0 (Ar-1-C), 165.1 (Ox-2'-C) ppm.

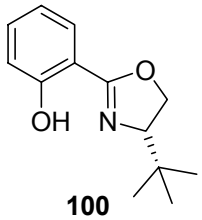
IR (NaCl): $\tilde{\nu}$ = 3449s, 2962m, 1643s, 1492m, 1365m, 1310w, 1259m, 1232w, 1154w, 1127w, 1067m, 959m, 755s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 205 (58, M$^+$), 162 (100, [M–C$_3$H$_7$]$^+$), 134 (26), 107 (17).

$[a]_D^{20}$ = –33.0 (*c* = 1.20, $CHCl_3$).

Elemental analysis calcd. (%) for $C_{12}H_{15}NO_2$: C 70.22, H 7.37, N 6.82, O 15.59; found: C 70.36, H 7.40, N 7.07, O 15.52.

(*S*)-2-(4'-*tert*-Butyl-4',5'-dihydrooxazol-2'-yl)-phenol (100)[110]



100

The oxazoline synthesis was accomplished in analogy to the preparation of **99** using (*S*)-*tert*-leucinol (**104**, 2.67 g, 22.8 mmol), 2-hydroxybenzonitrile (**102**, 2.26 g, 19.0 mmol) and $ZnCl_2$ (64.0 mg, 0.480 mmol) in toluene (30 mL). Purification of the crude product by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 15:1, F12-22) gave oxazoline **100** as colourless oil, which solidified at 4 °C (4.09 g, 98%).

$C_{13}H_{17}NO_2$ (219.28 g*mol^{-1}):

m.p. 27 °C.

R_f = 0.70 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (s, 9 H, CH_3), 4.12 (dd, *J*(H,H) = 10.0, 8.3 Hz, 1 H, Ox-5'-H), 4.22 (t, *J*(H,H) = 8.3 Hz, 1 H, Ox-4'-H), 4.35 (dd, *J*(H,H) = 10.0, 8.3 Hz, 1 H, Ox-5'-H), 6.87 (t, *J*(H,H) = 8.3 Hz, 1 H, Ar-6-H), 7.01 (d, *J*(H,H) = 8.3 Hz, 1 H, Ar-4-H), 7.37 (tt, *J*(H,H) = 7.8, 1.7 Hz, 1 H, Ar-5-H), 7.63 (dd, *J*(H,H) = 7.8, 1.7 Hz, 1 H, Ar-3-H), 12.41 (s, 1 H, OH) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 25.9 (C(CH_3)$_3$), 33.9 (C(CH_3)$_3$), 68.2 (Ox-4'-CH), 75.1 (Ox-5'-CH_2), 110.7 (Ar-2-C), 116.6 (Ar-6-CH), 118.5 (Ar-4-CH), 128.1 (Ar-3-CH), 133.4 (Ar-5-CH), 160.0 (Ar-1-C), 165.0 (Ox-2'-C) ppm.

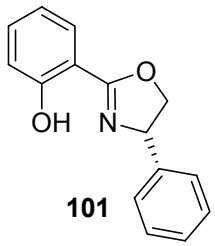
IR (NaCl): $\tilde{\nu}$ = 3425s, 2961s, 2870s, 1643s, 1492s, 1365s, 1260s, 1234m, 1154w, 1127w, 1073m, 1031m, 957m, 821m, 759s, 666m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 219 (46, M^+), 162 (100, $[M-C_4H_9]^+$), 134 (30), 107 (20).

$[a]_D^{20}$ = –19.2 (*c* = 1.00, $CHCl_3$).

Elemental analysis calcd. (%) for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39, O 14.59; found: C 71.48, H 7.81, N 6.42, O 14.64.

(*S*)-2-(4'-Phenyl-4',5'-dihydrooxazol-2'-yl)-phenol (101)[110]



101

The oxazoline synthesis was accomplished in analogy to the preparation of **99** using (*S*)-phenylglycinol (**105**, 1.30 g, 10.2 mmol), 2-hydroxybenzonitrile (**102**, 1.01 g, 8.52 mmol) and $ZnCl_2$ (28.5 mg, 0.210 mmol) in toluene (15 mL). Purification of the crude product by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 7:1, F7-14) afforded product **101** as colourless oil, which solidified at 4 °C (1.94 g, 95%).

$C_{15}H_{13}NO_2$ (239.27 g*mol^{-1}):

m.p. 29-33 °C.

R_f = 0.66 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.25 (t, J(H,H) = 8.3 Hz, 1 H, Ox-4'-H), 4.80 (dd, J(H,H) = 10.1, 8.3 Hz, 1 H, Ox-5'-H), 5.47 (dd, J(H,H) = 10.1, 8.3 Hz, 1 H, Ox-5'-H), 6.29 (t, J(H,H) = 7.8 Hz, 1 H, Ar-H), 7.06 (d, J(H,H) = 8.3 Hz, 1 H, Ar-H), 7.27-7.46 (m, 6 H, Ar-H), 7.73 (d, J(H,H) = 8.1 Hz, 1 H, Ar-H), 12.16 (s, 1 H, OH) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 69.0 (Ox-4'-CH), 74.2 (Ox-5'-CH_2), 110.6 (Ar-2-C), 117.0 (Ar-CH), 118.9 (Ar-CH), 126.6 (Ar-CH), 128.0 (Ar-CH), 128.4 (Ar-CH), 129.0 (Ar-CH), 133.8 (Ar-CH), 141.7 (Ph-*i*-C), 160.2 (Ar-1-C), 166.4 (Ox-2'-C) ppm.

IR (KBr): $\tilde{\nu}$ = 3266m, 3059m, 2917m, 1720w, 1640s, 1533s, 1485s, 1443s, 1313m, 1270m, 1179w, 1104s, 1028s, 920w, 760m, 699s, 639m, 595m cm^{-1}.

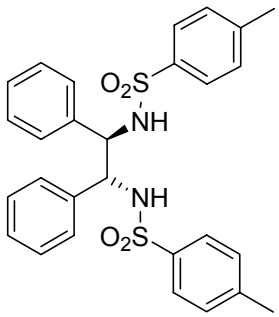
MS (EI, 70 eV): *m/z* (%) = 239 (100, M^+), 209 (21), 180 (16), 148 (45), 121 (44), 91 (35), 39 (9).

$[a]_D^{20}$ = +85.5 (c = 1.00, $CHCl_3$).

Elemental analysis calcd. (%) for $C_{15}H_{13}NO_2$: C 75.30, H 5.48, N 5.85, O 13.37; found: C 77.29, H 5.42, N 6.04, O 13.37.

7.4.2 Sulfonyldiamines

(1*R*,2*R*)-1,2-*N*,*N*'-Bis-(4'-toluenesulfonylamino)-1,2-diphenylethane ((*R*,*R*)-106)[108]



(*R*,*R*)-**106**

A solution of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine ((*R*,*R*)-**108**, 300 mg, 1.42 mmol) in abs. CH_2Cl_2 (5.0 mL) was treated with NEt(*i*Pr)$_2$ (1.10 mL, 6.43 mmol) at 0 °C. After the mixture had been cooled to –40 °C and stirred for 15 min, *p*-TsCl (540 mg, 2.83 mmol) was added. The reaction was allowed to warm to r.t. and stirred for 3 h at this temperature. It was

then quenched by the addition of 1 M HCl (30 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. After evaporation of the solvent (*R*,*R*)-**106** was obtained as colourless solid (689 mg, 94%).

$C_{28}H_{28}N_2O_4S_2$ (520.66 g*mol^{-1}):

m.p. 89 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 6 H, CH_3), 4.45 (dd, *J*(H,H) = 4.6, 2.5 Hz, 2 H, CH), 5.29 (m_c, 2 H, NH), 6.63 (d, *J*(H,H) = 8.4 Hz, 4 H, Ar-H), 6.97 (t, *J*(H,H) = 7.6 Hz, 4 H, Ph-*m*-H), 7.03 (m_c, 2 H, Ph-*p*-H), 7.08 (d, *J*(H,H) = 8.1 Hz, 4 H, Ar-H), 7.50 (d, *J*(H,H) = 8.3 Hz, 4 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 21.6 (CH_3), 62.3 (CH), 127.3 (Ar-CH), 127.7 (Ar-CH), 127.9 (Ar-CH), 128.2 (Ar-CH), 129.5 (Ar-CH), 136.4 (*p*Tol-*i*-C), 137.0 (*p*Tol-*p*-C), 143.4 (Ph-*i*-C) ppm.

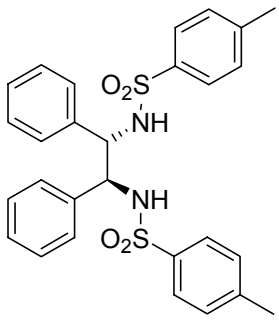
IR (KBr): $\tilde{\nu}$ = 3031w, 1597m, 1457s, 1328s, 1306m, 1221w, 1197m, 1159s, 1083s, 1063s, 914m, 814s, 700s, 669s cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 559 (50, $[M+K]^+$), 521 (22, $[M+H]^+$), 350 (100, $[M-C_7H_8NO_2S]^+$), 260 (42), 195 (24), 91 (61).

$[a]_D^{20}$ = +39.1 (*c* = 0.95, $CHCl_3$).

Elemental analysis calcd. (%) for $C_{28}H_{28}N_2O_4S_2$: C 64.59, H 5.42, N 5.38; found: C 64.40, H 5.30, N 5.27.

(1*S*,2*S*)-1,2-*N*,*N*'-Bis-(4'-toluenesulfonylamino)-1,2-diphenylethane ((*S*,*S*)-106)[108]

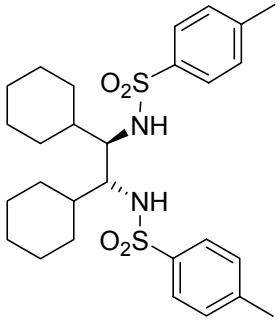


(*S*,*S*)-**106**

In analogy to the preparation of (*R*,*R*)-**106** the reaction of (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine ((*S*,*S*)-**108**, 100 mg, 0.473 mmol), NEt(*i*Pr)$_2$ (364 µL, 2.13 mmol) and *p*-TsCl (180 mg, 946 µmol) in abs. CH_2Cl_2 (2.0 mL) gave (*S*,*S*)-**106** as colourless solid (689 mg, 94%).

$[a]_D^{20} = -38.5$ ($c = 0.42$, $CHCl_3$).

(1*R*,2*R*)-1,2-*N*,*N*'-Bis-(4'-toluenesulfonylamino)-1,2-dicyclohexylethane ((*R*,*R*)-107)[108]



(*R*,*R*)-**107**

Diamide (*R*,*R*)-**107** was prepared in analogy to the synthesis of (*R*,*R*)-**106** from (1*R*,2*R*)-1,2-dicyclohexylethane-1,2-diamine ((*R*,*R*)-**109**, 300 mg, 1.34 mmol), NEt(*i*Pr)$_2$ (1.10 mL, 6.43 mmol) and *p*-TsCl (540 mg, 2.83 mmol) in abs. CH_2Cl_2 (7.0 mL). Purification of the crude product by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 4:1, F12-18) yielded (*R*,*R*)-**107** as colourless solid (245 mg, 34%).

$C_{28}H_{40}N_2O_4S_2$ (532.76 g*mol^{-1}):

R_f = 0.36 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61-1.76 (m, 22 H, Cy-H), 2.42 (s, 6 H, CH_3), 3.11 (m, 2 H, CH), 4.72 (br s, 2 H, NH), 7.26 (d, J(H,H) = 7.0 Hz, 4 H, Ar-H), 7.73 (d, J(H,H) = 7.0 Hz, 4 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 21.7 (CH_2), 26.2 (CH_3), 27.7 (CH_2), 31.1 (CH_2), 40.4 (CH), 58.8 (CH), 127.5 (Ar-CH), 129.7 (Ar-CH), 138.1 (*p*Tol-*i*-C), 143.6 (*p*Tol-*p*-C) ppm.

IR (KBr): $\tilde{\nu}$ = 2924s, 2848m, 1653w, 1598w, 1496w, 1448s, 1329s, 1152s, 1094s, 1050m, 950m, 879w, 813m, 709m, 684m cm^{-1}.

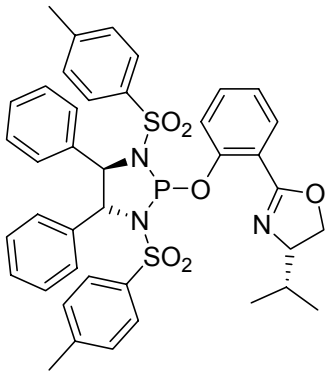
MS (FAB, NBA): *m/z* (%) = 533 (100, $[M+H]^+$), 435 (6), 377 (7), 362 (13), 266 (79, $C_{14}H_{20}NO_2S^+$), 184 (24), 155 (14), 91 (34), 39 (24).

$[a]_D^{20}$ = +30.1 (*c* = 0.82, $CHCl_3$).

Elemental analysis calcd. (%) for $C_{28}H_{40}N_2O_4S_2$: C 63.12, H 7.57, N 5.26; found: C 63.26, H 7.56, N 5.18.

7.4.3 Ligand Synthesis

(4*S*,4''*R*,5''*R*)-4-Isopropyl-2-{2'-[4'',5''-diphenyl-1'',3''-bis(4'''-methylphenylsulfonyl)-1'',3''-diazaphospholidine-2''-yl]-oxyphenyl}-4,5-dihydro-oxazole (112)



112

A solution of abs. NEt_3 (164 mg, 1.62 mmol) in abs. toluene (3.0 mL) was treated with PCl_3 (80.0 mg, 0.583 mmol) at –78 °C. A suspension of sulfonylated diamine (*R*,*R*)-**106** (200 mg, 0.384 mmol) in abs. toluene (5.0 mL) was slowly added and the reaction mixture was allowed to warm to r.t. overnight. After filtration over Celite under argon and concentration of the filtrate in high vacuum the residue was dissolved in abs. toluene (3.0 mL) and cooled to –78 °C. A solution of abs. NEt_3 (392 mg, 3.87 mmol) in abs. toluene (4.0 mL) was added, followed after 15 min by azeotropically dried (3 × 1.5 mL abs. toluene) oxazoline alcohol **99** (52.8 mg, 0.257 mmol) in abs. toluene (3.0 mL). The reaction mixture was allowed to warm to r.t. overnight and filtered over Celite under argon. After concentration of the filtrate in high vacuum the residue was purified by column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAC 4:1, F10-13) under argon to give ligand **112** as colourless solid (140 mg, 72%).

$C_{40}H_{40}N_3O_6PS_2$ (753.87 g*mol^{-1}):

m.p. 64 °C.

R_f = 0.15 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.90 (d, J(H,H) = 6.7 Hz, 3 H, CH(CH_3)(CH_3)), 1.01 (d, J(H,H) = 6.7 Hz, 3 H, CH(CH_3)(CH_3)), 1.82 (q, J(H,H) = 6.7 Hz, 1 H, CH(CH_3)$_2$), 2.33 (s, 3 H, pTol-CH_3), 2.34 (s, 3 H, pTol-CH_3), 3.99 (dd, J(H,H) = 12.6, 7.8 Hz, 1 H, Ox-5-H), 4.04 (dd, J(H,H) = 12.6, 7.8 Hz, 1 H, Ox-5-H), 4.30 (t, J(H,H) = 7.8 Hz, 1 H, Ox-4-H), 4.62 (dd, J(H,H) = 6.1 Hz, J(P,H) = 2.8 Hz, 1 H, NCH), 5.15 (d, J(H,H) = 6.1 Hz, 1 H, NCH), 6.54 (d, J(H,H) = 7.8 Hz, 2 H, Ar-H), 6.67 (d, J(H,H) = 8.0 Hz, 2 H, Ar-H), 6.82-7.39 (m, 15 H, Ar-H), 7.57 (m_c, 1 H, Ar-H), 7.71 (d, J(H,H) = 8.4 Hz, 1 H, Ar-H), 7.97 (d, J(H,H) = 8.4 Hz, 1 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 19.2 (CH(CH_3)$_2$), 21.5 (pTol-CH_3), 32.8 (CH(CH_3)$_2$), 70.4 (NCH), 72.0 (NCH), 73.5 (Ox-4-CH), 74.6 (Ox-5-CH_2), 116.5 (Ar-CH), 120.0-129.9 (diverse Ar-CH), 131.9 (Ar-CH), 132.3 (Ar-CH), 136.3 (Ar-C), 137.4 (Ar-C), 139.2 (Ar-C), 143.8 (Ar-C), 144.2 (Ar-C), 161.7 (Ar-2'-C), 167.2 (Ox-2-C) ppm.

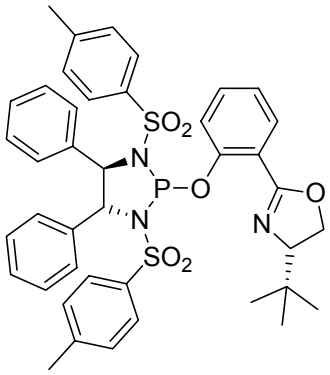
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 116.9 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 3032w, 2960m, 1734m, 1700m, 1653s, 1646m, 1599m, 1560w, 1496m, 1457m, 1355s, 1212m, 1161s, 1089m, 955m, 855m, 765m, 675s cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 792 (18, $[M+K]^+$), 754 (60, $[M+H]^+$), 549 (54, $[M-C_{12}H_{14}NO_2]^+$), 260 (43), 91 (100).

$[a]_D^{20}$ = +116.0 (c = 0.10, $CHCl_3$).

(4*S*,4''*R*,5''*R*)-4-*tert*-Butyl-2-{2'-[4'',5''-diphenyl-1'',3''-bis(4'''-methylphenylsulfonyl)-1'',3''-diazaphospholidine-2''-yl]-oxyphenyl}-4,5-dihydro-oxazole (113)



113

The ligand synthesis was accomplished in analogy to the preparation of **112**. The corresponding *P*-chlorodiazaphospholidine was obtained from sulfonated diamine (*R*,*R*)-**106** (200 mg, 0.384 mmol), PCl_3 (80.0 mg, 0.583 mmol) and abs. NEt_3 (164 mg, 1.62 mmol) in abs. toluene (8.0 mL). After filtration and removal of all volatiles in high vacuum, the reaction of the residue with oxazoline alcohol **100** (50.0 mg, 0.228 mmol) and abs. NEt_3 (392 mg, 3.87 mmol) in abs. toluene (11 mL) was carried out. Purification of the crude product by column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc 1:1, F11-15) under argon gave ligand **113** as colourless solid (80.0 mg, 46%).

$C_{41}H_{42}N_3O_6PS_2$ (767.89 g*mol^{-1}):

m.p. 76 °C.

R_f = 0.44 (hexanes/EtOAc 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (s, 9 H, $C(CH_3)_3$), 2.33 (s, 3 H, *p*Tol-CH_3), 2.34 (s, 3 H, *p*Tol-CH_3), 3.97 (dd, *J*(H,H) = 10.6, 8.1 Hz, 1 H, Ox-5-H), 4.16 (t, *J*(H,H) = 8.2 Hz, 1 H, Ox-4-H), 4.25 (dd, *J*(H,H) = 10.6, 8.1 Hz, 1 H, Ox-5-H), 4.77 (dd, *J*(H,H) = 5.9 Hz, *J*(P,H) = 2.9 Hz, 1 H, NCH), 5.16 (d, *J*(H,H) = 6.0 Hz, 1 H, NCH), 6.12 (d, *J*(H,H) = 7.0 Hz, 2 H, Ar-H), 6.84-7.26 (m, 15 H, Ar-H), 7.44-7.57 (m, 3 H, Ar-H), 7.73 (d, *J*(H,H) = 8.2 Hz, 1 H, Ar-H), 8.02 (d, *J*(H,H) = 7.7 Hz, 1 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 21.4 (*p*Tol-CH_3), 26.0 ($C(CH_3)_3$), 34.0 ($C(CH_3)_3$), 62.0 (NCH), 69.0 (NCH), 74.5 (Ox-4-CH), 75.3 (Ox-5-CH_2), 121.0-129.5 (diverse Ar-CH), 132.0 (Ar-CH), 132.2 (Ar-CH), 135.9 (Ar-C), 136.2 (Ar-C), 137.3 (Ar-C), 143.4 (Ar-C), 143.7 (Ar-C), 163.0 (Ar-2'-C), 165.9 (Ox-2-C) ppm.

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ = 116.7 (s) ppm.

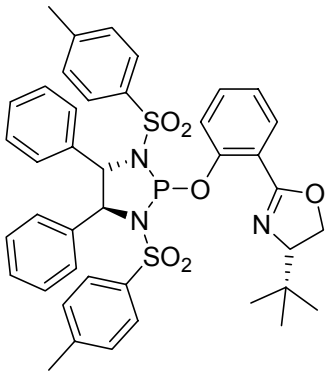
IR (KBr): $\tilde{\nu}$ = 2952s, 1772m, 1734m, 1700m, 1675m, 1653s, 1635m, 1490m, 1457m, 1355s, 1209m, 1160s, 1088m, 955m, 853m, 765m, 674s cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 806 (11, $[M+K]^+$), 768 (50, $[M+H]^+$), 549 (41, $[M-C_{13}H_{16}NO_2]^+$), 350 (25), 260 (61), 91 (100), 57 (25).

$[a]_D^{20}$ = +48.0 (*c* = 0.15, $CHCl_3$).

Elemental analysis calcd. (%) for $C_{41}H_{42}N_3O_6PS_2$: C 64.13, H 5.51, N 5.47; found: C 64.43, H.5.85, N 5.32.

(4*S*,4''*S*,5''*S*)-4-*tert*-Butyl-2-{2'-[4'',5''-diphenyl-1'',3''-bis(4'''-methylphenylsulfonyl)-1'',3''-diazaphospholidine-2''-yl]-oxyphenyl}-4,5-dihydro-oxazole (114)



114

The ligand synthesis was accomplished in analogy to the preparation of **112**. The corresponding *P*-chlorodiazaphospholidine was obtained from sulfonated diamine (*S*,*S*)-**106** (200 mg, 0.384 mmol), PCl_3 (80.0 mg, 0.583 mmol) and abs. NEt_3 (164 mg, 1.62 mmol) in abs. toluene (8.0 mL). After filtration and removal of all volatiles in high vacuum, reaction of the residue with oxazoline alcohol **100** (50.0 mg, 0.228 mmol) and abs. NEt_3 (392 mg, 3.87 mmol) in abs. toluene (10 mL) was carried out. Purification of the crude product by column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc 1:1, F11-15) under argon gave ligand **114** as colourless solid (140 mg, 80%).

$C_{41}H_{42}N_3O_6PS_2$ (767.89 g*mol^{-1}):

m.p. 65 °C.

R_f = 0.31 (hexanes/EtOAc 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (s, 9 H, $C(CH_3)_3$), 2.32 (s, 3 H, *p*Tol-CH_3), 2.33 (s, 3 H, *p*Tol-CH_3), 4.06 (dd, *J*(H,H) = 10.4, 8.3 Hz, 1 H, Ox-5-H), 4.15 (t, *J*(H,H) = 8.3 Hz, 1 H, Ox-4-H), 4.24 (dd, *J*(H,H) = 10.4, 8.3 Hz, 1 H, Ox-5-H), 4.82 (dd, *J*(H,H) = 6.4 Hz, *J*(P,H) = 2.7 Hz, 1 H, NCH), 5.24 (d, *J*(H,H) = 6.4 Hz, 1 H, NCH), 6.65 (d, *J*(H,H) = 7.9 Hz, 2 H, Ar-H), 6.89-7.28 (m, 15 H, Ar-H), 7.44 (d, *J*(H,H) = 8.2 Hz, 2 H, Ar-H), 7.52 (td, *J*(H,H) = 7.8, 1.7 Hz, 1 H, Ar-H), 7.79 (d, *J*(H,H) = 8.4 Hz, 1 H, Ar-H), 7.99 (dd, *J*(H,H) = 7.9, 1.7 Hz, 1 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 21.6 (*p*Tol-CH_3), 26.3 ($C(CH_3)_3$), 34.1 ($C(CH_3)_3$), 63.9 (NCH), 68.8 (NCH), 73.6 (Ox-4-CH), 74.9 (Ox-5-CH_2), 121.0-129.5 (diverse Ar-CH), 131.8 (Ar-CH), 132.2 (Ar-CH), 135.8 (Ar-C), 136.5 (Ar-C), 137.1 (Ar-C), 137.9 (Ar-C), 143.4 (Ar-C), 143.7 (Ar-C), 162.2 (Ar-2'-C), 169.5 (Ox-2-C) ppm.

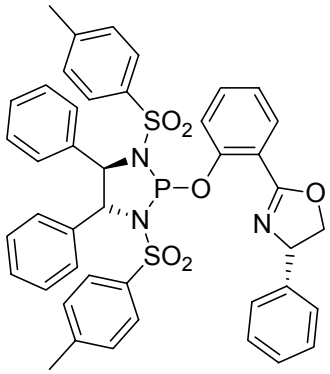
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 115.9 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 3032w, 2958m, 1734w, 1700w, 1684w, 1653m, 1646m, 1601m, 1496m, 1457m, 1355s, 1217m, 1159s, 1089m, 945m, 855m, 816w, 768m, 702m, 675s cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 806 (7, $[M+K]^+$), 768 (33, $[M+H]^+$), 549 (33, $[M-C_{13}H_{16}NO_2]^+$), 350 (6), 260 (31), 91 (100).

$[a]_D^{20}$ = –81.0 (*c* = 0.21, $CHCl_3$).

(4*S*,4''*R*,5''*R*)-4-Phenyl-2-{2'-[4'',5''-diphenyl-1'',3''-bis(4'''-methylphenylsulfonyl)-1'',3''-diazaphospholidine-2''-yl]-oxyphenyl}-4,5-dihydro-oxazole (115)



115

The ligand synthesis was accomplished in analogy to the preparation of **112**. The corresponding *P*-chlorodiazaphospholidine was obtained from sulfonated diamine (*R*,*R*)-**106**

(200 mg, 0.384 mmol), PCl_3 (80.0 mg, 0.583 mmol) and abs. NEt_3 (164 mg, 1.62 mmol) in abs. toluene (5.0 mL). After filtration and removal of all volatiles in high vacuum, the residue was reacted with oxazoline alcohol **101** (46.0 mg, 0.192 mmol) and abs. NEt_3 (392 mg, 3.87 mmol) in abs. toluene (12 mL). Purification of the crude product by column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc 1:1, F8-12) under argon gave ligand **115** as colourless solid (73.0 mg, 48%).

$C_{43}H_{38}N_3O_6PS_2$ (787.88 g*mol^{-1}):

m.p. 81 °C.

R_f = 0.44 (hexanes/EtOAc 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 4.19 (t, *J*(H,H) = 8.3 Hz, 1 H, Ox-4-H), 4.71 (dd, *J*(H,H) = 10.3, 8.3 Hz, 1 H, Ox-5-H), 4.78 (dd, *J*(H,H) = 6.0 Hz, *J*(P,H) = 3.0 Hz, 1 H, NCH), 5.12 (d, *J*(H,H) = 6.0 Hz, 1 H, NCH), 5.31 (dd, *J*(H,H) = 10.3, 8.3 Hz, 1 H, Ox-5-H), 6.57 (d, *J*(H,H) = 8.5 Hz, 2 H, Ar-H), 6.82-7.62 (m, 23 H, Ar-H), 7.78 (d, *J*(H,H) = 8.1 Hz, 1 H, Ar-H), 8.12 (dd, *J*(H,H) = 8.1, 1.8 Hz, 1 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 21.5 (CH_3), 62.0 (NCH), 69.5 (NCH), 73.4 (Ox-4-CH), 74.9 (Ox-5-CH_2), 116.5 (Ar-CH), 121-129 (diverse Ar-CH), 132.0 (Ar-CH), 132.6 (Ar-CH), 136.2 (Ar-C), 136.7 (Ar-C), 137.1 (Ar-C), 137.3 (Ar-C), 143.0 (Ar-C), 143.4 (Ar-C), 143.7 (Ar-C), 160.4 (Ar-2'-C), 164.0 (Ox-2-C) ppm.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 116.6 (s) ppm.

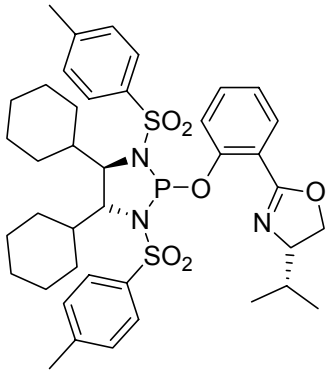
IR (KBr): $\tilde{\nu}$ = 3032w, 2924w, 1700s, 1653s, 1617m, 1457m, 1350s, 1160s, 1088m, 951m, 854m, 763m, 668s cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 669 (7), 559 (32), 521 (20), 350 (100), 260 (65), 195 (21), 91 (97), 57 (17).

$[a]_D^{20}$ = +84.0 (*c* = 0.33, $CHCl_3$).

Elemental analysis calcd. (%) for $C_{43}H_{38}N_3O_6PS_2$: C 65.55, H 4.86, N 5.33; found: C 65.00, H 5.23, N 5.21.

(4*S*,4''*R*,5''*R*)-4-Isopropyl-2-{2'-[4'',5''-dicyclohexyl-1'',3''-bis(4'''-methylphenyl-sulfonyl)-1'',3''-diazaphospholidine-2''-yl]-oxyphenyl}-4,5-dihydrooxazole (116)



116

The ligand synthesis was accomplished in analogy to the preparation of **112**. The corresponding *P*-chlorodiazaphospholidine was obtained from sulfonated diamine (*R*,*R*)-**107** (180 mg, 0.338 mmol), PCl_3 (80.0 mg, 0.583 mmol) and abs. NEt_3 (164 mg, 1.62 mmol) in abs. toluene (8.0 mL). After filtration and removal of all volatiles in high vacuum, the residue was reacted with oxazoline alcohol **99** (52.0 mg, 0.253 mmol) and abs. NEt_3 (392 mg, 3.87 mmol) in abs. toluene (10 mL). Purification of the crude product by column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc 4:1, F16-23) under argon gave ligand **116** as colourless solid (69.0 mg, 36%).

$C_{40}H_{52}N_3O_6PS_2$ (765.96 g*mol^{-1}):

m.p. 148 °C.

R_f = 0.14 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.74 (m_c, 1 H, Cy-CH_2), 0.07 (m_c, 1 H, Cy-CH_2), 0.41-0.89 (m, 6 H, Cy-CH_2), 0.93 (d, *J*(H,H) = 6.7 Hz, 3 H, CH(C*H*$_3$)(CH_3)), 0.96-1.03 (m, 2 H, Cy-CH_2), 1.04 (d, *J*(H,H) = 6.7 Hz, 3 H, CH(CH_3)(C*H*$_3$)), 1.09-1.76 (m, 10 H, Cy-CH_2), 1.87 (sept, *J*(H,H) = 6.7 Hz, 1 H, C*H*(CH_3)$_2$), 1.87-1.94 (m, 1 H, Cy-CH), 2.15 (d, *J*(H,H) = 13.1 Hz, 1 H, Cy-CH), 2.38 (s, 3 H, *p*Tol-CH_3), 2.39 (s, 3 H, *p*Tol-CH_3), 3.29 (t, *J*(P,H) = 5.0 Hz, 1 H, NCH), 3.69 (d, *J*(H,H) = 3.3 Hz, 1 H, NCH), 3.99 (m_c, 1 H, Ox-5-H), 4.21 (t, *J*(H,H) = 8.4 Hz, 1 H, Ox-4-H), 4.44 (dd, *J*(H,H) = 10.1, 8.4 Hz, 1 H, Ox-5-H), 7.15-7.33 (m, 5 H, Ar-H), 7.49 (td, *J*(H,H) = 7.8, 1.8 Hz, 1 H, Ar-H), 7.68-7.80 (m, 5 H, Ar-H), 7.98 (dd, *J*(H,H) = 7.8, 1.8 Hz, 1 H, Ar-H) ppm.

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 18.5 (CH(CH_3)(CH_3)), 19.5 (CH(CH_3)(CH_3)), 21.6 (*p*Tol-CH_3), 24.8 (Cy-CH_2), 25.7 (Cy-CH_2), 25.7 (Cy-CH_2), 25.8 (Cy-CH_2), 26.1 (Cy-CH_2), 26.3 (Cy-CH_2), 26.4 (Cy-CH_2), 26.5 (Cy-CH_2), 29.3 ($CH(CH_3)_2$), 31.4 (Cy-CH_2), 32.9 (Cy-CH_2), 39.7 (Cy-CH), 41.3 (Cy-CH), 66.0 (NCH), 67.5 (NCH), 70.7 (Ox-5-CH_2), 72.1 (Ox-4-CH), 121.9 (Ar-CH), 124.1 (Ar-CH), 127.9 (Ar-CH), 128.0 (Ar-CH), 128.1 (Ar-CH), 129.6 (Ar-CH), 129.8 (Ar-CH), 132.0 (Ar-CH), 132.3 (Ar-1'-C), 137.2 (*p*Tol-*i*-C), 137.3 (*p*Tol-*i*-C), 144.1 (*p*Tol-*p*-C), 144.4 (*p*Tol-*p*-C), 151.8 (Ar-2'-C), 163.6 (Ox-2-C) ppm.

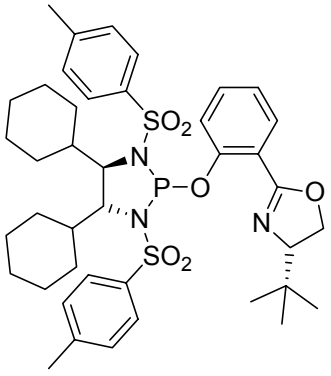
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 119.2 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 2925s, 2853m, 1653m, 1635m, 1601m, 1490w, 1448m, 1355s, 1204m, 1159s, 1086w, 1035w, 966s, 949m, 849m, 770m, 706m, 672s cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 804 (10, $[M+K]^+$), 766 (61, $[M+H]^+$), 561 (100, $[M-C_{12}H_{14}NO_2]^+$), 361 (8), 139 (32), 91 (40).

$[a]_D^{20}$ = –96.0 (*c* = 0.26, $CHCl_3$).

(4*S*,4''*R*,5''*R*)-4-*tert*-Butyl-2-{2'-[4'',5''-dicyclohexyl-1'',3''-bis(4'''-methylphenyl-sulfonyl)-1'',3''-diazaphospholidine-2''-yl]-oxyphenyl}-4,5-dihydrooxazole (117)



117

The ligand synthesis was accomplished in analogy to the preparation of **112**. The corresponding *P*-chlorodiazaphospholidine was obtained from sulfonated diamine (*R*,*R*)-**107** (180 mg, 0.338 mmol), PCl_3 (80.0 mg, 0.583 mmol) and abs. NEt_3 (164 mg, 1.62 mmol) in abs. toluene (8.0 mL). After filtration and removal of all volatiles in high vacuum, the reaction of the residue with oxazoline alcohol **100** (50.0 mg, 0.228 mmol) and abs. NEt_3 (392 mg, 3.87 mmol) in abs. toluene (10 mL) was carried out. Purification of the crude product by

column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc 4:1, F16-23) under argon gave ligand **117** as colourless solid (69.0 mg, 39%).

$C_{41}H_{54}N_3O_6PS_2$ (779.99 g*mol^{-1}):

m.p. 176 °C.

R_f = 0.15 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.70 (m_c, 1 H, Cy-CH_2), 0.01 (m_c, 1 H, Cy-CH_2), 0.34-1.00 (m, 10 H, Cy-CH_2), 0.96 (s, 9 H, C(CH_3)$_3$), 1.09-1.50 (m, 7 H, Cy-CH_2), 1.67 (m_c, 1 H, Cy-CH_2), 1.89 (m_c, 1 H, Cy-CH), 2.13 (m_c, 1 H, Cy-CH), 2.38 (s, 3 H, *p*Tol-CH_3), 2.39 (s, 3 H, *p*Tol-CH_3), 3.31 (t, *J*(P,H) = 5.2 Hz, 1 H, NCH), 3.72 (d, *J*(H,H) = 3.4 Hz, 1 H, NCH), 3.97 (dd, *J*(H,H) = 10.2, 8.4 Hz, 1 H, Ox-5-H), 4.28 (t, *J*(H,H) = 8.4 Hz, 1 H, Ox-4-H), 4.40 (dd, *J*(H,H) = 10.2, 8.4 Hz, 1 H, Ox-5-H), 7.14-7.34 (m, 5 H, Ar-H), 7.48 (t, *J*(H,H) = 7.9 Hz, 1 H, Ar-H), 7.66-7.81 (m, 5 H, Ar-H), 7.98 (dd, *J*(H,H) = 7.8, 1.8 Hz, 1 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 21.7 (*p*Tol-CH_3), 24.7 (Cy-CH_2), 24.9 (Cy-CH_2), 25.7 (Cy-CH_2), 25.8 (Cy-CH_2), 25.9 (Cy-CH_2), 26.1 (Cy-CH_2), 26.3 (C(CH_3)$_3$), 26.5 (Cy-CH_2), 29.3 (Cy-CH_2), 31.4 (Cy-CH_2), 34.2 (Cy-CH_2), 39.7 (Cy-CH), 39.8 (Cy-CH), 41.3 (*C*(CH_3)$_3$), 67.5 (NCH), 67.6 (NCH), 69.4 (Ox-5-CH_2), 75.4 (Ox-4-CH), 116.4 (Ar-CH), 124.1 (Ar-CH), 127.9 (Ar-CH), 128.1 (Ar-CH), 129.6 (Ar-CH), 129.9 (Ar-CH), 132.1 (Ar-CH), 132.3 (Ar-1'-C), 137.4 (*p*Tol-*i*-C), 144.1 (*p*Tol-*p*-C), 144.4 (*p*Tol-*p*-C), 151.8 (Ar-2'-C), 163.6 (Ox-2-C) ppm.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 118.6 (s) ppm.

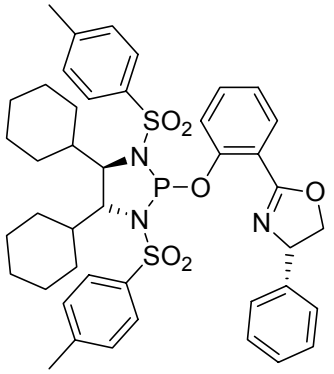
IR (KBr): $\tilde{\nu}$ = 2924s, 1700w, 1653m, 1635m, 1599w, 1451m, 1354m, 1209m, 1162s, 964m, 849m, 705m, 672s cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 818 (8, $[M+K]^+$), 780 (33, $[M+H]^+$), 561 (86, $[M–C_{13}H_{16}NO_2]^+$), 139 (58), 91 (100).

$[a]_D^{20}$ = –85.0 (*c* = 0.21, $CHCl_3$).

Elemental analysis calcd. (%) for $C_{41}H_{54}N_3O_6PS_2$: C 63.13, H 6.98, N 5.39; found: C 62.98, H 7.20, N 5.51.

(4*S*,4''*R*,5''*R*)-4-Phenyl-2-{2'-[4'',5''-dicyclohexyl-1'',3''-bis(4'''-methylphenyl-sulfonyl)-1'',3''-diazaphospholidine-2''-yl]-oxyphenyl}-4,5-dihydrooxazole (118)



118

The ligand synthesis was accomplished in analogy to the preparation of **112**. The corresponding *P*-chlorodiazaphospholidine was obtained from sulfonated diamine (*R*,*R*)-**107** (180 mg, 0.338 mmol), PCl_3 (80.0 mg, 0.583 mmol) and abs. NEt_3 (164 mg, 1.62 mmol) in abs. toluene (8.0 mL). After filtration and removal of all volatiles in high vacuum, reaction of the residue with oxazoline alcohol **101** (53.0 mg, 0.222 mmol) and abs. NEt_3 (392 mg, 3.87 mmol) in abs. toluene (10 mL) was carried out. Purification of the crude product by column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc 4:1, F16-23) under argon gave ligand **118** as colourless solid (80.0 mg, 45%).

$C_{43}H_{50}N_3O_6PS_2$ (799.98 g*mol^{-1}):

m.p. 124 °C.

R_f = 0.12 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.69 (m_c, 1 H, Cy-CH_2), –0.06 (m_c, 1 H, Cy-CH_2), 0.46-1.67 (m, 17 H, Cy-CH_2), 1.86 (m_c, 1 H, Cy-CH_2), 2.20 (m_c, 2 H, Cy-CH), 2.37 (s, 3 H, *p*Tol-CH_3), 2.40 (s, 3 H, *p*Tol-CH_3), 3.31 (d, *J*(H,H) = 4.8 Hz, 1 H, NCH), 3.71 (d, *J*(H,H) = 4.8 Hz, 1 H, NCH), 4.32 (t, *J*(H,H) = 8.4 Hz, 1 H, Ox-4-H), 4.83 (dd, *J*(H,H) = 10.4, 8.4 Hz, 1 H, Ox-5-H), 5.35 (dd, *J*(H,H) = 10.4, 8.4 Hz, 1 H, Ox-5-H), 7.23 (m_c, 3 H, Ar-H), 7.28 (d, *J*(H,H) = 9.3 Hz, 1 H, Ar-H), 7.32 (m_c, 2 H, Ar-H), 7.36 (m_c, 2 H, Ar-H), 7.53 (dd, *J*(H,H) = 8.3, 7.4 Hz, 1 H, Ar-H), 7.77 (m_c, 5 H, Ar-H), 7.90 (m_c, 2 H, Ar-H), 8.10 (d, *J*(H,H) = 7.4 Hz, 1 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 21.7 (*p*Tol-CH_3), 24.8 (Cy-CH_2), 25.8 (Cy-CH_2), 26.1 (Cy-CH_2), 26.2 (Cy-CH_2), 26.3 (Cy-CH_2), 26.5 (Cy-CH_2), 31.4 (Cy-CH_2), 34.2 (Cy-CH_2),

39.8 (Cy-CH), 41.4 (Cy-CH), 67.5 (NCH), 67.8 (NCH), 69.8 (Ox-5-CH_2), 76.4 (Ox-4-CH), 113.2 (Ar-CH), 122.8-129.9 (diverse Ar-CH), 139.4 (Ar-C), 143.7 (Ar-C), 144.2 (Ar-C), 154.8 (Ar-2'-C), 164.5 (Ox-2-C) ppm.

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 120.6 (s) ppm.

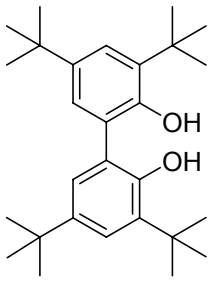
IR (KBr): $\tilde{\nu}$ = 2925s, 2851m, 1653m, 1635m, 1599m, 1496w, 1451m, 1351s, 1209m, 1162s, 1087m, 963s, 947m, 851w, 772w, 705m, 672s cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 838 (6, $[M+K]^+$), 800 (21, $[M+H]^+$), 561 (100, $[M-C_{15}H_{12}NO_2]^+$), 139 (44), 91 (68).

$[a]_D^{20} = -79.0$ (c = 0.15, $CHCl_3$).

7.5 Pyridyl-Phosphite Ligands

3,3',5,5'-Tetra-*tert*-butyl-(1,1'-biphenyl)-2,2'-diol (120)[111]



120

To a solution of 2,4-di-*tert*-butylphenol (**119**, 20.0 g, 96.9 mmol) in MeOH (40 mL) was added $CuCl_2$ (81.5 mg, 0.606 mmol) and TMEDA (129 µL, 0.860 mmol) at r.t. The resulting dark green solution was stirred for 48 h under a continuous flow of air. The colourless precipitate was filtered off, washed with MeOH (10 mL) and dried in high vacuum. The pure product **120** was obtained as colourless solid (13.6 g, 68%).

$C_{28}H_{42}O_2$ (410.63 g*mol^{-1}):

m.p. 190 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 18 H, CH_3), 1.45 (s, 18 H, CH_3), 5.21 (br s, 2 H, OH), 7.11 (d, J(H,H) = 2.4 Hz, 2 H, Ar-4-H and Ar-4'-H), 7.39 (d, J(H,H) = 2.4 Hz, 2 H, Ar-6-H and Ar-6'-H) ppm.

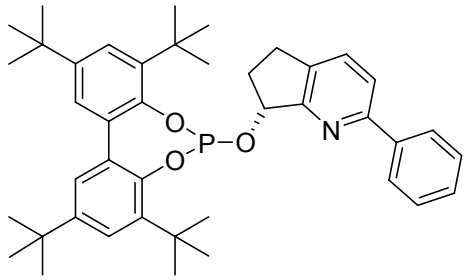
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 29.8 (CH_3), 31.7 (CH_3), 34.6 ($C(CH_3)_3$), 35.4 ($C(CH_3)_3$), 122.4 (Ar-C), 125.0 (Ar-CH), 125.4 (Ar-CH), 136.4 (Ar-C), 143.1 (Ar-C), 149.9 (Ar-C) ppm.

IR (KBr): $\tilde{\nu}$ = 3524s, 2961s, 2868m, 2830m, 1476s, 1457m, 1436s, 1400m, 1362s, 1332m, 1281m, 1237m, 1199m, 1169m, 1134w, 1094m, 880m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 410 (94, M^+), 395 (92, $[M-CH_3]^+$), 354 (18), 339 (75), 283 (31), 227 (15), 190 (40), 176 (9), 57 (100).

Elemental analysis calcd. (%) for $C_{28}H_{42}O_2$: C 81.90, H 10.31; found: C 81.86, H 10.25.

(*R*)-6-(6',7'-Dihydro-2'-phenyl-5'*H*-cyclopenta[b]pyridine-7'-yloxy)-2,4,8,10-tetrakis(*tert*-butyl)-dibenzo[d,f][1,3,2]dioxaphosphepin (124)



124

The ligand synthesis was accomplished in analogy to the preparation of **112**. The corresponding *P*-chlorodioxaphospholidine was obtained from diol **120** (166 mg, 0.405 mmol), PCl_3 (80.0 mg, 0.583 mmol) and abs. NEt_3 (164 mg, 1.62 mmol) in abs. toluene (8.0 mL). After filtration and removal of all volatiles in high vacuum, the residue was reacted with pyridyl alcohol **122** (20.0 mg, 95.7 μmol) and abs. NEt_3 (392 mg, 3.87 mmol) in abs. toluene (10 mL). Purification of the crude product by column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc 4:1, F4-8) under argon gave product **124** as colourless solid (60 mg, 97%).

$C_{42}H_{52}NO_3P$ (649.84 g*mol^{-1}):

m.p. 91 °C.

R_f = 0.66 (hexanes/EtOAc 4:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9 H, CH_3), 1.33 (s, 9 H, CH_3), 1.34 (s, 9 H, CH_3), 1.53 (s, 9 H, CH_3), 2.32 (m_c, 2 H, CH_2), 2.78 (m_c, 1 H, CH_2), 3.07 (m_c, 1 H, CH_2), 5.81 (m_c,

1 H, 7'-CH), 7.16 (dd, *J*(H,H) = 6.2, 2.5 Hz, 2 H, Ar-H), 7.34-7.49 (m, 5 H, Ar-H), 7.61 (m_c, 2 H, Ar-H), 8.06 (d, *J*(H,H) = 8.2 Hz, 2 H, Ar-H) ppm.

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 27.6 (CH_2), 31.0 ($C(CH_3)_3$), 31.1 ($C(CH_3)_3$), 31.2 ($C(CH_3)_3$), 31.3 ($C(CH_3)_3$), 31.5 ($C(CH_3)_3$), 32.5 (CH_2), 34.6 ($C(CH_3)_3$), 35.3 ($C(CH_3)_3$), 35.4 ($C(CH_3)_3$), 74.6 (7'-CH), 120.1 (Ar-CH), 124.1 (Ar-CH), 126.4 (Ar-CH), 126.5 (Ar-CH), 127.1 (Ar-CH), 128.5 (Ar-CH), 128.6 (Ar-CH), 133.4 (Ar-C), 135.4 (Ar-C), 139.3 (Ar-C), 140.4 (Ar-C), 146.1 (Ar-C), 146.3 (Ar-C), 156.6 (Ar-C), 161.9 (Ar-C) ppm.

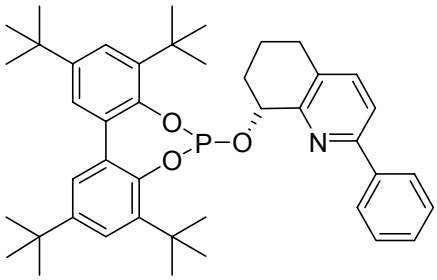
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 142.6 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 2958s, 1772w, 1734w, 1653w, 1590m, 1457m, 1437m, 1399m, 1362m, 1323w, 1281w, 1228s, 1123w, 1090m, 1013m, 980m, 908w, 872s, 848m, 770m, 693m cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 649 (6, M^+), 194 (100, $C_{14}H_{12}N^+$), 91 (4), 57 (70).

$[a]_D^{20}$ = –47.0 (*c* = 0.12, $CHCl_3$).

(*R*)-6-(5',6',7',8'-Tetrahydro-2'-phenylquinolin-8'-yloxy)-2,4,8,10-tetrakis(*tert*-butyl)-dibenzo[d,f][1,3,2]dioxaphosphepin (125)



125

The ligand synthesis was accomplished in analogy to the preparation of **112**. The corresponding *P*-chlorodioxaphospholidine was obtained from diol **120** (166 mg, 0.405 mmol), PCl_3 (80.0 mg, 0.583 mmol) and abs. NEt_3 (164 mg, 1.62 mmol) in abs. toluene (8.0 mL). After filtration and removal of all volatiles in high vacuum, the residue was reacted with pyridyl alcohol **123** (30.0 mg, 0.133 mmol) and abs. NEt_3 (392 mg, 3.87 mmol) in abs. toluene (10 mL). Purification of the crude product by column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc/NEt_3 8:1:1, F7-10) under argon gave ligand **125** as colourless solid (88.0 mg, 99%).

$C_{43}H_{54}NO_3P$ (663.87 g*mol^{-1}):

m.p. 96 °C.

R_f = 0.65 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 9 H, CH_3), 1.32 (s, 9 H, CH_3), 1.35 (s, 9 H, CH_3), 1.51 (s, 9 H, CH_3), 1.71 (m_c, 1 H, CH_2), 1.86 (m_c, 1 H, CH_2), 1.98 (m_c, 1 H, CH_2), 2.16 (m_c, 1 H, CH_2), 2.64-2.90 (m, 2 H, CH_2), 5.60 (m_c, 1 H, 8'-CH), 7.08-7.51 (m, 8 H, Ar-H), 7.62 (d, *J*(H,H) = 8.1 Hz, 1 H, Ar-H), 8.09 (d, *J*(H,H) = 8.5 Hz, 2 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 18.7 (CH_2), 28.0 (CH_2), 29.7 (CH_2), 30.8 (CH_3), 31.2 (CH_3), 31.5 (CH_3), 31.6 (CH_3), 34.5 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 35.1 ($C(CH_3)_3$), 35.4 ($C(CH_3)_3$), 73.3 (8'-CH), 119.6 (Ar-CH), 124.0 (Ar-CH), 125.3 (Ar-CH), 126.4 (Ar-CH), 127.0 (Ar-CH), 128.2 (Ar-CH), 128.5 (Ar-CH), 128.6 (Ar-CH), 129.0 (Ar-CH), 131.2 (Ar-C), 137.7 (Ar-C), 139.1 (Ar-C), 140.2 (Ar-C), 140.3 (Ar-C), 145.6 (Ar-C), 145.8 (Ar-C), 146.2 (Ar-C), 154.1 (Ar-C), 155.0 (Ar-C) ppm.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 143.2 (s) ppm.

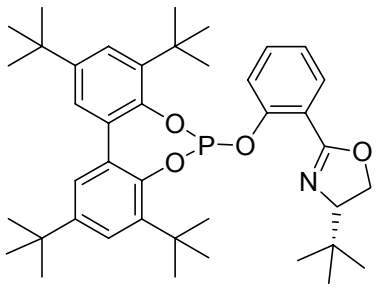
IR (KBr): $\tilde{\nu}$ = 2961s, 1734w, 1653w, 1600m, 1465m, 1399m, 1361m, 1229s, 1090m, 970m, 926w, 878s, 761m, 695m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 663 (54, M^+), 606 (57, $[M-C_4H_9]^+$), 441 (58), 208 (100, $C_{15}H_{14}N^+$), 57 (73).

$[a]_D^{20}$ = +105.0 (*c* = 0.13, $CHCl_3$).

7.6 Phosphite-Oxazoline Ligands

(*S*)-4-(*tert*-Butyl)-2-{2'-[(2'',4'',8'',10''-tetrakis(*tert*-butyl)-dibenzo[d,f][1''',3''',2''']-dioxaphosphepin-6'''-yl)oxy]-phenyl}-4,5-dihydrooxazole (59)[94]



59

A solution of abs. NEt_3 (525 µL, 3.77 mmol) in abs. THF (3.0 mL) was treated with PCl_3 (200 µL, 2.29 mmol) at –78 °C. Azeotropically dried (3 × 1.5 mL toluene) diol **120** (700 mg,

1.71 mmol) in abs. THF (5.0 mL) was slowly added at –60 °C and the reaction mixture was allowed to warm to r.t. overnight. After filtration over Celite under argon and concentration of the filtrate in high vacuum, the residue was re-dissolved in abs. toluene (4.0 mL) and cooled to –78 °C. Abs. pyridine (500 µL, 6.12 mmol) was added, followed by a solution of azeotropically dried (3 × 1.5 mL toluene) oxazoline alcohol **100** (180 mg, 0.821 mmol) and abs. pyridine (200 µL, 2.47 mmol) in abs. toluene (8.0 mL). The reaction mixture was allowed to warm to r.t. overnight. After filtration over Celite under argon and removal of the solvent in high vacuum, the crude product was purified by column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc 15:3:1, F2-3) under argon to give product **59** as colourless solid (162 mg, 30%).

$C_{41}H_{56}NO_4P$ (657.86 g*mol^{-1}):

R_f = 0.82 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, C_6D_6): δ = 0.87 (s, 9 H, Ox-4-C(CH_3)$_3$), 1.24 (s, 9 H, CH_3), 1.29 (s, 9 H, CH_3), 1.30 (s, 9 H, CH_3), 1.39 (s, 9 H, CH_3), 3.99 (dd, *J*(H,H) = 10.0, 8.2 Hz, 1 H, Ox-5-H), 4.06 (t, *J*(H,H) = 8.2 Hz, 1 H, Ox-4-H), 4.20 (dd, *J*(H,H) = 10.0, 8.2 Hz, 1 H, Ox-5-H), 5.78 (br s, 1 H, Ar-H), 6.84 (m_c, 2 H, Ar-H), 7.02 (d, *J*(H,H) = 2.5 Hz, 1 H, Ar-H), 7.06 (d, *J*(H,H) = 2.5 Hz, 1 H, Ar-H), 7.30 (d, *J*(H,H) = 2.4 Hz, 1 H, Ar-H), 7.42 (d, *J*(H,H) = 2.4 Hz, 1 H, Ar-H), 7.64 (m_c 1 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ = 25.5 (Ox-4-C(*C*H_3)$_3$), 30.7 (CH_3), 31.2 (CH_3), 33.7 (*C*(CH_3)$_3$), 34.0 (*C*(CH_3)$_3$), 34.8 (Ox-4-*C*(CH_3)$_3$), 35.2 (*C*(CH_3)$_3$), 35.6 (*C*(CH_3)$_3$), 68.2 (Ox-5-CH_2), 75.1 (Ox-4-CH), 123.7 (Ar-CH), 124.5 (Ar-CH), 125.2 (Ar-CH), 126.5 (Ar-CH), 126.7 (Ar-CH), 127.9 (Ar-CH), 130.1 (Ar-C), 131.5 (Ar-CH), 133.3 (Ar-CH), 140.2 (Ar-C), 140.6 (Ar-C), 146.8 (Ar-C), 147.1 (Ar-C), 148.5 (Ar-C), 161.1 (Ox-2-C) ppm.

^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 132.4 (s) ppm.

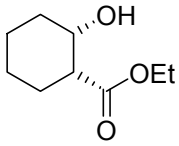
IR (KBr): $\tilde{\nu}$ = 2958s, 1655s, 1595w, 1465s, 1396s, 1359s, 1281m, 1234s, 1200s, 1122m, 1049m, 971m, 910m, 864m, 842m, 766m, 698m, 657w, 615m, 541w, 479w cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 657 (9, M^+), 573 (100, $[M–C_6H_{12}]^+$), 441 (55), 376 (14, $C_{28}H_{40}^+$).

Elemental analysis calcd. (%) for $C_{41}H_{56}NO_4P$: C 74.86, H 8.58, N 2.13; found: C 75.15, H 8.65, N 1.83.

7.7 Cyclohexyl-Based Phosphite-Oxazolines

(1*R*,2*S*)-Ethyl 2-hydroxycyclohexanecarboxylate (135)[112]



135

A suspension of baker's yeast (126 g) in water (1.0 L) was mechanically stirred at 30 °C for 30 min. Ethyl 2-oxocyclohexanecarboxylate (**134**, 5.00 g, 29.4 mmol) was added and the brown suspension was stirred for another 24 h at 30 °C. After centrifugation and decanting the supernatant was extracted with Et_2O (7 × 100 mL) and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 7:1, F12-19) yielded carboxylate **135** as colourless oil (2.20 g, 43%).

$C_9H_{16}O_3$ (172.22 g*mol^{-1}):

R_f = 0.34 (hexanes/EtOAc 7:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J*(H,H) = 7.0 Hz, 3 H, CH_3), 1.31 (m_c, 1 H, CH_2), 1.36-1.52 (m, 2 H, CH_2), 1.67 (m_c, 3 H, CH_2), 1.86 (m_c, 2 H, CH_2), 2.45 (d, *J*(H,H) = 11.4 Hz, 1 H, 1-H), 3.21 (d, *J*(H,H) = 3.6 Hz, 1 H, 2-H), 4.15 (q, *J*(H,H) = 7.0 Hz, 2 H, C*H*$_2$CH$_3$), 4.12 (m_c, 1 H, OH) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 14.3 (CH_3), 21.2 (CH_2), 24.2 (CH_2), 24.9 (CH_2), 31.9 (CH_2), 46.8 (1-CH), 60.7 (*C*H$_2$CH$_3$), 66.8 (2-CH), 176.1 (CO_2) ppm.

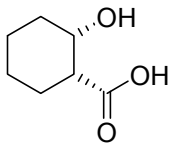
IR (NaCl): $\tilde{\nu}$ = 3514m, 2935s, 1713s, 1447m, 1373m, 1308w, 1249m, 1186s, 1119m, 1040m, 976m, 894w cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 172 (2, M^+), 154 (5, $[M–H_2O]^+$), 144 (57, $[M–C_2H_4]^+$), 101 (100), 73 (54), 55 (11).

$[a]_D^{20}$ = +26.4 (*c* = 0.850, $CHCl_3$); Lit.: +26.4 (*c* = 1.99, $CHCl_3$).[112]

Elemental analysis calcd. (%) for $C_9H_{16}O_3$: C 62.77, H 9.36; found: C 62.37, H 9.10.

(1*R*,2*S*)-2-Hydroxycyclohexanecarboxylic acid (136)[112]



136

An aqueous solution of LiOH (1 M, 80.0 mL, 80.0 mmol) was added to ethyl carboxylate **135** (2.00 g, 11.6 mmol) in THF (160 mL) and the resulting solution was stirred at r.t. for 1 h. The reaction mixture was acidified with 6 M HCl to pH 2 at 0 °C, saturated with NaCl and continuously extracted with Et_2O (300 mL) at reflux for 36 h. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification of the residue by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 1:1, F9-15) gave carboxylic acid **136** as colourless oil (1.25 g, 75%).

$C_7H_{12}O_3$ (144.17 g*mol^{-1}):

R_f = 0.34 (hexanes/EtOAc 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15-2.07 (m, 9 H, CH_2 and OH), 2.55 (dt, J(H,H) = 10.5, 3.4 Hz, 1 H, 1-H), 4.19 (m_c, 1 H, 2-H), 6.59 (br s, 1 H, CO_2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 20.4 (CH_2), 24.0 (CH_2), 24.6 (CH_2), 31.9 (CH_2), 46.6 (1-CH), 66.9 (2-CH), 180.3 (CO_2H) ppm.

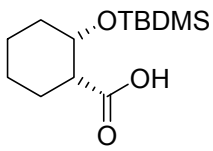
IR (NaCl): $\tilde{\nu}$ = 3514br, 2937s, 1706s, 1448m, 1185m, 1063w, 972m, 926m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 126 (34, [M–H_2O]$^+$), 98 (42, [M–CH_2O_2]$^+$), 73 (100), 55 (31).

$[a]_D^{20}$ = +23.1 (c = 0.91, $CHCl_3$).

Elemental analysis calcd. (%) for $C_7H_{12}O_3$: C 58.32, H 8.39; found: C 57.92, H 8.45.

(1*R*,2*S*)-2-(*tert*-Butyldimethylsilyloxy)-cyclohexanecarboxylic acid (137)[113]



137

A solution of carboxylic acid **136** (1.25 g, 8.68 mmol), DMAP (20.0 mg, 0.164 μmol) and abs. NEt_3 (3.90 mL, 26.0 mmol) in abs. CH_2Cl_2 (50 mL) was treated with TBDMSCl (2.83 g, 17.4 mmol) at 0 °C. The reaction mixture was allowed to warm to r.t. within 60 min. It was then washed with saturated aqueous solutions of NH_4Cl (50 mL), $NaHCO_3$ (50 mL) as well as NaCl (50 mL) and dried over $MgSO_4$. After evaporation of the solvent, purification of the crude product by column chromatography (silica gel, 3 × 22 cm, hexanes/EtOAc 10:1, F9-15) gave silyl ether **137** as colourless oil (1.13 g, 75%).

$C_{13}H_{26}O_3Si$ (258.43 g*mol^{-1}):

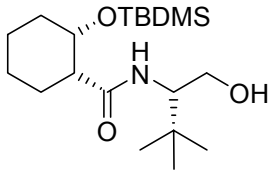
$\boldsymbol{R_f}$ = 0.41 (hexanes/EtOAc 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.27 (s, 6 H, $Si(CH_3)_2$), 0.94 (s, 9 H, $C(CH_3)_3$), 1.39 (m_c, 3 H, CH_2), 1.67 (m_c, 3 H, CH_2), 1.87 (m_c, 2 H, CH_2), 2.49 (ddd, *J*(H,H) = 10.6, 4.0, 2.8 Hz, 1 H, 1-H), 3.25 (br s, 1 H, CO_2H), 4.10 (td, 1 H, *J*(H,H) = 5.1, 2.5 Hz, 2-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = –3.4 ($Si(CH_3)_2$), 17.8 ($C(CH_3)_3$), 24.9 (CH_2), 25.8 (CH_2), 25.9 ($C(CH_3)_3$), 26.0 (CH_2), 31.9 (CH_2), 48.1 (1-CH), 67.2 (2-CH), 176.6 (CO_2H) ppm.

MS (FAB, NBA): *m/z* (%) = 259 (61, $[M+H]^+$), 183 (13), 115 (23), 73 (100).

(1*R*,2*S*,2'*S*)-2-(*tert*-Butyldimethylsilyloxy)-*N*-(1'-hydroxy-3',3'-dimethylbutan-2'-yl)-cyclohexanecarboxamide (138)



138

EDC (595 mg, 3.10 mmol) and HOBt (475 mg, 3.10 mmol) were added to a solution of carboxylic acid **137** (600 mg, 2.32 mmol) in CH_2Cl_2 (6.0 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and then stirred for 10 min. (*S*)-*tert*-Leucinol (578 mg, 2.44 mmol) and NEt(*i*Pr)$_2$ (1.60 ml, 9.35 mmol) in CH_2Cl_2 (6.0 mL) were added then. After 16 h the mixture was washed with saturated aqueous solutions of NH_4Cl (30 mL), NaCl (30 mL), $NaHCO_3$ (2 × 30 mL) and again NaCl (30 mL). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification of the residue by column chromatography (silica gel, 3 × 30 cm, hexanes/EtOAc 2:1, F6-18) gave amide **138** as colourless solid (510 mg, 61%).

$C_{19}H_{39}NO_3Si$ (357.27 g*mol^{-1}):

m.p. 100-101 °C.

R_f = 0.48 (hexanes/EtOAc 1:1).

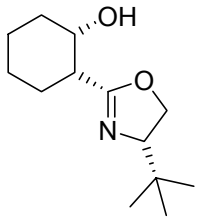
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.12 (s, 3 H, Si(CH_3)(CH$_3$)), 0.12 (s, 3 H, Si(CH$_3$)(CH_3)), 0.92 (s, 9 H, SiC(CH$_3$)$_3$), 0.97 (s, 9 H, C(CH$_3$)$_3$), 1.22-1.49 (m, 4 H, CH$_2$), 1.64-1.80 (m, 3 H, CH$_2$), 2.33 (m$_c$, 1 H, CH$_2$), 2.63 (m$_c$, 1 H), 2.98 (dd, *J*(H,H) = 6.5, 4.1 Hz, 1 H), 3.50 (m$_c$, 1 H), 3.89 (m$_c$, 2 H), 4.03 (m$_c$, 1 H), 7.44 (br s, 1 H, NH) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = –3.4 (Si(CH$_3$)$_2$), 18.1 (Si*C*(CH$_3$)$_3$), 19.9 (CH$_2$), 24.4 (CH$_2$), 25.1 (C(*C*H$_3$)$_3$), 25.6 (SiC(*C*H$_3$)$_3$), 26.9 (CH$_2$), 32.4 (*C*(CH$_3$)$_3$), 33.5 (CH$_2$), 49.1 (1-CH), 59.5 (CH$_2$OH), 63.1 (NCH), 67.3 (2-CH), 177.0 (CONH) ppm.

MS (FAB, NBA+KCl): *m/z* (%) = 396 (27, [M+K]$^+$), 358 (100, [M+H]$^+$), 300 (26, [M–C$_4$H$_9$]$^+$), 136 (11), 73 (69).

$[a]_D^{20}$ = –56.5 (*c* = 0.31, $CHCl_3$).

(1*S*,2*R*,4'*S*)-2-(4'-*tert*-Butyl-4',5'-dihydrooxazol-2'-yl)-cyclohexanol (140)



140

To a solution of **138** (200 mg, 0.560 mmol) and abs. NEt_3 (400 µL, 2.87 mmol) in CH_2Cl_2 (4.0 mL) was added *p*-TsCl (134 mg, 0.953 mmol) at r.t. The resulting mixture was stirred under reflux for 24 h. After the addition of some H_2O (200 µL) the solution was heated under reflux for another 60 min. The mixture was cooled to r.t. and then washed with H_2O (3 × 10 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. ^{1}H NMR analysis of the residue indicated the complete conversion of amide **138** to the silyl-protected oxazoline **139**. The crude product was dissolved in THF (4.0 mL) without further purification and treated with TBAF × 3 H_2O (1.10 g, 3.48 mmol) at 0 °C. The mixture was allowed to warm to r.t., stirred for 16 h, then poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (40 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a yellow oil, which was purified by column chromatography (silica gel, 3 × 30 cm, hexanes/EtOAc 4:1, F8-16) to yield oxazoline **140** as colourless solid (68.0 mg, 54%).

$C_{13}H_{23}NO_2$ (225.33 g*mol^{-1}):

m.p. 44-45 °C.

R_f = 0.35 (hexanes/EtOAc 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (s, 9 H, CH_3), 1.29 (m_c, 1 H, 5-H), 1.36-1.48 (m, 2 H, 3-H and 6-H), 1.59-1.70 (m, 3 H, 3-H, 4-H and 5-H), 1.76 (m_c, 1 H, 4-H), 1.84 (m_c, 1 H, 6-H), 2.37 (d, *J*(H,H) =11.2 Hz, 1 H, 2-H), 3.84 (dd, *J*(H,H) =10.4, 7.9 Hz, 1 H, Ox-4'-H), 3.98-4.02 (m, 2 H, Ox-5'-H and 1-H), 4.11 (dd, *J*(H,H) =10.4, 8.8 Hz, 1 H, Ox-5'-H), 4.77 (br s, 1 H, OH) ppm.

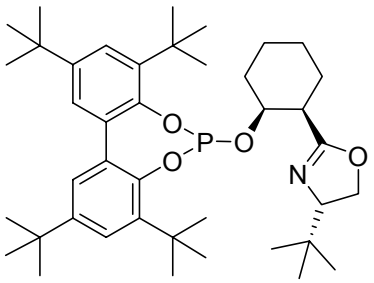
^{13}C{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 20.3 (3-CH_2), 25.1 (5-CH_2), 25.1 (4-CH_2), 25.4 (CH_3), 31.6 (6-CH_2), 33.4 ($C(CH_3)_3$), 40.8 (2-CH), 66.5 (1-CH), 67.9 (Ox-5'-CH_2), 75.2 (Ox-4'-CH) ppm; despite prolonged data acquisition time the signal for Ox-2'-C was not detected.

IR (KBr): $\tilde{\nu}$ = 3369m, 2935s, 1700w, 1653s, 1560m, 1448m, 1365m, 1182m, 1118w, 1055m, 1029m, 979m, 937m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 225 (2, M^+), 197 (9), 182 (16), 168 (100, $[M–C_4H_9]^+$), 154 (42), 96 (7), 81 (14), 43 (13).

$[a]_D^{20}$ = –22.0 (*c* = 0.25, $CHCl_3$).

(1'*S*,2'*R*,4''*S*)-2-[2'-(4''-*tert*-Butyl-4'',5''-dihydrooxazol-2''-yl)-cyclohexyloxy]-2,4,8,10-tetrakis(*tert*-butyl)-dibenzo[d,f][1,3,2]dioxaphosphepin (133)



133

A solution of abs. NEt_3 (192 mg, 1.89 mmol) in abs. THF (2.0 mL) was treated with PCl_3 (147 mg, 1.07 mmol) at –78 °C. Azeotropically dried (3 × 1.5 mL toluene) diol **120** (304 mg, 0.740 mmol) in abs. THF (2.0 mL) was slowly added at –60 °C and the reaction mixture was allowed to warm to r.t. overnight. The reaction was filtered over Celite under argon, which was washed with abs. THF (10 mL). After concentration of the filtrate in high vacuum the residue was re-dissolved in abs. toluene (4.0 mL) and cooled to –78 °C. This solution was then slowly added to azeotropically dried (3 × 1.5 mL abs. toluene) oxazoline alcohol **140** (39.0 mg, 0.173 mmol), DMAP (20.0 mg, 0.163 mmol) and abs. NEt_3 (70.0 mg, 0.692 mmol) in abs. toluene (4.0 mL) at –78 °C. The pink reaction mixture was allowed to slowly warm to r.t. overnight. After filtration over Celite under argon and removal of the solvent in high vacuum, the crude product was purified by column chromatography (silica gel, 3 × 18 cm, hexanes/EtOAc 10:1, F11-19) under argon to give ligand **133** as colourless solid (85.0 mg, 30%).

$C_{41}H_{62}NO_4P$ (663.91 g*mol^{-1}):

R_f = 0.27 (hexanes/EtOAc 10:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 0.79 (s, 9 H, Ox-4''-C$(CH_3)_3$), 0.86 (br s, 1 H, 2'-H) 1.35 (s, 18 H, CH_3), 1.47 (s, 9 H, CH_3), 1.49 (s, 9 H, CH_3), 1.59 (m_c, 2 H, CH_2), 1.70 (m_c, 2 H, CH_2), 1.83 (m_c, 2 H, CH_2), 1.91 (m_c, 2 H, CH_2), 2.53 (d, J(H,H) = 10.7 Hz, 1 H, 1'-H), 3.75 (t, J(H,H) = 9.3 Hz, 1 H, Ox-4''-H), 3.90 (t, J(H,H) = 8.7 Hz, 1 H, Ox-5''-H), 4.03 (d, J(H,H) = 9.0 Hz, 1 H, Ox-5''-H), 7.15 (s, 2 H, Ar-H), 7.43 (t, J(P,H) = 3.0 Hz, 2 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (162 MHz, CD_2Cl_2): δ = 24.0 (3'-CH_2), 25.1 (5'-CH_2), 25.2 (4'-CH_2), 25.6 (2'-CH), 25.7 (Ox-4''-C(CH_3)$_3$), 30.9 (CH_3), 30.9 (CH_3), 31.3 (CH_3), 31.3 (CH_3), 31.6 (6'-CH_2) 33.4 (Ox-4''-$C(CH_3)_3$), 33.4 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 35.3 ($C(CH_3)_3$), 41.5 (1'-CH), 67.0 (Ox-5''-CH_2), 75.8 (Ox-4''-CH), 124.2 (Ar-CH), 126.5 (Ar-CH), 140.3 (Ar-C), 140.3 (Ar-C), 146.3 (Ar-C), 146.4 (Ar-C), 166.5 (Ox-2''-C) ppm.

^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 146.2 (s) ppm.

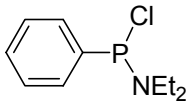
IR (KBr): $\tilde{\nu}$ = 2957s, 2866s, 1678s, 1620w, 1595w, 1475m, 1435m, 1414w, 1397m, 1361s, 1258w, 1225s, 1176m, 1089m, 1019w, 978m, 926m, 881s, 839s, 777m, 702m, 616w, 527w cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 663 (3, M^+), 606 (15, $[M-C_4H_9]^+$), 456 (45, $C_{28}H_{41}O_3P^+$), 441 (100), 208 (14, $C_{13}H_{22}NO^+$), 150 (44), 57 (34).

7.8 Phosphinooxazolines with Stereogenic Phosphorus Atoms

7.8.1 Amino- and Chlorophosphines

Chloro-diethylamino-phenylphosphine (147)[119]



147

At 0 °C abs. $HNEt_2$ (10.8 g, 148 mmol) in abs. Et_2O (10 mL) was added over 30 min to a solution of $PhPCl_2$ (**146**, 13.2 g, 73.7 mmol) in abs. Et_2O (100 mL). The reaction mixture was allowed to warm to r.t. and then stirred for 15 h. The resulting suspension was filtered over Celite under argon, which was washed with abs. Et_2O (3 × 10 mL) afterwards. The filtrate was concentrated under reduced pressure and the crude product purified by distillation in high vacuum to give the phosphine **147** as a colourless liquid (13.4 g, 83%).

$C_{10}H_{15}ClNP$ (215.67 g*mol^{-1}):

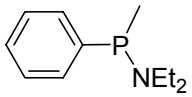
b.p. 79 °C/0.09 mbar.

^{1}H NMR (400 MHz, C_6D_6): δ = 1.10 (t, J(H,H) = 7.1 Hz, 6 H, CH_3), 3.09 (dq, J(H,H) = 7.1 Hz, J(P,H) = 12.0 Hz, 4 H, CH_2), 7.40-7.52 (m, 3 H, Ar-H), 7.72-7.80 (m, 2 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ = 14.0 (d, J(C,P) = 6 Hz, CH_3), 44.0 (d, J(C,P) = 13 Hz, CH_2), 128.5 (d, J(C,P) = 4 Hz, Ar-*m*-CH), 129.8 (d, J(C,P) = 1 Hz, Ar-*p*-CH), 130.7 (d, J(C,P) = 20 Hz, Ar-*o*-CH), 139.6 (d, J(C,P) = 29 Hz, Ar-*i*-C) ppm.

^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 139.4 (s) ppm.

Diethylamino-methyl-phenylphosphine (148)[119]



148

A solution of chlorophosphine **147** (1.32 g, 6.12 mmol) in abs. Et_2O (36 mL) was cooled to –18 °C in an ice/NaCl bath and methylmagnesium bromide in Et_2O (3.0 M, 2.04 mL, 6.12 mmol) was slowly added within 15 min. After the mixture had been stirred 2 h at r.t. and 1 h at reflux, the colourless precipitate was filtered off with the help of Celite under argon. Concentration of the filtrate under reduced pressure was followed by vacuum distillation to give product **148** as colourless liquid (720 mg, 60%).

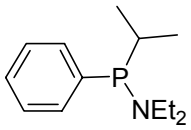
$C_{11}H_{18}NP$ (195.24 g*mol^{-1}):

b.p. 85 °C/0.2 mbar.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, J(H,H) = 7.0 Hz, 6 H, CH_2CH_3), 1.47 (d, J(P,H) = 5.6 Hz, 3 H, PCH_3), 2.99 (dq, J(H,H) = 7.0 Hz, J(P,H) = 9.5 Hz, 4 H, CH_2CH_3), 7.21-7.27 (m, 2 H, Ar-H), 7.30-7.42 (m, 3 H, Ar-H) ppm.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 45.7 (s) ppm.

Diethylamino-isopropyl-phenylphosphine (149)[119]



149

A solution of chlorophosphine **147** (3.19 g, 14.8 mmol) in abs. Et_2O (70 mL) was cooled to –18 °C in an ice/NaCl bath and isopropylmagnesium chloride in Et_2O (2.0 M, 7.40 mL, 14.8 mmol) was slowly added within 10 min. After the mixture had been stirred 1 h at r.t. and 1 h at reflux, the colourless precipitate was filtered off with the help of Celite under argon. Concentration of the filtrate under reduced pressure was followed by vacuum distillation to give the product **149** as colourless liquid (2.50 g, 76%).

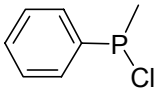
$C_{13}H_{22}NP$ (223.29 g*mol^{-1}).

b.p. 79 °C/0.09 mbar.

^{1}H NMR (400 MHz, C_6D_6): δ = 0.97 (t, J(H,H) = 7.1 Hz, 6 H, CH_2CH_3), 1.06 (dd, J(H,H) = 7.1 Hz, J(P,H) = 17.9 Hz, 3 H, $CH(CH_3)(CH_3)$), 1.29 (dd, J(H,H) = 7.1 Hz, J(P,H) = 14.2 Hz, 3 H, $CH(CH_3)(CH_3)$), 2.42 (dsept, J(H,H) = 6.8 Hz, J(P,H) = 6.8 Hz, 1 H, $CH(CH_3)_2$), 2.95 (m_c, 4 H, CH_2CH_3), 7.25 (m_c, 3 H, Ar-H), 7.64 (m_c, 2 H, Ar-H) ppm.

^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 66.0 (s) ppm.

Chloro-methyl-phenylphosphine (144)[117]



144

Diethylaminophosphine **148** (712 mg, 3.65 mmol) was dissolved in abs. pentane (15 mL) and HCl in abs. Et_2O (2.0 M, 3.70 mL, 7.40 mmol) was added at 0 °C within 15 min. The mixture was allowed to warm to r.t. and stirred for 15 h. The colourless suspension was filtered over Celite under argon, which was washed with abs. pentane (10 mL) afterwards. The filtrate was

concentrated under reduced pressure and the crude product distilled under vacuum to give **144** as colourless liquid (336 mg, 58%).

C_7H_8ClP (158.57 g*mol^{-1}):

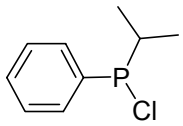
b.p. 55 °C/0.025 mbar.

^{1}H NMR (400 MHz, C_6D_6): δ = 1.44 (d, J(P,H) = 10.0 Hz, 3 H, CH_3), 7.03 (m_c, 3 H, Ar-H), 7.51 (m_c, 2 H, Ar-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ = 21.9 (d, J(C,P) = 31 Hz, CH_3), 128.9 (d, J(C,P) = 7 Hz, Ar-*m*-CH), 130.8 (d, J(C,P) = 8 Hz, Ar-*o*-CH), 131.1 (s, Ar-*p*-CH), 140.6 (d, J(C,P) = 34 Hz, Ar-*i*-C) ppm.

^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 83.7 (s) ppm.

Chloro-isopropyl-phenylphosphine (145)[119]



145

Diethylaminophosphine **149** (2.42 g, 10.8 mmol) was dissolved in abs. pentane (60 mL) and HCl in abs. Et_2O (2.0 M, 10.8 mL, 21.6 mmol) was added at 0 °C within 15 min. The mixture was allowed to warm to r.t. and stirred for 2 h. The colourless suspension was filtered over Celite under argon, which was washed with abs. pentane (10 mL) afterwards. The filtrate was concentrated under reduced pressure and the crude product distilled under vacuum to give **145** as colourless liquid (1.59 g, 79%).

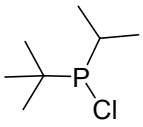
$C_9H_{12}ClP$ (186.61 g*mol^{-1}):

b.p. 58 °C/0.1 mbar.

^{1}H NMR (400 MHz, C_6D_6): δ = 0.75 (dd, J(H,H) = 6.9 Hz, J(P,H) = 16.9 Hz, 3 H, CH(CH_3)(CH_3)), 1.01 (dd, J(H,H) = 6.9 Hz, J(P,H) = 14.2 Hz, 3 H, CH(CH_3)(CH_3)), 1.90 (m_c, 1 H, CH(CH_3)$_2$), 7.06 (m_c, 3 H, Ar-H), 7.55 (m_c, 2 H, Ar-H) ppm.

^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 98.9 (s) ppm.

tert-Butyl-chloro-isopropylphosphine (150)[117]



150

A solution of *t*BuPCl$_2$ (**151**, 3.69 g, 23.2 mmol) in abs. Et$_2$O (130 mL) was treated with isopropylmagnesium chloride in Et$_2$O (2.0 M, 11.6 mL, 23.2 mmol) at 0 °C within 30 min. After warming the colourless suspension to r.t. it was stirred for 16 h and filtered over Celite under argon, which was washed with abs. Et$_2$O (2 × 15 mL) afterwards. The filtrate was concentrated and the crude product distilled under reduced pressure to give **150** as colourless liquid (2.76 g, 71%).

$C_7H_{16}ClP$ (166.63 g*mol^{-1}).

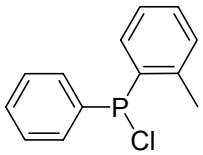
b.p. 60 °C/20 mbar.

^{1}H NMR (400 MHz, C_6D_6): δ = 0.91 (dd, *J*(H,H) = 7.1 Hz, *J*(P,H) = 17.5 Hz, 3 H, CH(C*H*$_3$)(CH$_3$)), 1.03 (d, *J*(P,H) = 12.1 Hz, 9 H, C(C*H*$_3$)$_3$), 1.15 (dd, *J*(H,H) = 7.1 Hz, *J*(P,H) = 11.4 Hz, 3 H, CH(CH$_3$)(C*H*$_3$)), 1.78 (sept, *J*(H,H) = 7.1 Hz, 1 H, C*H*(CH$_3$)$_2$) ppm.

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ = 20.2 (d, *J*(C,P) = 19 Hz, CH(*C*H$_3$)(CH$_3$)), 20.4 (s, CH(CH$_3$)(*C*H$_3$)), 26.5 (d, *J*(C,P) = 17 Hz, C(*C*H$_3$)$_3$), 29.1 (d, *J*(C,P) = 37 Hz, *C*H(CH$_3$)$_2$), 33.4 (d, *J*(C,P) = 33 Hz, *C*(CH$_3$)$_3$) ppm.

^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 137.6 (s) ppm.

Chloro-phenyl-(*ortho*-tolyl)phosphine (167)



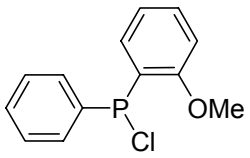
167

The Grignard reagent, which had been prepared from 2-bromotoluene (2.95 g, 17.2 mmol) and oven-dried magnesium turnings (450 mg, 18.5 mmol) in abs. Et$_2$O (20 mL), was added at –5 °C to a solution of chlorophosphine **147** (3.00 g, 13.9 mmol) in abs. Et$_2$O (15 mL). The

brown suspension was stirred at r.t. for 16 h and filtered over Celite under argon, which was washed with abs. Et_2O (2 × 10 mL) afterwards. HCl in abs. Et_2O (2.0 M, 14.0 mL, 28.0 mmol) was added at –15 °C within 15 min. The mixture was allowed to warm to r.t. and stirred for 15 h. The yellow suspension was filtered over Celite under argon, which was washed then with abs. Et_2O (10 mL). The filtrate was concentrated under reduced pressure and the crude product was distilled in high vacuum to give **167** as yellow oil (2.09 g, 64%).

$C_{13}H_{12}ClP$ (234.66 g*mol^{-1}):
b.p. 140 °C/1.1 mbar.
^{1}H NMR (400 MHz, C_6D_6): δ = 2.50 (d, J(P,H) = 2.4 Hz, 3 H, CH_3), 7.21-7.33 (m, 2 H, Ar-H), 7.38 (t, J(H,H) = 7.7 Hz, 1 H, Ar-H), 7.42-7.48 (m, 3 H, Ar-H), 7.61 (m_c, 3 H, Ar-H) ppm.
^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ = 20.5 (d, J(C,P) = 24 Hz, CH_3), 126.5 (d, J(C,P) = 1 Hz, Ar-CH), 128.5 (d, J(C,P) = 7 Hz, Ar-CH), 130.5 (d, J(C,P) = 4 Hz, Ar-CH), 130.5 (d, J(C,P) = 6 Hz, Ar-CH), 131.3 (d, J(C,P) = 5 Hz, Ar-CH), 132.0 (d, J(C,P) = 25 Hz, Ar-CH), 136.2 (d, J(C,P) = 35 Hz, *o*Tol-*i*-C), 138.0 (d, J(C,P) = 33 Hz, *o*Tol-*o*-C), 141.5 (d, J(C,P) = 29 Hz, Ph-*i*-C) ppm.
^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 75.5 (s) ppm.

Chloro-(2-methoxyphenyl)-phenylphosphine (169)



169

The Grignard reagent, which had been prepared from 2-bromoanisole (3.18 g, 17.0 mmol) and oven-dried magnesium turnings (440 mg, 18.1 mmol) in abs. Et_2O (20 mL) was treated with chlorophosphine **147** (3.00 g, 13.9 mmol) in abs. Et_2O (15 mL) at 0 °C. The reaction mixture was stirred at r.t. for 16 h, filtered over Celite under argon and washed with abs. Et_2O (3 × 10 mL). HCl in abs. Et_2O (2.0 M, 14.5 mL, 29.0 mmol) was added at –15 °C within 15 min. The mixture was allowed to warm to r.t. and stirred for 15 h. The yellow suspension was filtered over Celite under argon, which was washed with abs. Et_2O (10 mL) afterwards. The

filtrate was concentrated under reduced pressure and the crude product distilled in high vacuum to give **169** as colourless solid (500 mg, 14%).

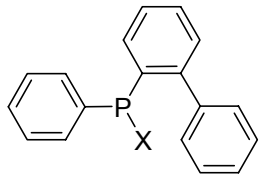
$C_{13}H_{12}ClOP$ (250.66 g*mol^{-1}):

b.p. 138 °C/0.13 mbar.

^{1}H NMR (400 MHz, C_6D_6): δ = 3.79 (s, 3 H, CH_3), 6.80-7.95 (m, 9 H, Ar-H) ppm.

^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 16.1 (s) ppm.

(2-Biphenyl)-chloro-phenylphosphine (170a)/(2-Biphenyl)-bromo-phenyl-phosphine (170b)



170
X = Cl/Br

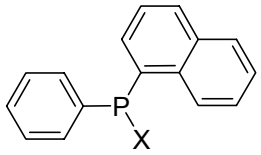
The phosphine synthesis was accomplished in analogy to the preparation of **167** using 2-bromobiphenyl (1.03 g, 4.42 mmol) and magnesium turnings (120 mg, 4.43 mmol) in abs. Et_2O (5.0 mL), chlorophosphine **147** (639 mg, 3.57 mmol) in abs. Et_2O (5.0 mL) and HCl in Et_2O (2.0 M, 3.60 mL, 7.20 mmol). The product was obtained as yellow oil in quantitative yield, representing a 3:2 mixture of **170a** and **170b**, and used without further purification.

$C_{18}H_{14}ClP$ (296.73 g*mol^{-1}) and $C_{18}H_{14}BrP$ (341.18 g*mol^{-1}):

^{1}H NMR (400 MHz, C_6D_6): δ = 6.97-7.03 (m, 3 H, Ar-H), 7.10-7.33 (m, 8 H, Ar-H), 7.42-7.54 (m, 2 H, Ar-H), 8.12-8.23 (m, 1 H, Ar-H) ppm.

^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 67.1 (s, X = Cl), 75.0 (s, X = Br) ppm (in a ratio of 3:2).

Chloro-(1-naphthalenyl)-phenylphosphine (171a)/Bromo-(1-naphthalenyl)-phenylphosphine (171b)

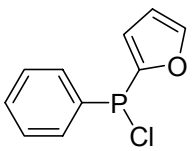


171
X = Cl/Br

The Grignard reagent, which had been prepared from 1-bromonaphthalene (6.40 g, 30.9 mmol) and oven-dried magnesium turnings (817 mg, 33.6 mmol) in abs. Et_2O (40 mL) was cooled to 0 °C and chlorophosphine **147** (5.50 g, 25.5 mmol) in abs. Et_2O (30 mL) was added. The greenish solution was stirred at r.t. for 16 h and the resulting brown suspension filtered over Celite under argon, which was washed with abs. Et_2O (3 × 15 mL) afterwards. HCl in abs. Et_2O (1.0 M, 54.0 mL, 54.0 mmol) was added at –15 °C within 15 min. The mixture was allowed to warm to r.t. and then stirred for 15 h. The yellow suspension was filtered over Celite under argon, which was washed with abs. Et_2O (10 mL). The filtrate was concentrated under reduced pressure and the crude product distilled in high vacuum to give a 9:2 mixture of **171a** and **171b** as yellow liquid (4.40 g, 64%).

$C_{16}H_{12}ClP$ (270.69 g*mol^{-1}) and $C_{16}H_{12}BrP$ (313.14 g*mol^{-1}):
b.p. 211-213 °C/0.8 mbar.
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.05 (m_c, 2 H, Ar-H), 7.11-7.34 (m, 4 H, Ar-H), 7.53-7.75 (m, 4 H, Ar-H), 7.77-7.92 (m, 1 H, Ar-H), 8.56-8.75 (m, 1 H, Ar-H) ppm.
^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 77.1 (s, X = Cl), 66.5 (s, X = Br) ppm (in a ratio of 9:2).

Chloro-(2-furanyl)-phenylphosphine (172)[125]



172

*n*BuLi in hexane (2.5 M, 14.0 mL, 35.0 mmol) was slowly added to a solution of furan (2.42 g, 35.5 mmol) in abs. Et_2O (20 mL) at –40 °C. The mixture was allowed to warm to 10 °C and then stirred for 2 h at this temperature, resulting in the formation of a yellow suspension. $PhPCl_2$ (**146**, 5.29 g, 29.5 mmol) in abs. Et_2O (230 mL) was cooled to –78 °C and the 2-furyllithium slurry was added over the course of 60 min using a wide teflon cannula. The mixture was allowed to warm to r.t. overnight and the slightly yellow suspension was filterd over Celite under argon. The filtrate was concentrated under reduced pressure and the crude product purified by distillation in high vacuum to yield **172** as colourless solid (4.50 g, 65%).

$C_{10}H_8ClOP$ (210.59 g*mol^{-1}):

b.p. 120-125 °C/0.06 mbar.

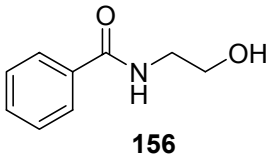
^{1}H NMR (400 MHz, C_6D_6): δ = 5.96 (m_c, 1 H, Fur-H), 6.61 (m_c, 1 H, Fur-H), 7.10-7.16 (m, 3 H, Ph-H), 7.17 (m_c, 1 H, Fur-H), 7.76 (m_c, 2 H, Ph-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ = 111.7 (d, *J*(C,P) = 6 Hz, Fur-CH), 123.2 (d, *J*(C,P) = 1 Hz, Fur-CH), 128.9 (d, *J*(C,P) = 8 Hz, Ph-*m*-CH), 130.8 (s, Ar-CH), 132.1 (d, *J*(C,P) = 26 Hz, Ph-*o*-CH), 136.4 (d, *J*(C,P) = 25 Hz, Ar-*i*-C), 149.1 (d, *J*(C,P) = 3 Hz, Ar-CH), 153.3 (d, *J*(C,P) = 45 Hz, Ar-*i*-C) ppm.

^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 46.2 (s) ppm.

7.8.2 Oxazolines

N-(2-Hydroxyethyl)-benzamide (156)[120]



156

BzCl (16.8 g, 120 mmol) in THF (120 mL) was added dropwise within 20 min to a solution of 2-aminoethanol (**154**, 31.5 g, 457 mmol) in THF (260 mL) at 4 °C. The reaction mixture was stirred for 2.5 h at r.t. After evaporation of the solvent the residue was dissolved in ice water (250 mL). The solution was acidified to pH 6 with concentrated HCl and extracted with EtOAc (4 × 150 mL). The combined organic phases were washed with brine (350 mL), dried

over Na_2SO_4 and evaporated. The crude product was re-crystallised from hexanes/EtOAc, which yielded the product **156** as colourless needles (15.9 g, 81%).

$C_9H_{11}NO_2$ (165.19 g*mol^{-1}):

m.p. 62 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (m_c, 2 H, HNCH_2), 3.72 (m_c, 2 H, HOCH_2), 4.06 (br s, 1 H, OH), 7.24 (br s, 1 H, NH), 7.32 (t, J(H,H) = 8.1 Hz, 2 H, Bz-*m*-H), 7.42 (t, J(H,H) = 8.6 Hz, 1 H, Bz-*p*-H), 7.72 (d, J(H,H) = 8.5 Hz, 2 H, Bz-*o*-H) ppm.

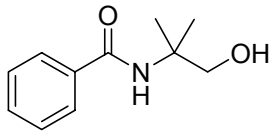
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 42.9 ($HNCH_2$), 61.8 ($HOCH_2$), 127.1 (Bz-*o*-CH), 128.6 (Bz-*m*-CH), 131.7 (Bz-*p*-CH), 134.1 (Bz-*i*-C), 168.9 (CONH) ppm.

IR (KBr): $\tilde{\nu}$ = 3306s, 2937m, 2874m, 1637s, 1539s, 1327m, 1297s, 1205m, 1040s, 865m, 802w, 695s, 554m cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 204 (24, $[M+K]^+$), 166 (100, $[M+H]^+$), 105 (32, $C_7H_5O^+$), 44 (10).

Elemental analysis calcd. (%) for $C_9H_{11}NO_2$: C 65.44, H 6.71, N 8.48, O 19.37; found: C 65.55, H 6.66, N 8.33, O 19.44.

N-(1-Hydroxy-2-methylpropan-2-yl)-benzamide (157)[120]



157

The synthesis in analogy to the preparation of **156** using BzCl (12.4 g, 88.2 mmol) and 2-amino-2-methylpropan-1-ol (**155**, 31.5 g, 353 mmol) in THF (300 mL) gave amide **157** as colourless solid after re-crystallisation from hexanes/EtOAc (13.7 g, 79%).

$C_{11}H_{15}NO_2$ (193.24 g*mol^{-1}):

m.p. 93 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 6 H, CH_3), 3.68 (m_c, 2 H, CH_2), 4.88 (br s, 1 H, OH), 6.31 (br s, 1 H, NH), 7.37-7.45 (m, 2 H, Bz-*m*-H), 7.45-7.52 (m, 1 H, Bz-*p*-H), 7.72 (m_c, 2 H, Bz-*o*-H) ppm.

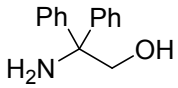
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 24.7 (CH_3), 56.5 ($C(CH_3)_2$), 70.8 (CH_2), 127.0 (Bz-*o*-CH), 128.7 (Bz-*m*-CH), 131.7 (Bz-*p*-CH), 134.9 (Bz-*i*-C), 168.6 (CONH) ppm.

IR (KBr): $\tilde{\nu}$ = 3188s, 2980s, 2895s, 1628s, 1543s, 1491s, 1388m, 1367m, 1315m, 1263s, 1177s, 1066s, 1021m, 932w, 873w, 806w, 776w, 691s, 518m, 471w, 421m cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 232 (19, $[M+K]^+$), 194 (100, $[M+H]^+$), 162 (16), 122 (23), 105 (35, $C_7H_5O^+$).

Elemental analysis calcd. (%) for $C_{11}H_{15}NO_2$: C 68.37, H 7.82, N 7.25, O 16.56; found: C 68.40, H 7.84, N 7.20, O 16.56.

2-Amino-2,2-diphenylethanol (178)[126, 149]



178

To a suspension of $LiAlH_4$ (670 mg, 17.7 mmol) in abs. THF (16 mL) was added diphenylglycine (2.04 g, 8.95 mmol) at 0 °C and the mixture was refluxed for 5 h. After the reaction had been cooled to r.t. water (1.0 mL), 15% aqueous NaOH solution (2.0 mL), and water (1.0 mL) were successively added. The mixture was dried over K_2CO_3 and filtered. The solvent was removed under reduced pressure and the crude product was re-crystallised from EtOAc/MeOH to give aminoalcohol **178** as colourless needles (1.23 g, 64%).

$C_{14}H_{15}NO$ (213.28 g*mol^{-1}):

m.p. 127-129 °C.

R_f = 0.08 (hexanes/EtOAc 2:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.23 (br s, 3 H, OH and NH_2), 4.12 (s, 2 H, CH_2), 7.20-7.38 (m, 10 H, Ph-H) ppm.

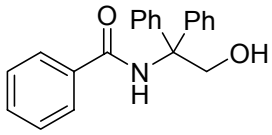
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 62.4 ($C(C_6H_5)_2$), 70.2 (CH_2), 126.7 (Ph-CH), 126.9 (Ph-CH), 128.3 (Ph-CH), 145.9 (Ph-*i*-C) ppm.

IR (KBr): $\tilde{\nu}$ = 3424m, 3285m, 3147m, 2885m, 2822m, 1961w, 1894w, 1824w, 1587s, 1488m, 1442s, 1285m, 1254m, 1101m, 1068s, 1001s, 935s, 908m, 857w, 766m, 703s, 645m, 593m, 535w, 494w cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 252 (10, $[M+K]^+$), 214 (41, $[M+H]^+$), 197 (84, $[M-NH_2]^+$), 182 (100, $[M-CH_2OH]^+$), 105 (30).

Elemental analysis calcd. (%) for $C_{14}H_{15}NO$: C 78.84, H 7.09, N 6.57, O 7.50; found: C 78.88, H 7.08, N 6.54, O 7.43.

N-(2-Hydroxy-1,1-diphenylethyl)-benzamide (179)



179

A solution of diphenylglycinol (**178**, 1.23 g, 5.76 mmol) and abs. NEt_3 (1.16 g, 11.5 mmol) in dioxane (10 mL) and CH_2Cl_2 (6.0 mL) was cooled to 0 °C and BzCl (810 mg, 5.76 mmol) was slowly added. The mixture was stirred for 7 h at r.t. and the solvents were removed under reduced pressure. The residue was re-dissolved in EtOAc (150 mL) and filtered over silica gel (3 × 4 cm). Concentration of the filtrate and re-crystallisation of the crude product from EtOAc gave **179** as colourless solid (1.10 g, 40%).

$C_{21}H_{19}NO_2$ (317.38 g*mol^{-1}):

m.p. 186-187 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50 (d, *J*(H,H) = 6.5 Hz, 2 H, CH_2), 5.73 (t, *J*(H,H) = 6.5 Hz, 1 H, OH), 7.02 (br s, 1 H, NH), 7.29-7.59 (m, 12 H, Ar-H), 7.81-7.85 (m, 3 H, Ar-H) ppm.

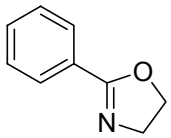
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 69.5 ($C(C_6H_5)_2$), 70.2 (CH_2), 127.2 (Ar-CH), 127.4 (Ar-CH), 128.0 (Ar-CH), 129.9 (Ar-CH), 130.0 (Ar-CH), 132.3 (Ar-CH), 134.3 (Bz-*i*-C), 142.0 (Ph-*i*-C), 168.5 (CONH) ppm.

IR (KBr): $\tilde{\nu}$ = 3058m, 2919m, 2861m, 1962w, 1890w, 1815w, 1718s, 1641s, 1598m, 1529s, 1486s, 1445s, 1377w, 1313m, 1268s, 1216m, 1179m, 1109m, 1052s, 979m, 934w, 914w, 844w, 760s, 699s, 569m cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 356 (15, $[M+K]^+$), 318 (48, $[M+H]^+$), 197 (40), 122 (32), 105 (100, $C_7H_5O^+$).

Elemental analysis calcd. (%) for $C_{21}H_{19}NO_2$: C 79.47, H 6.03, N 4.41, O 10.08; found: C 79.20, H 6.02, N 4.39, O 10.14.

2-Phenyl-4,5-dihydrooxazole (152)[116]



152

To hydroxyamide **156** (6.42 g, 38.9 mmol) and abs. NEt_3 (27.0 mL, 194 mmol) in abs. CH_2Cl_2 (120 mL) was added *p*-TsCl (8.16 g, 42.8 mmol) at r.t. The resulting solution was stirred under reflux for 24 h. After the addition of H_2O (2.0 mL) the solution was heated under reflux for another 60 min. The mixture was cooled to r.t. and then washed with H_2O (3 × 100 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by means of a Kugelrohr distillation in high vacuum yielding **152** as colourless oil (4.86 g, 85%).

C_9H_9NO (147.17 g*mol^{-1}):

b.p. 120 °C/6.0 mbar.

R_f = 0.33 (hexanes/EtOAc 4:1).

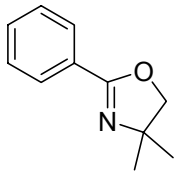
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.98 (t, *J*(H,H) = 9.6 Hz, 2 H, Ox-4-H), 4.33 (t, *J*(H,H) = 9.6 Hz, 2 H, Ox-5-H), 7.29-7.46 (m, 3 H, Ph-*m*-H and Ph-*p*-H), 7.90 (d, *J*(H,H) = 7.6 Hz, 2 H, Ph-*o*-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 54.9 (Ox-4-CH_2), 67.5 (Ox-5-CH_2), 127.7 (Ph-*i*-C), 128.1 (Ph-*m*-CH), 128.2 (Ph-*o*-CH), 131.2 (Ph-*p*-CH), 164.5 (Ox-2-C) ppm.

IR (NaCl): $\tilde{\nu}$ = 3061m, 2964m, 2900m, 1966w, 1910w, 1822w, 1648s, 1576m, 1487m, 1447m, 1366s, 1266s, 1192w, 1062s, 1021w, 940m, 893m, 776m, 694s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 147 (64, M^+), 117 (100, $[M–CH_2O]^+$), 77 (35, $C_6H_5^+$), 51 (12).

4,4-Dimethyl-2-phenyl-4,5-dihydrooxazole (153)[116]

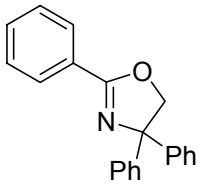


153

The synthesis in analogy to the preparation of **152** using hydroxy amide **157** (3.80 g, 19.7 mmol), abs. NEt_3 (14.0 mL, 100 mmol) and *p*-TsCl (4.10 g, 21.5 mmol) in abs. CH_2Cl_2 (60 mL) yielded oxazoline **153** as colourless oil after Kugelrohr distillation under reduced pressure (3.51 g, 70%).

$C_{11}H_{13}NO$ (175.23 g*mol^{-1}):
b.p. 125 °C/20.0 mbar.
R_f = 0.44 (hexanes/EtOAc 4:1).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 6 H, CH_3), 4.10 (s, 2 H, Ox-5-H), 7.39 (m_c, 2 H, Ph-*m*-H), 7.46 (m_c, 1 H, Ph-*p*-H), 7.93 (d, *J*(H,H) = 8.5 Hz, 2 H, Ph-*o*-H) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 28.5 (CH_3), 67.7 (Ox-4-C), 79.2 (Ox-5-CH_2), 128.1 (Ph-*i*-C), 128.3 (Ph-*m*-CH), 128.4 (Ph-*o*-CH), 131.3 (Ph-*p*-CH), 162.2 (Ox-2-C) ppm.
IR (NaCl): $\tilde{\nu}$ = 2964m, 1650s, 1455s, 1354s, 1313s, 1185s, 1062s, 968s, 924m, 781w, 693s cm^{-1}.
MS (EI, 70 eV): *m/z* (%) = 175 (12, M^+), 160 (100, $[M–CH_3]^+$), 145 (18, $[M–2\times CH_3]^+$), 132 (16), 104 (51), 77 (21, $C_6H_5^+$).
Elemental analysis calcd. (%) for $C_{11}H_{13}NO$: C 75.40, H 7.48, N 7.99; found: C 75.76, H 7.66, N 8.04.

2,4,4-Triphenyl-4,5-dihydrooxazole (176)



176

The synthesis in analogy to the preparation of **152** using hydroxy amide **179** (222 mg, 0.700 mmol), abs. NEt_3 (326 mg, 3.22 mmol) and *p*-TsCl (147 mg, 0.771 mmol) in abs. CH_2Cl_2 (3.5 mL) gave oxazoline **176** after column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc 4:1, F6-19) as colourless solid (142 mg, 68%).

$C_{21}H_{17}NO$ (299.13 g*mol^{-1}):

m.p. 92-93 °C.

$\boldsymbol{R_f}$ = 0.59 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.96 (s, 2 H, Ox-5-H), 7.20-7.55 (m, 13 H, Ph-H), 8.07-8.14 (m, 2 H, Ph-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 79.7 (Ox-4-C), 80.0 (Ox-5-CH_2), 126.8 (Ph-CH), 127.3 (Ph-CH), 127.9 (2-Ph-*i*-C), 128.5 (Ph-CH), 128.6 (Ph-CH), 128.7 (Ph-CH), 131.6 (Ph-CH), 146.3 (4-Ph-*i*-C), 163.0 (Ox-2-C) ppm.

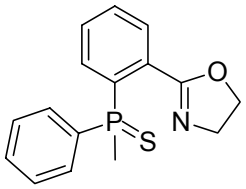
IR (KBr): $\tilde{\nu}$ = 3056m, 2898m, 1636s, 1486m, 1444m, 1356m, 1317m, 1280s, 1212m, 1170m, 1066s, 1023s, 901m, 853w, 752m, 694s, 560m, 532m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 299 (18, M^+), 269 (100), 222 (76, $[M–C_6H_5]^+$), 156 (86), 91 (25).

Elemental analysis calcd. (%) for $C_{21}H_{17}NO$: C 84.25, H 5.72, N 4.68; found: C 84.22, H 5.89, N 4.54.

7.8.3 Dialkyl- and Alkylaryl-Substituted Phosphinooxazolines

2-[2'-(Methyl-phenyl-thiophosphino)-phenyl]-4,5-dihydrooxazole (158a)



158a

A solution of azeotropically dried (2 × 2.0 mL toluene) phenyloxazoline **152** (321 mg, 2.18 mmol) and TMEDA (279 mg, 2.40 mmol) in abs. pentane (20 mL) was cooled to –78 °C and *s*BuLi in cyclohexane (1.3 M, 1.80 mL, 2.34 mmol) was added dropwise. After the reaction mixture had been stirred for 30 min at –78 °C and then 15 min at 0 °C, the orange suspension was re-cooled to –78 °C and treated with chlorophosphine **144** (500 mg, 3.15 mmol). The yellow mixture was allowed to slowly reach r.t. overnight. After removal of all volatiles in high vacuum the crude product was dissolved in abs. toluene (20 mL) and sulfur powder (101 mg, 3.15 mmol) was added. After 16 h at r.t. the reaction was filtered over Celite and the filtrate was concentrated under reduced pressure. Column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 7:3, F60-73) of the crude product gave ligand **158a** as colourless solid (440 mg, 67%). A portion of the racemic ligand was separated into its enantiomers by semipreparative HPLC on a chiral column.

$C_{16}H_{16}NOPS$ (301.34 g*mol^{-1}):

m.p. 100-101 °C.

R_f = 0.20 (hexanes/EtOAc 1:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 2.49 (d, J(P,H) = 13.3 Hz, 3 H, CH_3), 3.48 (ddd, J(H,H) = 14.0, 10.5, 8.8 Hz, 1 H, Ox-4-H), 3.72 (m_c, 2 H, Ox-5-H), 3.99 (ddd, J(H,H) = 10.2, 8.8, 7.6 Hz, 1 H, Ox-4-H), 7.40-7.50 (m, 3 H, Ar-H), 7.55-7.68 (m, 5 H, Ar-H), 8.45 (m_c, 1 H, Ar-3'-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ = 23.0 (d, J(C,P) = 61 Hz, CH_3), 54.7 (s, Ox-4-CH_2), 67.2 (s, Ox-5-CH_2), 128.3 (d, J(C,P) = 13 Hz, Ar-CH), 129.5 (d, J(C,P) = 11 Hz, Ar-CH), 130.1 (d, J(C,P) = 6 Hz, Ar-CH), 130.2 (d, J(C,P) = 2 Hz, Ar-CH), 130.6 (d, J(C,P) = 3 Hz, Ar-CH), 131.3 (d, J(C,P) = 3 Hz, Ar-CH), 131.4 (s, Ar-1'-C), 132.2 (d, J(C,P) = 77 Hz, Ar-2'-C), 134.6 (d, J(C,P) = 13 Hz, Ar-3'-CH), 135.6 (d, J(C,P) = 87 Hz, Ph-1''-C), 163.3 (d, J(C,P) = 3 Hz, Ox-2-C) ppm.

$^{31}P\{^{1}H\}$ NMR (162 MHz, CD_2Cl_2): δ = 36.8 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 2973m, 2928m, 2868m, 1657s, 1583w, 1573w, 1471m, 1431m, 1352s, 1322s, 1279m, 1242s, 1091m, 1043m, 977w, 938s, 891m, 750s, 699s, 603s, 486m cm^{-1}.

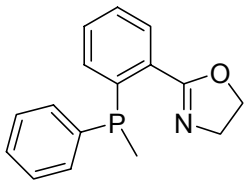
MS (EI, 70 eV): *m/z* (%) = 301 (22, M^+), 286 (28), 259 (81), 192 (100, $[M-C_6H_5]^+$), 183 (13).

$[a]_D^{20}$ = –45.8 ((–)-**158a**, *c* = 0.61, $CHCl_3$); +44.0 ((+)-**158a**, *c* = 0.61, $CHCl_3$).

HPLC (Daicel Chiracel OD, heptane/isopropanol 90:10, 6.0 mL*min^{-1}, 20 °C, 254 nm): t_R = 72.5 ((–)-**158a**), 93.5 ((+)-**158a**) min.

Elemental analysis calcd. (%) for $C_{16}H_{16}NOPS$: C 63.77, H 5.35, N 4.65; found: C 63.78, H 5.50, N 4.52.

2-[2'-(Methyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole (158)



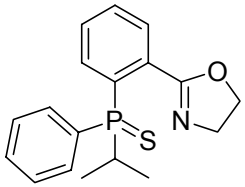
158

A solution of phosphine sulfide **158a** (150 mg, 0.497 mmol) in abs. benzene (20 mL) was treated with Si_2Cl_6 (410 mg, 1.52 mmol) at r.t. and heated under reflux for 60 min. More Si_2Cl_6 (432 mg, 1.61 mmol) was added then and the mixture was refluxed for another 60 min. A yellow-brownish suspension was obtained, which was cooled to 10 °C and hydrolysed with 30% degassed, aqueous NaOH solution (8.3 mL). The colourless biphasic mixture was vigorously stirred for ten minutes and the two phases were separated under argon. The organic layer was washed with degassed water (3 × 8 mL) and the solvent removed under reduced pressure afterwards. The residue was re-dissolved with degassed CH_2Cl_2 (25 mL) and the solution filtered through a teflon cannula equipped with a glass fibre filter. Removal of the solvent gave ligand **158** as colourless oil (28.1 mg, 21%).

$C_{16}H_{16}NOP$ (269.28 g*mol^{-1}):

$^{31}P\{^{1}H\}$ NMR (162 MHz, CD_2Cl_2): δ = –30.9 (s) ppm.

2-[2'-(Isopropyl-phenyl-thiophosphino)-phenyl]-4,5-dihydrooxazole (159a)



159a

In analogy to the preparation of **158a** phenyloxazoline **152** (256 mg, 1.74 mmol), TMEDA (228 mg, 1.96 mmol), *s*BuLi in cyclohexane (1.3 M, 1.80 mL, 2.34 mmol) and chlorophosphine **145** (422 mg, 2.26 mmol) were reacted in abs. pentane (15 mL). Protection of the residue was accomplished with sulfur powder (76.0 mg, 2.37 mmol) in abs. toluene (15 mL) and column chromatography (silica gel, 4 × 15 cm, hexanes/EtOAc 7:3, F38-62) of the crude product gave phosphine sufide **159a** as colourless solid (261 mg, 79%). A portion of the racemic ligand was separated into its enantiomers by semipreparative HPLC on a chiral column. Some of the isolated crystals were suitable for structure determination by X-ray analysis.

$C_{18}H_{20}NOPS$ (329.40 g*mol^{-1}):

m.p. 108 °C.

R_f = 0.16 (hexanes/EtOAc 1:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.03 (dd, *J*(H,H) = 6.9 Hz, *J*(P,H) = 19.4 Hz, 3 H, CH(C*H*$_3$)(CH$_3$)), 1.26 (dd, *J*(H,H) = 6.9 Hz, *J*(P,H) = 19.4 Hz, 3 H, CH(CH$_3$)(C*H*$_3$)), 3.56 (septd, *J*(H,H) = 6.9 Hz, *J*(P,H) = 14.4 Hz, 1 H, C*H*(CH$_3$)$_2$), 3.67 (ddd, *J*(H,H) = 11.2, 11.0, 8.9 Hz, 1 H, Ox-4-H), 3.77 (m$_c$, 2 H, Ox-5-H), 4.11 (m$_c$, 1 H, Ox-4-H), 7.36-7.48 (m, 3 H, Ar-H), 7.56 (m$_c$, 2 H, Ar-H), 7.59-7.68 (m$_c$, 3 H, Ar-H), 8.50 (dd, *J*(H,H) = 7.9 Hz, *J*(P,H) = 14.2 Hz, 1 H, Ar-3'-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ = 16.2 (s, CH(*C*H$_3$)(CH$_3$)), 17.2 (s, CH(CH$_3$)(*C*H$_3$)), 27.8 (d, *J*(C,P) = 57 Hz, *C*H(CH$_3$)$_2$), 55.0 (s, Ox-4-CH$_2$), 67.4 (s, Ox-5-CH$_2$), 128.1 (d, *J*(C,P) = 14 Hz, Ar-CH), 129.8 (d, *J*(C,P) = 12 Hz, Ar-CH), 130.5 (d, *J*(C,P) = 9 Hz, Ar-CH), 130.6 (d, *J*(C,P) = 3 Hz, Ar-CH), 130.9 (d, *J*(C,P) = 10 Hz, Ar-CH), 131.1 (d, *J*(C,P) = 6 Hz, Ar-1'-C), 131.3 (d, *J*(C,P) = 70 Hz, Ar-C), 131.9 (d, *J*(C,P) = 44 Hz, Ar-CH), 134.2 (d, *J*(C,P) = 80 Hz, Ar-C), 134.8 (d, *J*(C,P) = 10 Hz, Ar-CH), 161.2 (d, *J*(C,P) = 3 Hz, Ox-2-C) ppm.

$^{31}P\{^1H\}$ NMR (162 MHz, CD_2Cl_2): δ = 53.9 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 2968m, 2872m, 1656s, 1587m, 1466m, 1432m, 1357s, 1247m, 1099s, 1056m, 937m, 847w, 692s cm^{-1}.

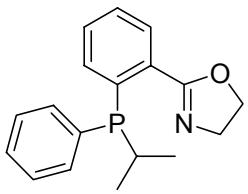
MS (EI, 70 eV): *m/z* (%) = 329 (12, M^+), 296 (38), 286 (65, $[M-C_3H_7]^+$), 254 (100), 220 (68), 212 (11), 178 (15), 139 (6).

$[a]_D^{20}$ = +91.3 ((*R*)-**159a**, *c* = 0.50, $CHCl_3$); –90.0 ((*S*)-**159a**, *c* = 0.50, $CHCl_3$).

HPLC (Daicel Chiracel AD, heptane/isopropanol 85:15, 6.0 mL*min^{-1}, 20 °C, 254 nm): t_R = 35.2 ((*R*)-**159a**), 40.3 ((*S*)-**159a**) min.

Elemental analysis calcd. (%) for $C_{18}H_{20}NOPS$: C 65.63, H 6.12, N 4.25; found: C 65.46, H 6.08, N 4.30.

2-[2'-(Isopropyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole (159)



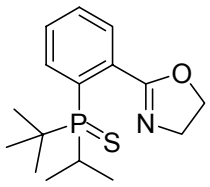
159

The deprotection was accomplished in analogy to the preparation of **158** using phosphine sulfide **159a** (164 mg, 0.497 mmol) and Si_2Cl_6 (349 mg, 1.29 mmol) in abs. benzene (20 mL), followed by the treatment with 30% degassed aqueous NaOH solution (3.5 mL). The free ligand **159** was isolated as colourless oil (65 mg, 44%).

$C_{18}H_{20}NOP$ (297.33 g*mol^{-1}):

$^{31}P\{^1H\}$ NMR (162 MHz, C_6D_6): δ = –8.1 (s) ppm.

2-[2'-(*tert*-Butyl-isopropyl-thiophosphino)-phenyl]-4,5-dihydrooxazole (160a)



160a

In analogy to the preparation of **158a** phenyloxazoline **152** (284 mg, 1.93 mmol), TMEDA (251 mg, 2.16 mmol), *s*BuLi in cyclohexane (1.3 M, 1.90 mL, 2.47 mmol) and chlorophosphine **150** (412 mg, 2.47 mmol) were reacted in abs. pentane (15 mL). Protection of the residue was accomplished with sulfur powder (79.2 mg, 2.46 mmol) in abs. toluene (15 mL) and column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 7:3, F80-105) of the crude product gave phoshine sufide **160a** as colourless solid (529 mg, 89%). A portion of the racemic ligand was separated into its enantiomers by semipreparative HPLC on a chiral column. Some of the isolated crystals were suitable for structure determination by X-ray analysis.

$C_{16}H_{24}NOPS$ (309.41 g*mol^{-1}):

m.p. 158-159 °C.

R_f = 0.21 (hexanes/EtOAc 1:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.92 (dd, J(H,H) = 6.8 Hz, J(P,H) = 17.5 Hz, 3 H, CH(CH_3)(CH_3)), 1.02 (d, J(P,H) = 16.4 Hz, 9 H, C(CH_3)$_3$) 1.31 (dd, J(H,H) = 6.8 Hz, J(P,H) = 17.5 Hz, 3 H, CH(CH_3)(CH_3)), 3.05 (m_c, 1 H, CH(CH_3)$_2$), 3.99 (m_c, 2 H, Ox-4-H), 4.39 (m_c, 2 H, Ox-5-H), 7.47-7.50 (m, 3 H, Ar-3'-H, Ar-4'-H and Ar-5'-H), 8.08 (br s, 1 H, Ar-6'-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ = 17.3 (s, CH(*C*H_3)(CH_3)), 17.9 (s, CH(CH_3)(*C*H_3)), 26.7 (d, J(C,P) = 47 Hz, *C*H(CH_3)$_2$), 26.9 (d, J(C,P) = 2 Hz, C(*C*H_3)$_3$), 36.2 (s, *C*(CH_3)$_3$), 55.5 (s, Ox-4-CH_2), 67.5 (s, Ox-5-CH_2), 129.1 (d, J(C,P) = 10 Hz, Ar-CH), 130.7 (d, J(C,P) = 5 Hz, Ar-CH), 131.5 (s, Ar-CH), 131.6 (s, Ar-CH), 134.1 (s, Ar-1'-C), 164.3 (s, Ox-2-C) ppm; despite prolonged data acquisition time the signal for Ph-2'-C was not detected.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ = 77.4 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 2900s, 1673s, 1582w, 1470s, 1353s, 1238s, 1187w, 1127w, 1093m, 1043m, 969m, 936s, 780s, 692s, 627s, 561m, 487m cm^{-1}.

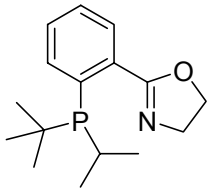
MS (FAB, NBA+KCl): *m/z* (%) = 348 (12, $[M+K]^+$), 310 (100, $[M+H]^+$), 252 (16), 220 (47), 57 (50).

$[a]_D^{20}$ = –33.3 ((*R*)-**160a**, *c* = 0.50, $CHCl_3$); +30.3 ((*S*)-**160a**, *c* = 0.50, $CHCl_3$).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 85:15, 6.0 mL*min^{-1}, 20 °C, 254 nm): t_R = 19.2 ((*R*)-**160a**), 20.8 ((*S*)-**160a**) min.

Elemental analysis calcd. (%) for $C_{16}H_{24}NOPS$: C 62.11, H 7.82, N 4.53; found: C 62.04, H 7.85, N 4.53.

2-[2'-(*tert*-Butyl-isopropylphosphino)-phenyl]-4,5-dihydrooxazole (160)



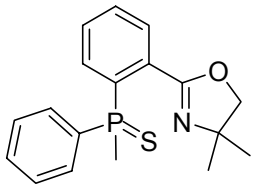
160

The deprotection was accomplished in analogy to the preparation of **158** using phosphine sulfide **160a** (112 mg, 0.362 mmol), Si_2Cl_6 (304 mg, 1.13 mmol) in abs. benzene (14 mL), followed by the treatment with 30% degassed aqueous NaOH solution (3.0 mL). The free ligand **160** was isolated as colourless oil (42.5 mg, 43%).

$C_{16}H_{24}NOPS$ (277.34 g*mol^{-1}):

$^{31}P\{^1H\}$ NMR (162 MHz, C_6D_6): δ = 9.1 (s) ppm.

4,4-Dimethyl-2-[2'-(methyl-phenyl-thiophosphino)-phenyl]-4,5-dihydrooxazole (161a)



161a

In analogy to the preparation of **158a** phenyloxazoline **153** (429 mg, 2.45 mmol), TMEDA (343 mg, 2.95 mmol), *s*BuLi in cyclohexane (1.3 M, 2.50 mL, 3.25 mmol) and chlorophosphine **144** (505 mg, 3.18 mmol) were reacted in abs. pentane (20 mL). Protection of the residue was accomplished with sulfur powder (102 mg, 3.18 mmol) in abs. toluene (20 mL) and column chromatography (silica gel, 4 × 20 cm, hexanes/EtOAc 7:3, F29-55) of the crude product gave phosphine sufide **161a** as colourless solid (514 mg, 64%). A portion of the racemic ligand was separated into its enantiomers by semipreparative HPLC on a chiral column.

$C_{18}H_{20}NOPS$ (329.40 g*mol^{-1}):

m.p. 130 °C.

$\boldsymbol{R_f}$ = 0.17 (hexanes/EtOAc 7:3).

^{1}H NMR (500 MHz, CD_2Cl_2): δ=1.01 (s, 3 H, Ox-4-CH_3), 1.13 (s, 3 H, Ox-4-CH_3), 2.48 (d, J(P,H) = 13.6 Hz, 3 H, PCH_3), 3.65 (d, J(H,H) = 7.8 Hz, 1 H, Ox-5-H), 3.70 (d, J(H,H) = 7.8 Hz, 1 H, Ox-5-H), 7.45 (m_c, 3 H, Ar-H), 7.61 (m_c, 4 H, Ar-H), 7.80 (m_c, 1 H, Ar-6'-H), 8.35 (ddd, J(H,H) = 7.6, 1.5 Hz, J(P,H) = 16.0 Hz, 1 H, Ar-3'-H) ppm.

^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2): δ = 23.5 (d, J(C,P) = 64 Hz, PCH_3), 27.5 (s, Ox-4-C(CH_3)(CH_3)), 27.6 (s, Ox-4-C(CH_3)(CH_3)), 67.9 (s, Ox-4-C(CH_3)$_2$), 78.7 (s, Ox-5-CH_2), 128.7 (d, J(C,P) = 13 Hz, Ar-CH), 129.5 (d, J(C,P) = 11 Hz, Ar-CH), 130.3 (d, J(C,P) = 13 Hz, Ar-CH), 130.8 (d, J(C,P) = 3 Hz, Ar-CH), 131.1 (d, J(C,P) = 8 Hz, Ar-6'-CH), 131.5 (d, J(C,P) = 3 Hz, Ar-CH), 131.6 (d, J(C,P) = 7 Hz, Ar-1'-C), 131.7 (d, J(C,P) = 75 Hz, Ar-2'-C), 134.8 (d, J(C,P) = 14 Hz, Ar-3'-CH), 136.8 (d, J(C,P) = 88 Hz, Ph-1''-C), 161.2 (d, J(C,P) = 2 Hz, Ox-2-C) ppm.

^{31}P{^{1}H} NMR (202 MHz, CD_2Cl_2): δ = 37.4 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 2973m, 2900m, 1650s, 1578m, 1460m, 1439s, 1352m, 1306m, 1252m, 1212m, 1169s, 1102m, 1045s, 961m, 887s, 820w, 767m, 747s, 712m, 610m cm^{-1}.

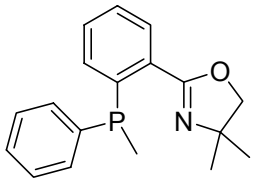
MS (FAB, NBA+KCl): *m/z* (%) = 368 (16, $[M+K]^+$), 330 (100, $[M+H]^+$), 258 (59), 220 (31), 55 (9).

$[a]_D^{20}$ = –58.0 ((–)-**161a**, *c* = 0.50, $CHCl_3$); +58.7 ((+)-**161a**, *c* = 0.50, $CHCl_3$).

HPLC (Daicel Chiracel AD, heptane/isopropanol 85:15, 6.0 mL*min^{-1}, 20 °C, 254 nm): t_R = 49.1 ((–)-**161a**), 58.6 ((+)-**161a**) min.

Elemental analysis calcd. (%) for $C_{18}H_{20}NOPS$: C 65.63, H 6.12, N 4.25; found: C 65.30, H 6.17, N 4.28.

4,4-Dimethyl-2-[2'-(methyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole (161)



161

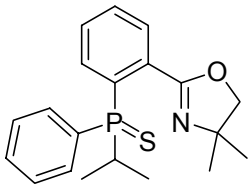
The deprotection was accomplished in analogy to the preparation of **158** using phosphine sulfide **161a** (103 mg, 0.313 mmol) and Si_2Cl_6 (259 mg, 0.963 mmol) in abs. benzene (13 mL), followed by the treatment with 30% degassed aqueous NaOH solution (2.6 mL). Ligand **161** was isolated as colourless oil (34.4 mg, 37%).

$C_{18}H_{20}NOP$ (297.33 g*mol^{-1}):

^{1}H NMR (400 MHz, C_6D_6): δ = 1.17 (s, 6 H, Ox-4-CH_3), 1.60 (d, *J*(P,H) = 5.1 Hz, 3 H, PCH_3), 3.65 (d, *J*(H,H) = 8.0 Hz, 1 H, Ox-5-H), 3.70 (d, *J*(H,H) = 8.0 Hz, 1 H, Ox-5-H), 6.96-7.14 (m, 5 H, Ar-H), 7.22 (m_c, 1 H, Ar-6'-H), 7.46 (m_c, 2 H, Ar-H), 8.01 (m_c, 1 H, Ar-3'-H) ppm.

^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 31.3 (s) ppm.

4,4-Dimethyl-2-[2'-(isopropyl-phenyl-thiophosphino)-phenyl]-4,5-dihydro-oxazole (162a)



162a

In analogy to the preparation of **158a** phenyloxazoline **153** (305 mg, 1.73 mmol), TMEDA (223 mg, 1.92 mmol), *s*BuLi in cyclohexane (1.3 M, 1.80 mL, 2.34 mmol) and chloro-phosphine **145** (469 mg, 2.51 mmol) were reacted in abs. pentane (15 mL). Protection of the residue was accomplished with sulfur powder (73.0 mg, 2.27 mmol) in abs. toluene (15 mL) and column chromatography (silica gel, 4 × 15 cm, hexanes/EtOAc 7:3, F36-72) of the crude product gave phosphine sufide **162a** as colourless solid (195 mg, 31%). A portion of the racemic ligand was separated into its enantiomers by semipreparative HPLC on a chiral column. Some of the isolated crystals were suitable for structure determination by X-ray analysis.

$C_{20}H_{24}NOPS$ (357.45 g*mol^{-1}):

m.p. 122 °C.

R_f = 0.13 (hexanes/EtOAc 7:3).

^{1}H NMR (500 MHz, C_6D_6): δ = 1.03 (s, 3 H, Ox-4-CH_3), 1.14 (dd, J(H,H) = 6.8 Hz, J(P,H) = 18.6 Hz, 3 H, CH(CH_3)(CH_3)), 1.15 (s, 3 H, Ox-4-CH_3), 1.21 (dd, J(H,H) = 6.8 Hz, J(P,H) = 18.6 Hz, 3 H, CH(CH_3)(CH_3)), 3.14 (m_c, 1 H, CH(CH_3)$_2$), 3.39 (d, J(H,H) = 7.7 Hz, 1 H, Ox-5-H), 3.72 (d, J(H,H) = 7.7 Hz, 1 H, Ox-5-H), 6.96-7.10 (m, 5 H, Ar-H), 7.74-7.82 (m, 3 H, Ar-H), 8.28 (dd, J(H,H) = 7.9 Hz, J(P,H) = 13.2 Hz, 1 H, Ar-3'-H) ppm.

^{13}C{^{1}H} NMR (126 MHz, C_6D_6): δ = 17.1 (d, J(C,P) = 41 Hz, CH(CH_3)$_2$), 27.9 (s, Ox-4-C(CH_3)(CH_3)), 28.0 (s, Ox-4-C(CH_3)(CH_3)), 28.9 (d, J(C,P) = 56 Hz, CH(CH_3)$_2$), 68.9 (s, Ox-4-C(CH_3)$_2$), 78.7 (s, Ox-5-CH_2), 128.5 (d, J(C,P) = 14 Hz, Ar-CH), 129.7 (d, J(C,P) = 11 Hz, Ar-CH), 130.4 (d, J(C,P) = 2 Hz, Ar-CH), 130.9 (d, J(C,P) = 3 Hz, Ar-CH), 131.3 (d, J(C,P) = 11 Hz, Ar-CH), 131.9 (d, J(C,P) = 8 Hz, Ar-CH), 132.1 (d, J(C,P) = 71 Hz, Ar-2'-C), 133.5 (d, J(C,P) = 6 Hz, Ar-1'-C), 134.3 (d, J(C,P) = 10 Hz, Ar-3'-CH), 135.7 (d, J(C,P) = 80 Hz, Ph-1''-C), 161.2 (d, J(C,P) = 4 Hz, Ox-2-C) ppm.

^{31}P{^{1}H} NMR (202 MHz, C_6D_6): δ = 70.0 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 2967m, 1653s, 1578m, 1457m, 1436s, 1349m, 1310m, 1103m, 1056m, 962m, 716s, 696s, 594m, 501m cm^{-1}.

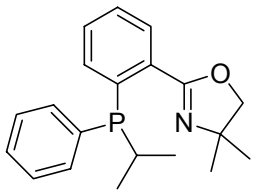
MS (FAB, NBA+KCl): *m/z* (%) = 396 (15, $[M+K]^+$), 358 (100, $[M+H]^+$), 314 (17), 286 (55), 282 (46), 248 (23), 210 (20), 55 (17).

$[a]_D^{20}$ = –57.0 ((*R*)-**162a**, *c* = 1.10, $CHCl_3$); +61.0 ((*S*)-**162a**, *c* = 1.00, $CHCl_3$).

HPLC (Daicel Chiracel AD, heptane/isopropanol 85:15, 6.0 mL*min^{-1}, 20 °C, 254 nm): t_R = 20.5 ((*R*)-**162a**), 24.9 ((*S*)-**162a**) min.

Elemental analysis calcd. (%) for $C_{20}H_{24}NOPS$: C 67.20, H 6.77, N 3.92; found: C 67.00, H 6.75, N 3.95.

4,4-Dimethyl-2-[2'-(isopropyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole (162)



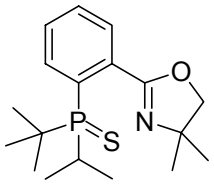
162

The deprotection was accomplished in analogy to the preparation of **158** using phosphine sulfide **162a** (160 mg, 0.447 mmol) and Si_2Cl_6 (313 mg, 1.16 mmol) in abs. benzene (20 mL), followed by the treatment with 30% degassed aqueous NaOH solution (3.1 mL). Ligand **162** was isolated as colourless oil (48.1 mg, 33%).

$C_{20}H_{24}NOPS$ (325.28 g*mol^{-1}):

$^{31}P\{^1H\}$ NMR (162 MHz, C_6D_6): δ = –8.2 (s) ppm.

4,4-Dimethyl-2-[2'-(*tert*-butyl-isopropyl-thiophosphino)-phenyl]-4,5-dihydro-oxazole (163a)



163a

In analogy to the preparation of **158a** phenyloxazoline **153** (294 mg, 1.68 mmol), TMEDA (214 mg, 1.83 mmol), *s*BuLi in cyclohexane (1.3 M, 1.70 mL, 2.21 mmol) and chloro-phosphine **150** (440 mg, 2.64 mmol) were reacted in abs. pentane (20 mL). Protection of the residue was accomplished with sulfur powder (95.0 mg, 2.96 mmol) in abs. toluene (20 mL) and column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 7:3, F35-65) of the crude product gave phosphine sufide **163a** as colourless solid (361 mg, 64%). A portion of the racemic ligand was separated into its enantiomers by semipreparative HPLC on a chiral column.

$C_{18}H_{28}NOPS$ (337.46 g*mol^{-1}):

m.p. 162 °C.

R_f = 0.21 (hexanes/EtOAc 2:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 0.95 (dd, J(H,H) = 6.7 Hz, J(P,H) = 17.4 Hz, 3 H, CH(CH_3)(CH_3)), 1.21 (d, J(P,H) = 15.8 Hz, 9 H, C(CH_3)$_3$), 1.31 (dd, J(H,H) = 6.6 Hz, J(P,H) = 17.4 Hz, 3 H, CH(CH_3)(CH_3)), 1.37 (s, 3 H, Ox-4-CH_3), 1.38 (s, 3 H, Ox-4-CH_3), 3.06 (m_c, 1 H, CH(CH_3)$_2$), 4.09 (d, J(H,H) = 8.0 Hz, 1 H, Ox-5-H), 4.14 (d, J(H,H) = 8.0 Hz, 1 H, Ox-5-H), 7.47-7.35 (m, 3 H, Ar-3'-H, Ar-4'-H and Ar-5'-H), 8.10 (br s, 1 H, Ar-6'-H) ppm.

^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2): δ = 17.1 (s, CH(*C*H_3)(CH_3)), 18.1 (s, CH(CH_3)(*C*H_3)), 26.7 (d, J(C,P) = 48 Hz, *C*H(CH_3)$_2$), 26.9 (d, J(C,P) = 2 Hz, C(*C*H_3)$_3$), 27.6 (s, Ox-4-C(*C*H_3)$_2$), 36.4 (d, J(C,P) = 47 Hz, *C*(CH_3)$_3$), 68.3 (s, Ox-4-*C*(CH_3)$_2$), 79.0 (s, Ox-5-CH_2), 128.9 (d, J(C,P) = 10 Hz, Ar-CH), 129.2 (d, J(C,P) = 61 Hz, Ar-2'-C), 130.6 (d, J(C,P) = 4 Hz, Ar-CH), 131.9 (d, J(C,P) = 10 Hz, Ar-CH), 134.3 (s, Ar-6'-CH), 134.6 (s, Ar-1'-C), 162.7 (s, Ox-2-C) ppm.

^{31}P{^{1}H} NMR (202 MHz, CD_2Cl_2): δ = 77.9 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 2973s, 1734m, 1695m, 1663s, 1559m, 1457m, 1362m, 1305m, 1096w, 1045m, 963m, 774s, 729m, 697s, 668m, 634m, 566w cm^{-1}.

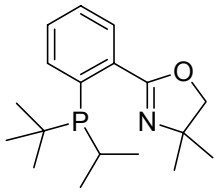
MS (FAB, NBA+KCl): *m/z* (%) = 376 (13, $[M+K]^+$), 338 (100, $[M+H]^+$), 248 (48), 210 (28), 150 (7), 57 (42).

$[a]_D^{20}$ = +15.0 ((+)-**163a**, *c* = 0.50, $CHCl_3$); –17.0 ((–)-**163a**, *c* = 0.50, $CHCl_3$).

HPLC (Daicel Chiracel OD, heptane/isopropanol 98:2, 6.0 mL*min^{-1}, 25 °C, 254 nm): t_R = 28.2 ((+)-**163a**), 37.0 ((–)-**163a**) min.

Elemental analysis calcd. (%) for $C_{18}H_{28}NOPS$: C 64.06, H 8.36, N 4.15, O 4.74; found: C 64.05, H 8.12, N 4.26, O 4.67.

4,4-Dimethyl-2-[2'-(*tert*-butyl-isopropylphosphino)-phenyl]-4,5-dihydrooxazole (163)



163

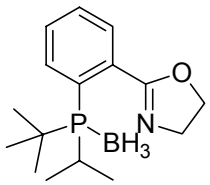
The deprotection was accomplished in analogy to the preparation of **158** using phosphine sulfide **163a** (105 mg, 0.311 mmol) and Si_2Cl_6 (320 mg, 1.19 mmol) in abs. benzene (13 mL), followed by the treatment with 30% degassed aqueous NaOH solution (3.2 mL). Ligand **163** was isolated as colourless oil (48.0 mg, 51%).

$C_{18}H_{28}NOPS$ (305.39 g*mol^{-1}):

^{1}H NMR (400 MHz, C_6D_6): δ = 0.91 (dd, *J*(H,H) = 6.9 Hz, *J*(P,H) = 14.0 Hz, 3 H, $CH(CH_3)(CH_3)$), 1.15 (d, *J*(P,H) = 11.1 Hz, 9 H, $C(CH_3)_3$), 1.20 (dd, *J*(H,H) = 6.8 Hz, *J*(P,H) = 14.1 Hz, 3 H, $CH(CH_3)(CH_3)$), 1.30 (s, 3 H, Ox-4-CH_3), 1.36 (s, 3 H, Ox-4-CH_3), 2.13 (m_c, 1 H, $CH(CH_3)_2$), 3.86 (d, *J*(H,H) = 7.9 Hz, 1 H, Ox-5-H), 3.92 (d, *J*(H,H) = 7.9 Hz, 1 H, Ox-5-H), 7.01-7.12 (m, 2 H, Ar-H), 7.41 (td, *J*(H,H) = 7.5 Hz, *J*(P,H) = 1.7 Hz, 1 H, Ar-H), 7.60 (m_c, 1 H, Ar-6'-H) ppm.

^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ = 8.5 (s) ppm.

2-[2'-(*tert*-Butyl-isopropylphosphino)-phenyl]-4,5-dihydrooxazole borane (164a)



164a

A solution of azeotropically dried (2 × 2.0 mL toluene) phenyloxazoline **152** (181 mg, 1.23 mmol) and TMEDA (159 mg, 1.37 mmol) in abs. pentane (10 mL) was cooled to –78 °C and *s*BuLi in cyclohexane (1.3 M, 1.20 mL, 2.34 mmol) was added dropwise. After the reaction mixture had been stirred for 30 min at –78 °C and then 15 min at 0 °C, the orange suspension was re-cooled to –78 °C and treated with chlorophosphine **150** (273 mg, 1.64 mmol). The resulting yellow mixture was allowed to warm to r.t. overnight and then filtered over Celite under argon. Afterwards BH_3 in THF (1.0 M, 2.50 mL, 2.50 mmol) was added to the filtrate at 0 °C. After 16 h at r.t. the solvent was evaporated. Column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 1:1, F20-29) of the residue yielded a colourless solid (125 mg, 35%). According to mass spectrometric analysis this consisted of a mixture of **164a** and and the bis(borane) adduct **164b**.

$C_{16}H_{27}BNOP$ (291.18 g*mol^{-1}):

$\boldsymbol{R_f}$ = 0.19 (pentane/Et_2O 1:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.09-0.77 (br m, 3 H, BH_3), 0.92 (dd, J(H,H) = 6.9 Hz, J(P,H) = 15.7 Hz, 3 H, CH(CH_3)(CH_3)), 1.18 (d, J(P,H) = 13.5 Hz, 9 H, C(CH_3)$_3$), 1.38 (dd, J(H,H) = 6.9 Hz, J(P,H) = 14.9 Hz, 3 H, CH(CH_3)(CH_3)), 2.68 (sept, J(H,H) = 6.9 Hz, 1 H, CH(CH_3)$_2$), 4.10 (t, J(H,H) = 10.2 Hz, 2 H, Ox-4-H), 4.67 (m_c, 1 H, Ox-5-H), 4.84 (m_c, 1 H, Ox-5-H), 7.47-7.51 (m, 1 H, Ar-H), 7.64 (m_c, 2 H, Ar-H), 7.80 (m_c, 1 H, Ar-H) ppm.

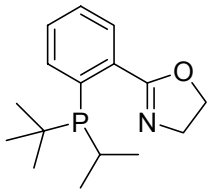
^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ = 17.8 (d, J(C,P) = 3 Hz, CH(*C*H_3)(CH_3)), 18.6 (s, CH(CH_3)(*C*H_3)), 24.1 (d, J(C,P) = 33 Hz, *C*H(CH_3)$_2$), 27.1 (d, J(C,P) = 2 Hz, C(*C*H_3)$_3$), 31.2 (d, J(C,P) = 28 Hz, *C*(CH_3)$_3$), 55.6 (s, Ox-4-CH_2), 68.7 (s, Ox-5-CH_2), 128.2 (d, J(C,P) = 48 Hz, Ar-C), 130.5 (d, J(C,P) = 6 Hz, Ar-CH), 130.7 (d, J(C,P) = 2 Hz, Ar-CH), 131.4 (d, J(C,P) = 8 Hz, Ar-CH), 132.0 (d, J(C,P) = 9 Hz, Ar-C), 132.6 (s, Ar-CH) ppm; despite prolonged data acquisition time the signal for Ox-2-C was not detected.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ = 40.1 (d, J(P,B) = 60 Hz) ppm.

IR (KBr): $\tilde{\nu}$ = 2979s, 2930s, 2067m, 1839s, 1671s, 1588m, 1468s, 1389s, 1272s, 1167s, 1076s, 921s, 809s, 765m, 616m, 551m cm^{-1}.

MS (FAB, NBA): *m/z* (%) = 304 (25, $[M+BH_2]^+$), 290 (100, $[M-H]^+$), 234 (17, $[M-C_4H_9]^+$), 190 (20), 57 (31).

2-[2'-(*tert*-Butyl-isopropylphosphino)-phenyl]-4,5-dihydrooxazole (160)



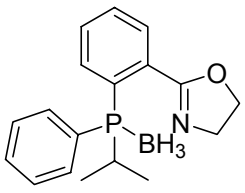
160

The BH_3 protecting group was removed by stirring **164a** (107 mg, 0.368 mmol) in abs. $HNEt_2$ (2.0 mL) at r.t. for 12 h. After all volatiles had been removed under reduced pressure, the free ligand **160** was isolated as colourless oil (103 mg, quant.).

$C_{16}H_{24}NOPS$ (277.34 g*mol^{-1}):

$^{31}P\{^1H\}$ NMR (162 MHz, C_6D_6): δ = 9.1 (s) ppm.

2-[2'-(Isopropyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole borane (165a)



165a

In analogy to the preparation of **164a** phenyloxazoline **152** (189 mg, 1.28 mmol), TMEDA (187 mg, 1.61 mmol), *s*BuLi in cyclohexane (1.3 M, 1.30 mL, 1.69 mmol) and chlorophosphine **145** (311 mg, 1.67 mmol) were reacted in abs. pentane (10 mL). Protection of the residue was accomplished with BH_3 in THF (1.0 M, 5.00 mL, 5.00 mmol) and column chromatography (silica gel, 4 × 15 cm, pentane/Et_2O 1:2, F34-49) of the crude product gave a

colourless solid (266 mg, 67%). According to mass spectrometric analysis this consisted of a mixture of **165a** and bis(borane) adduct **165b**.

$C_{18}H_{23}BNOP$ (311.17 g*mol^{-1}):

R_f = 0.14 (pentane/Et_2O 1:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.29-2.91 (br m, 3 H, BH_3), 1.07 (dd, J(H,H) = 7.1 Hz, J(P,H) = 16.8 Hz, 3 H, CH(CH_3)(CH_3)), 1.17 (dd, J(H,H) = 6.9 Hz, J(P,H) = 15.6 Hz, 3 H, CH(CH_3)(CH_3)), 3.88 (m_c, 1 H, CH(CH_3)$_2$), 3.62 (m_c, 1 H, Ox-4-H), 3.76 (m_c, 1 H, Ox-4-H), 3.91 (m_c, 1 H, Ox-5-H), 4.33 (m_c, 1 H, Ox-5-H), 7.49-7.57 (m, 3 H, Ar-H), 7.60-7.73 (m, 5 H, Ar-H), 7.96 (m_c, 1 H, Ar-3'-H) ppm.

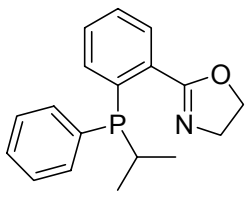
^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ = 17.2 (d, J(C,P) = 2 Hz, CH(CH_3)(CH_3)), 17.4 (s, CH(CH_3)(CH_3)), 24.6 (d, J(C,P) = 35 Hz, CH(CH_3)$_2$), 55.8 (s, Ox-4-CH_2), 68.2 (s, Ox-5-CH_2), 127.4 (d, J(C,P) = 54 Hz, Ar-C), 128.8 (d, J(C,P) = 4 Hz, Ar-1'-C), 129.1 (d, J(C,P) = 10 Hz, Ar-CH), 129.5 (d, J(C,P) = 45 Hz, Ar-C), 130.8 (d, J(C,P) = 2 Hz, Ar-CH), 131.7 (d, J(C,P) = 3 Hz, Ar-CH), 131.9 (d, J(C,P) = 9 Hz, Ar-CH), 132.8 (d, J(C,P) = 6 Hz, Ar-CH), 132.9 (d, J(C,P) = 9 Hz, Ar-CH), 134.5 (d, J(C,P) = 8 Hz, Ar-CH), 167.6 (d, J(C,P) = 3 Hz, Ox-2-C) ppm.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ = 26.6 (d, J(P,B) = 64 Hz) ppm.

IR (KBr): $\tilde{\nu}$ = 3023m, 2955m, 2067m, 1645s, 1470s, 1399s, 1351m, 1308m, 1249m, 1163s, 1009s, 872s, 795m, 685m, 633w, 593w cm^{-1}.

MS (FAB, NBA): *m/z* (%) = 324 (29, [M+BH_2]$^+$), 310 (100, [M–H]$^+$), 266 (11), 129 (45), 58 (29).

2-[2'-(Isopropyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole (159)



159

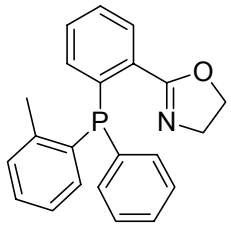
The BH_3 protecting group was removed by stirring **165a** (100 mg, 0.322 mmol) in degassed abs. $HNEt_2$ (2.0 mL) at r.t. for 12 h. After all volatiles had been removed under reduced pressure the free ligand **159** was isolated as colourless oil (98.0 mg, quant.).

$C_{18}H_{20}NOP$ (297.33 g*mol^{-1}):

$^{31}P\{^1H\}$ NMR (162 MHz, C_6D_6): δ = –8.1 (s) ppm.

7.8.4 Diaryl-Substituted Phosphinooxazolines

2-{2'-[Phenyl-(2''-tolyl)-phosphino]-phenyl}-4,5-dihydrooxazole (180)



180

A solution of azeotropically dried (2 × 2.0 mL toluene) phenyloxazoline **152** (180 mg, 1.22 mmol) and TMEDA (156 mg, 1.34 mmol) in abs. pentane (10 mL) was cooled to –78 °C and *s*BuLi in cyclohexane (1.3 M, 1.00 mL, 1.30 mmol) was added dropwise. After the reaction mixture had been stirred for 30 min at –78 °C and then 15 min at 0 °C, the yellow-orange suspension was re-cooled to –78 °C and treated with chlorophosphine **167** (375 mg, 1.59 mmol). The yellow mixture was allowed to slowly reach r.t. overnight. The suspension was diluted with abs. CH_2Cl_2 (30 mL) and filtered over Celite, which was washed with abs. CH_2Cl_2 (2 × 10 mL). After removal of all volatiles in high vacuum the crude product was purified by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 4:1, F30-35) under argon. Ligand **180** was obtained as colourless foam (105 mg, 25%).

$C_{22}H_{20}NOP$ (345.37 g*mol^{-1}):

$\boldsymbol{R_f}$ = 0.42 (hexanes/EtOAc 4:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 2.42 (s, 3 H, CH_3), 3.81 (m_c, 2 H, Ox-4-H), 4.14 (t, *J*(H,H) = 9.3 Hz, 2 H, Ox-5-H), 6.81 (dd, *J*(H,H) = 7.7 Hz, *J*(P,H) = 4.1 Hz, 1 H, Ar-H), 6.93 (ddd, *J*(H,H) = 7.7, 1.0 Hz, *J*(P,H) = 4.2 Hz, 1 H, Ar-H), 7.06 (t, *J*(H,H) = 7.0 Hz, 1 H, Ar-

H), 7.19-7.40 (m, 9 H, Ar-H), 7.83 (dd, *J*(H,H) = 7.6 Hz, *J*(P,H) = 3.7 Hz, 1 H, Ar-6'-H) ppm.

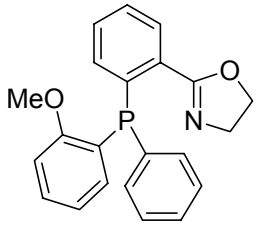
$^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2): δ = 21.1 (d, *J*(C,P) = 23 Hz, CH_3), 55.2 (s, Ox-4-CH_2), 67.3 (s, Ox-5-CH_2), 125.9 (s, Ar-CH), 128.1 (s, Ar-CH), 128.5 (d, *J*(C,P) = 7 Hz, Ar-CH), 128.6 (d, *J*(C,P) = 8 Hz, Ar-CH), 129.8 (d, *J*(C,P) = 3 Hz, Ar-CH), 129.9 (d, *J*(C,P) = 5 Hz, Ar-6'-CH), 130.4 (s, Ar-CH), 132.6 (s, Ar-1'-C), 133.3 (s, Ar-CH), 134.1 (s, Ar-CH), 134.3 (d, *J*(C,P) = 21 Hz, Ar-CH), 137.2 (d, *J*(C,P) = 12 Hz, Ar-C), 137.6 (d, *J*(C,P) = 12 Hz, Ph-*i*-C), 138.6 (d, *J*(C,P) = 25 Hz, Ar-2'-C), 142.3 (d, *J*(C,P) = 27 Hz, *o*Tol-2''-C), 164.0 (d, *J*(C,P) = 2 Hz, Ox-2-C) ppm.

$^{31}P\{^1H\}$ NMR (202 MHz, CD_2Cl_2): δ = −15.3 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 3046m, 2963m, 2892m, 1956w, 1737w, 1643s, 1582m, 1465s, 1430s, 1346s, 1245s, 1194m, 1128m, 1086m, 1036m, 970m, 938s, 894m, 802w, 750s, 693s, 549w cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 384 (8, $[M+K]^+$), 346 (100, $[M+H]^+$), 254 (39), 165 (28), 77 (33).

2-[2'-(2''-Methoxyphenyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole (181)



181

The ligand synthesis was accomplished in analogy to the preparation of **180** using phenyloxazoline **152** (84.0 mg, 0.571 mmol), TMEDA (72.0 mg, 0.620 mmol) in abs. pentane (5.0 mL), *s*BuLi in cyclohexane (1.3 M, 480 µL, 0.624 mmol) and chlorophosphine **169** (180 mg, 0.718 µmol). Purification of the crude product by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 2:1, F29-37) under argon gave ligand **181** as colourless solid (128 mg, 62%).

$C_{22}H_{20}NO_2P$ (361.37 g*mol^{-1}).

R_f = 0.32 (hexanes/EtOAc 2:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 3.71 (s, 3 H, OCH_3), 3.83 (t, *J*(H,H) = 9.5 Hz, 2 H, Ox-4-H), 4.16 (t, *J*(H,H) = 9.5 Hz, 2 H, Ox-5-H), 6.67 (m_c, 1 H, Ar-H), 6.84 (t, *J*(H,H) = 7.6 Hz, 1 H, Ar-H), 6.91 (dd, *J*(H,H) = 8.3 Hz, *J*(P,H) = 4.7 Hz, 1 H, Ar-H), 6.96 (dd, *J*(H,H) = 7.8 Hz, *J*(P,H) = 3.8 Hz,1 H, Ar-H), 7.22-7.39 (m, 8 H, Ar-H), 7.82 (ddd, *J*(H,H) = 7.7, 3.7 Hz, *J*(P,H) = 4.1 Hz, 1 H, Ar-H) ppm.

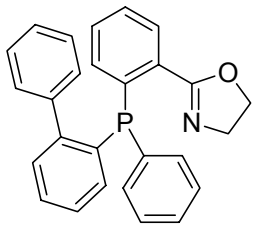
^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2): δ = 55.2 (s, Ox-4-CH_2), 55.7 (s, OCH_3), 67.3 (s, Ox-5-CH_2), 110.5 (s, Ar-CH), 120.9 (s, Ar-CH), 126.8 (d, *J*(C,P) = 14 Hz, Ar-C), 128.0 (s, Ar-CH), 128.3 (s, Ar-CH), 128.3 (s, Ar-CH), 125.5 (s, Ar-CH), 129.6 (d, *J*(C,P) = 45 Hz, Ar-CH), 130.2 (s, Ar-CH), 132.6 (d, *J*(C,P) = 22 Hz, Ar-C), 134.0 (s, Ar-CH), 134.0 (d, *J*(C,P) = 3 Hz, Ar-CH), 134.2 (d, *J*(C,P) = 22 Hz, Ar-CH), 138.0 (d, *J*(C,P) = 12 Hz, Ar-C), 138.6 (d, *J*(C,P) = 27 Hz, Ar-C), 161.3 (d, *J*(C,P) = 17 Hz, Ar-2''-C), 164.1 (s, Ox-2-C) ppm.

^{31}P{^{1}H} NMR (202 MHz, CD_2Cl_2): δ = –17.4 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 3055m, 2963m, 2891m, 1971w, 1732w, 1640s, 1575s, 1463s, 1429s, 1349m, 1239s, 1180m, 1125w, 1088m, 1018s, 972m, 938m, 896w, 778m, 747s, 691s, 483w cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 361 (16, M^+), 332 (100), 302 (23), 270 (41), 227 (34), 183 (20), 77 (8).

2-[2'-(2''-Biphenylyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole (182)



182

The ligand synthesis was accomplished in analogy to the preparation of **180** using phenyloxazoline **152** (115 mg, 0.781 mmol), TMEDA (107 mg, 0.921 mmol), *s*BuLi in cyclohexane (1.3 M, 660 µL, 0.858 mmol) and chlorophosphine **170 (**270 mg, 0.910 mmol) in abs. pentane (6.0 mL). Purification of the crude product by column chromatography (silica gel, 3 × 20 cm, pentane/Et_2O/NEt_3 10:20:1, F9-17) under argon gave ligand **182** as colourless solid (136 mg, 43%).

$C_{27}H_{22}NOP$ (407.44 g*mol^{-1}):

R_f = 0.33 (hexanes/EtOAc 2:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 3.75 (t, J(H,H) = 9.7 Hz, 2 H, Ox-4-H), 4.08 (m_c, 2 H, Ox-5-H), 6.95 (dd, J(H,H) = 7.7 Hz, J(P,H) = 3.5 Hz, 1 H, Ar-H), 7.07 (dd, J(H,H) = 7.6 Hz, J(P,H) = 3.4 Hz, 1 H, Ar-H), 7.17-7.43 (m, 15 H, Ar-H), 7.81 (ddd, J(H,H) = 7.7, 1.3 Hz, J(P,H) = 3.7 Hz, 1 H, Ar-6'-H) ppm.

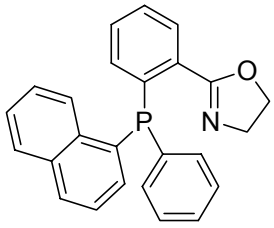
^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2): δ = 55.2 (s, Ox-4-CH_2), 67.3 (s, Ox-5-CH_2), 127.1 (s, Ar-CH), 127.3 (s, Ar-CH), 127.5 (s, Ar-CH), 127.9 (s, Ar-CH), 128.4 (d, J(C,P) = 4 Hz, Ar-CH), 128.5 (s, Ar-CH), 129.6 (s, Ar-CH), 129.7 (d, J(C,P) = 4 Hz, Ar-CH), 130.0 (d, J(C,P) = 4 Hz, Ar-CH), 130.2 (s, Ar-CH), 131.9 (d, J(C,P) = 22 Hz, Ar-1'-C), 133.8 (d, J(C,P) = 2 Hz, Ar-CH), 134.2 (s, Ar-CH), 134.3 (s, Ar-CH), 134.5 (s, Ar-CH), 136.8 (d, J(C,P) = 12 Hz, Ar-C), 138.9 (d, J(C,P) = 16 Hz, Ar-C), 140.1 (d, J(C,P) = 28 Hz, Ar-C), 142.3 (d, J(C,P) = 8 Hz, Ar-C), 147.9 (d, J(C,P) = 31 Hz, Ar-C), 164.0 (d, J(C,P) = 2 Hz, Ox-2-C) ppm.

^{31}P{^{1}H} NMR (202 MHz, CD_2Cl_2): δ = –14.2 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 3047m, 2968m, 1951w, 1816w, 1765w, 1733w, 1642s, 1581m, 1462s, 1428s, 1347m, 1242m, 1180w, 1084m, 1036s, 970m, 938s, 747s, 697s, 613m, 499s cm^{-1}.

MS (EI, 70 eV): m/z (%) = 407 (35, M^+), 378 (100), 316 (27), 302 (27), 254 (34), 240 (18), 183 (31).

2-[2'-(1''-Naphthalenyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole (183)



183

The ligand synthesis was accomplished in analogy to the preparation of **180** using phenyloxazoline **152** (212 mg, 1.40 mmol), TMEDA (184 mg, 1.58 mmol), *s*BuLi in cyclohexane (1.3 M, 1.20 mL, 1.56 mmol) and chlorophosphine **171** (506 mg, 1.87 mmol) in abs. pentane (10 mL). Purification of the crude product by column chromatography (silica gel, 3 × 25 cm, hexanes/EtOAc/NEt_3 10:1:1, F9-15) under argon gave ligand **183** as colourless solid (362 mg, 71%).

$C_{25}H_{20}NOP$ (381.41 g*mol^{-1}):

R_f = 0.49 (hexanes/EtOAc 1:1).

^{1}H NMR (600 MHz, C_6D_6): δ = 3.38 (m_c, 2 H, Ox-4-H), 3.45 (m_c, 2 H, Ox-5-H), 6.85 (td, *J*(H,H) = 7.6, 1.2 Hz, 1 H, Ar-4'-H), 6.95-7.24 (m, 8 H, Ar-H), 7.33 (dd, *J*(H,H) = 7.3 Hz, *J*(P,H) =4.6 Hz, 1 H, Ar-2''-H), 7.46 (m_c, 2 H, Ph-*o*'-H), 7.60 (d, *J*(H,H) = 8.3 Hz, 1 H, Ar-4''-H), 7.62 (d, *J*(H,H) = 8.1 Hz, 1 H, Ar-5''-H), 8.12 (ddd, *J*(H,H) = 7.8, 1.1 Hz, *J*(P,H) = 3.5 Hz, 1 H, Ar-6'-H), 8.90 (m_c, 1 H, Ar-4a''-H) ppm.

^{13}C{^{1}H} NMR (151 MHz, C_6D_6): δ = 55.3 (s, Ox-4-CH_2), 66.6 (s, Ox-5-CH_2), 125.7 (s, Ar-3''-CH), 125.9 (d, *J*(C,P) = 1 Hz, Ar-6''-CH), 126.2 (d, *J*(C,P) = 1 Hz, Ar-7''-CH), 126.8 (d, *J*(C,P) = 25 Hz, Ar-8''-CH), 128.1 (s, Ar-5'-CH), 128.5 (s, Ph-*m*-CH and Ph-*p*-CH), 128.7 (s, Ar-5''-CH), 129.0 (s, Ar-4''-CH), 129.9 (d, *J*(C,P) = 3 Hz, Ar-6'-CH), 130.3 (s, Ar-4'-CH), 132.3 (s, Ar-2''-CH), 133.0 (d, *J*(C,P) = 21 Hz, Ar-8a''-C), 133.8 (d, *J*(C,P) = 6 Hz, Ar-1'-C), 134.6 (d, *J*(C,P) = 12 Hz, Ph-*o*-CH), 135.1 (s, Ar-3'-CH), 136.0 (d, *J*(C,P) = 24 Hz, Ar-4a''-C), 136.2 (d, *J*(C,P) = 14 Hz, Ph-*i*-C), 137.0 (d, *J*(C,P) = 14 Hz, Ar-1''-C), 139.3 (d, *J*(C,P) = 24 Hz, Ar-2'-C), 163.5 (s, Ox-2-C) ppm.

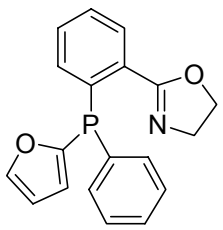
^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ = –19.6 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 3050m, 2966m, 2874m, 1730m, 1636s, 1499m, 1471s, 1427m, 1354s, 1320s, 1245m, 1132m, 1090m, 1040s, 970m, 938s, 749s, 700s, 675s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 381 (19, M^+), 352 (100), 290 (21), 240 (40), 227 (54).

Elemental analysis calcd. (%) for $C_{25}H_{20}NOP$: C 78.73, H 5.29, N 3.67; found: C 78.18, H 5.45, N 3.42.

2-[2'-(2''-Furanyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole (184)



184

The ligand synthesis was accomplished in analogy to the preparation of **180** using phenyloxazoline **152** (232 mg, 1.58 mmol), TMEDA (201 mg, 1.73 mmol), *s*BuLi in cyclohexane (1.3 M, 1.30 mL, 1.69 mmol) and chlorophosphine **172** (480 mg, 2.28 mmol) in

abs. pentane (12 mL). Purification of the crude product by column chromatography (silica gel, 3 cm × 20 cm, hexanes/EtOAc 2:1, F23-30) under argon gave ligand **184** as colourless solid (215 mg, 42%).

$C_{19}H_{16}NO_2P$ (321.30 g*mol^{-1}):

R_f = 0.39 (hexanes/EtOAc 4:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 3.75 (t, *J*(H,H) = 9.7 Hz, 1 H, Ox-4-H), 3.83 (t, *J*(H,H) = 9.7 Hz, 1 H, Ox-4-H), 4.14 (t, *J*(H,H) = 9.7 Hz, 2 H, Ox-5-H), 6.42 (m_c, 1 H, Fu-4''-H), 6.61 (m_c, 1 H, Fu-3''-H), 7.05 (m_c, 1 H, Ar-H), 7.28-7.43 (m, 8 H, Ar-H), 7.81 (m_c, 1 H, Ar-6'-H) ppm.

^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2): δ = 55.0 (s, Ox-4-CH_2), 67.3 (s, Ox-5-CH_2), 110.8 (d, *J*(C,P) = 6 Hz, Fu-4''-CH), 121.8 (d, *J*(C,P) = 23 Hz, Fu-3''-CH), 128.3 (d, *J*(C,P) = 15 Hz, Ar-CH), 128.7 (s, Ar-CH), 129.6 (d, *J*(C,P) = 2 Hz, Ar-CH), 130.4 (s, Ar-CH), 131.6 (d, *J*(C,P) = 18 Hz, Ar-C), 133.4 (s, Ar-CH), 133.5 (s, Ar-CH), 133.6 (s, Ar-CH), 137.1 (d, *J*(C,P) = 2 Hz, Ar-C), 138.3 (d, *J*(C,P) = 24 Hz, Ar-C), 147.4 (s, Fu-5''-CH), 154.0 (d, *J*(C,P) = 22 Hz, Fu-2''-C), 161.5 (dd, *J*(C,P) = 4 Hz, Ox-2-C) ppm.

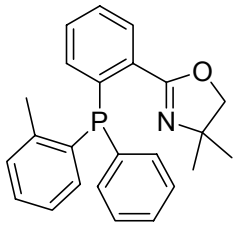
^{31}P{^{1}H} NMR (202 MHz, CD_2Cl_2): δ = –27.9 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 3063m, 2963m, 2909m, 1726m, 1646s, 1469s, 1431s, 1355m, 1250m, 1207m, 1136m, 1090m, 1038s, 1003m, 972m, 938m, 896m, 745s, 694s, 670m, 596w cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 321 (5, M^+), 292 (100), 240 (67), 227 (72), 202 (15), 183 (19).

Elemental analysis calcd. (%) for $C_{19}H_{16}NO_2P$: C 71.02, H 5.02, N 4.36; found: C 70.93, H 5.26, N 3.98.

4,4-Dimethyl-2-{2'-[Phenyl-(2''-tolyl)-phosphino]-phenyl}-4,5-dihydrooxazole (185)



185

The ligand synthesis was accomplished in analogy to the preparation of **180** using phenyloxazoline **153** (196 mg, 1.12 mmol), TMEDA (150 mg, 1.29 mmol), *s*BuLi in cyclohexane (1.3 M, 970 µL, 1.24 mmol), and chlorophosphine **167** (340 mg, 1.45 mmol) in abs. pentane (10 mL). Purification of the crude product by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 4:1, F16-23) under argon gave ligand **185** as colourless oil (168 mg, 40%).

$C_{24}H_{24}NOP$ (373.43 g*mol^{-1}):

$\boldsymbol{R_f}$ = 0.20 (hexanes/EtOAc 4:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 0.99 (s, 3 H, Ox-4-CH_3), 1.10 (s, 3 H, Ox-4-CH_3), 2.44 (d, J(P,H) = 2.6 Hz, 3 H, *o*Tol-CH_3), 3.77 (m_c, 2 H, Ox-5-H), 6.81 (dd, J(H,H) = 7.7 Hz, J(P,H) = 4.1 Hz, 1 H, Ar-H), 6.86 (ddd, J(H,H) = 7.7, 1.0 Hz, J(P,H) = 3.9 Hz, 1 H, Ar-H), 7.05 (td, J(H,H) = 7.1, 1.7 Hz, 1 H, Ar-H), 7.21 (m_c, 2 H, Ar-H), 7.25-7.39 (m, 7 H, Ar-H), 7.83 (ddd, J(H,H) = 7.7, 1.2 Hz, J(P,H) = 3.7 Hz, 1 H, Ar-6'-H) ppm.

^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2): δ = 21.1 (d, J(C,P) = 23 Hz, *o*Tol-CH_3), 27.6 (s, Ox-4-C(CH_3)(CH_3)), 27.8 (s, Ox-4-C(CH_3)(CH_3)), 68.0 (s, Ox-4-C(CH_3)$_2$), 78.6 (s, Ox-5-CH_2), 125.9 (s, Ar-CH), 127.9 (s, Ar-CH), 128.5 (d, J(C,P) = 4 Hz, Ar-CH), 128.6 (d, J(C,P) = 19 Hz, Ar-CH), 128.8 (d, J(C,P) = 3 Hz, Ar-CH), 130.0 (d, J(C,P) = 5 Hz, Ar-6'-CH), 130.3 (s, Ar-CH), 132.4 (s, Ar-1'-C), 132.7 (s, Ar-CH), 133.6 (d, J(C,P) = 2 Hz, Ar-CH), 134.7 (d, J(C,P) = 22 Hz, Ar-CH), 137.4 (d, J(C,P) = 11 Hz, *o*Tol-1''-C), 137.5 (d, J(C,P) = 14 Hz, Ph-*i*-C), 138.7 (d, J(C,P) = 26 Hz, Ar-2'-C), 142.3 (d, J(C,P) = 28 Hz, *o*Tol-2''-C), 161.5 (d, J(C,P) = 3 Hz, Ox-2-C) ppm.

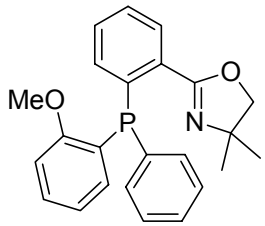
^{31}P{^{1}H} NMR (202 MHz, CD_2Cl_2): δ = –14.3 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 3053m, 2963m, 2883m, 1971w, 1936w, 1735w, 1639s, 1585m, 1437s, 1348m, 1309s, 1249m, 1184m, 1125m, 1087m, 1029m, 961s, 919m, 871m, 815w, 754s, 696s, 613w, 549w cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 412 (8, $[M+K]^+$), 374 (100, $[M+H]^+$), 318 (81), 302 (43), 183 (21), 165 (22), 77 (20), 55 (52).

Elemental analysis calcd. (%) for $C_{24}H_{24}NOP$: C 77.19, H 6.48, N 3.75; found: C 77.13, H 6.50, N 3.65.

4,4-Dimethyl-2-[2'-(2''-methoxyphenyl-phenylphosphino)-phenyl]-4,5-dihydro-oxazole (186)



186

The ligand synthesis was accomplished in analogy to the preparation of **180** using phenyloxazoline **153** (135 mg, 0.771 mmol), TMEDA (100 mg, 0.861 mmol), *s*BuLi in cyclohexane (1.3 M, 650 µL, 0.845 mmol) and chlorophosphine **169** (250 mg, 0.998 mmol) in abs. pentane (6.0 mL). Purification of the crude product by column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 4:1, F20-30) under argon gave ligand **186** as colourless oil (85.2 mg, 28%).

$C_{24}H_{24}NO_2P$ (389.43 g*mol^{-1}):

R_f = 0.37 (hexanes/EtOAc 1:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 1.06 (s, 3 H, Ox-4-CH_3), 1.07 (s, 3 H, Ox-4-CH_3), 3.74 (s, 3 H, OCH_3), 3.79 (m_c, 2 H, Ox-5-H), 6.69 (ddd, *J*(H,H) = 7.5, 1.7 Hz, *J*(P,H) = 4.3 Hz, 1 H, Ar-H), 6.82 (t, *J*(H,H) = 7.0 Hz, 1 H, Ar-H), 6.87-6.94 (m, 2 H, Ar-H), 7.24-7.83 (m, 8 H, Ar-H), 7.78 (m_c, 1 H, Ar-6'-H) ppm.

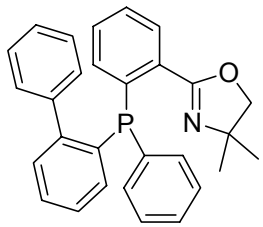
^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2): δ = 27.7 (s, Ox-4-C(CH_3)(CH_3)), 27.7 (s, Ox-4-C(CH_3)(CH_3)), 55.7 (s, OCH_3), 68.2 (s, Ox-4-C(CH_3)$_2$), 78.6 (s, Ox-5-CH_2), 110.5 (d, *J*(C,P) = 2 Hz, Ar-CH), 121.0 (s, Ar-CH), 123.3 (s, Ar-CH), 127.8 (s, Ar-CH), 128.5 (d, *J*(C,P) = 22 Hz, Ar-CH), 130.0 (d, *J*(C,P) = 49 Hz, Ar-CH), 130.3 (s, Ar-6'-CH), 130.5 (d, *J*(C,P) = 15 Hz, Ar-CH), 133.7 (d, *J*(C,P) = 63 Hz, Ar-CH), 134.5 (d, *J*(C,P) = 15 Hz, Ar-CH), 134.8 (s, Ar-CH), 135.8 (s, Ar-CH), 137.7 (d, *J*(C,P) = 13 Hz, Ar-C), 137.9 (d, *J*(C,P) = 16 Hz, Ar-C), 138.7 (d, *J*(C,P) = 27 Hz, Ar-C), 161.4 (d, *J*(C,P) = 16 Hz, Ar-2''-C) ppm; despite prolonged data acquisition time the signal for Ox-2-C was not detected.

^{31}P{^{1}H} NMR (202 MHz, CD_2Cl_2): δ = –19.8 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 3054m, 2962m, 1971w, 1953w, 1735w, 1648s, 1577m, 1463s, 1429s, 1350m, 1306s, 1240m, 1180m, 1127m, 1083m, 1030s, 962s, 919m, 871w, 817w, 746s, 693s, 613w, 482w cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 412 (8, $[M+K]^+$), 374 (100, $[M+H]^+$), 318 (81), 302 (43), 183 (21), 165 (22), 77 (20), 55 (52).

4,4-Dimethyl-2-[2'-(2''-biphenylyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole (187)



187

The ligand synthesis was accomplished in analogy to the preparation of **180** using phenyloxazoline **153** (94.4 mg, 0.539 mmol), TMEDA (86.0 mg, 0.740 mmol), *s*BuLi in cyclohexane (1.3 M, 460 µL, 0.598 mmol) and chlorophosphine **170** (188 mg, 0.634 mmol) in abs. pentane (5.0 mL). Purification of the crude product by column chromatography (silica gel, 3 × 15 cm, pentane/Et_2O/NEt_3 20:10:1, F6-14) under argon gave ligand **187** as colourless solid (86.0 mg, 37%).

$C_{29}H_{26}NOP$ (435.49 g*mol^{-1}):

R_f = 0.13 (pentane/Et_2O 1:2).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 0.97 (s, 3 H, Ox-4-CH_3), 1.05 (s, 3 H, Ox-4-CH_3), 3.72 (m_c, 2 H, Ox-5-H), 6.87 (dd, *J*(H,H) = 7.8 Hz, *J*(P,H) = 3.5 Hz, 1 H, Ar-H), 7.06 (dd, *J*(H,H) = 7.9 Hz, *J*(P,H) = 3.3 Hz, 1 H, Ar-H), 7.16-7.44 (m, 15 H, Ar-H), 7.85 (dd, *J*(H,H) = 7.7 Hz, *J*(P,H) = 3.7 Hz, 1 H, Ar-6'-H) ppm.

^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2): δ = 27.6 (s, Ox-4-C(CH_3)(CH_3)), 27.7 (s, Ox-4-C(CH_3)(CH_3)), 67.9 (s, Ox-4-*C*(CH_3)$_2$), 78.6 (s, Ox-5-CH_2), 127.2 (d, *J*(C,P) = 30 Hz, Ar-CH), 127.5 (s, Ar-CH), 127.7 (s, Ar-CH), 128.4 (s, Ar-CH), 128.5 (d, *J*(C,P) = 7 Hz, Ar-CH), 128.6 (s, Ar-CH), 129.6 (s, Ar-CH), 129.8 (d, *J*(C,P) = 4 Hz, Ar-CH), 130.0 (d, *J*(C,P) = 2 Hz, Ar-CH), 130.2 (d, *J*(C,P) = 7 Hz, Ar-CH), 130.3 (s, Ar-CH), 131.9 (d, *J*(C,P) = 21 Hz, Ar-1'-C), 133.6 (s, Ar-CH), 134.2 (d, *J*(C,P) = 3 Hz, Ar-CH), 134.5 (d, *J*(C,P) = 22 Hz, Ar-CH), 136.9 (d, *J*(C,P) = 15 Hz, Ar-C), 138.8 (d, *J*(C,P) = 15 Hz, Ar-C),

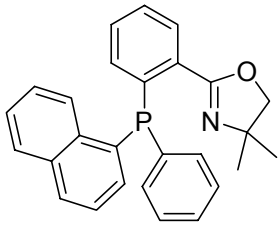
139.7 (d, *J*(C,P) = 28 Hz, Ar-C), 142.1 (d, *J*(C,P) = 7 Hz, Ar-C), 147.5 (d, *J*(C,P) = 33 Hz, Ar-C), 161.5 (s, Ox-2-C) ppm.

^{31}P{^{1}H} NMR (202 MHz, CD_2Cl_2): δ = –12.0 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 2961m, 1651s, 1462s, 1430s, 1347m, 1305m, 1177w, 1129w, 1081m, 1031s, 961m, 776m, 742s, 696s, 519m, 485m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 435 (15, M^+), 378 (100), 350 (11), 282 (37), 228 (12), 183 (21).

4,4-Dimethyl-2-[2'-(1'''-naphthalenyl-phenylphosphino)-phenyl]-4,5-dihydro-oxazole (188)



188

The ligand synthesis was accomplished in analogy to the preparation of **180** using phenyloxazoline **153** (205 mg, 1.17 mmol), TMEDA (159 mg, 1.37 mmol), *s*BuLi in cyclohexane (1.3 M, 900 µL, 1.17 mmol), chlorophosphine **171** (428 mg, 1.58 mmol) in abs. pentane (10 mL). Purification of the crude product by column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc/NEt_3 18:1:1, F5-9) under argon gave ligand **188** as colourless foam (334 mg, 70%).

$C_{27}H_{24}NOP$ (409.46 g*mol^{-1}):

R_f = 0.55 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.70 (s, 3 H, Ox-4-CH_3), 0.96 (s, 3 H, Ox-4-CH_3), 3.46 (m_c, 2 H, Ox-5-H), 6.87 (t, *J*(H,H) = 7.8 Hz, 1 H, Ar-H), 6.99-7.14 (m, 6 H, Ar-H), 7.23 (m_c, 2 H, Ar-H), 7.35 (m_c, 1 H, Ar-H), 7.48 (m_c, 2 H, Ar-H), 7.57-7.67 (m, 2 H, Ar-H), 8.15 (ddd, *J*(H,H) = 7.8, 1.2 Hz, *J*(P,H) = 3.7 Hz, 1 H, Ar-6'-H), 9.02 (m_c, 1 H, Ar-2''-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ = 27.9 (s, Ox-4-C(CH_3)(CH_3)), 28.3 (s, Ox-4-C(CH_3)(CH_3)), 68.3 (s, Ox-4-$C(CH_3)_2$), 78.6 (s, Ox-5-CH_2), 126.0 (s, Ar-CH), 126.2 (d, *J*(C,P) = 2 Hz, Ar-CH), 126.4 (d, *J*(C,P) = 3 Hz, Ar-CH), 127.1 (d, *J*(C,P) = 30 Hz, Ar-CH), 128.1 (s, Ar-CH), 128.8 (d, *J*(C,P) = 7 Hz, Ar-CH), 128.9 (s, Ar-CH), 129.3 (s, Ar-CH),

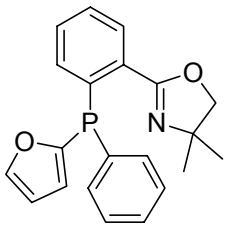
130.2 (s, Ar-CH), 130.5 (s, Ar-CH), 132.0 (s, Ar-C), 132.6 (s, Ar-CH), 132.8 (s, Ar-CH), 134.1 (d, *J*(C,P) = 5 Hz, Ar-C), 134.9 (d, *J*(C,P) = 2 Hz, Ar-CH), 135.1 (s, Ar-CH), 136.5 (d, *J*(C,P) = 25 Hz, Ar-C), 137.6 (d, *J*(C,P) = 13 Hz, Ar-C), 138.9 (d, *J*(C,P) = 15 Hz, Ar-C), 140.1 (d, *J*(C,P) = 27 Hz, Ar-8a''-C), 161.0 (d, *J*(C,P) = 3 Hz, Ox-2-C) ppm.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ = –18.5 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 3051m, 2964m, 1942w, 1827w, 1736m, 1656s, 1585s, 1501m, 1461s, 1432s, 1381m, 1348m, 1307s, 1250m, 1187m, 1084m, 1031s, 959s, 918m, 869w, 797m, 773s, 743s, 694s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 409 (8, M^+), 352 (100), 282 (17), 233 (13), 127 (5).

4,4-Dimethyl-2-[2'-(2''-furanyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole (189)



189

The ligand synthesis was accomplished in analogy to the preparation of **180**, using phenyloxazoline **153** (262 mg, 1.50 mmol), TMEDA (193 mg, 1.66 mmol), *s*BuLi in cyclohexane (1.3 M, 1.30 mL, 1.69 mmol), and chlorophosphine **172** (460 mg, 2.18 mmol) in abs. pentane (12 mL). Purification of the crude product by column chromatography (silica gel, 3 × 15 cm, hexanes/EtOAc 3:1, F18-25) under argon gave ligand **189** as colourless solid (115 mg, 22%).

$C_{21}H_{20}NO_2P$ (349.36 g*mol^{-1}):

R_f = 0.48 (hexanes/EtOAc 1:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.01 (s, 3 H, Ox-4-CH_3), 1.13 (s, 3 H, Ox-4-CH_3), 3.77 (d, *J*(H,H) = 8.0 Hz, 1 H, Ox-5-H), 3.83 (d, *J*(H,H) = 8.0 Hz, 1 H, Ox-5-H), 6.44 (m_c, 1 H, Fu-4''-H), 6.59 (m_c, 1 H, Fu-3''-H), 6.98 (m_c, 1 H, Ar-H), 7.27-7.41 (m, 8 H, Ar-H), 7.83 (m_c, 1 H, Ar-6'-H) ppm.

$^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2): δ = 27.7 (s, Ox-4-C(CH_3)(CH_3)), 28.1 (s, Ox-4-C(CH_3)(CH_3)), 68.1 (s, Ox-4-C(CH_3)$_3$), 78.7 (s, Ox-5-CH_2), 110.8 (d, J(C,P) = 6 Hz, Fu-4''-CH), 121.8 (d, J(C,P) = 27 Hz, Fu-3''-CH), 128.2 (s, Ar-CH), 128.5 (d, J(C,P) = 30 Hz, Ar-CH), 129.0 (s, Ar-CH), 129.7 (d, J(C,P) = 3 Hz, Ar-CH), 130.3 (s, Ar-CH), 131.6 (d, J(C,P) = 18 Hz, Ar-C), 133.4 (s, Ar-CH), 133.6 (s, Ar-CH), 137.2 (d, J(C,P) = 3 Hz, Ar-C), 138.2 (d, J(C,P) = 21 Hz, Ar-C), 147.3 (d, J(C,P) = 2 Hz, Fu-5''-CH), 154.2 (d, J(C,P) = 21 Hz, Fu-2''-C), 161.1 (d, J(C,P) = 3 Hz, Ox-2-C) ppm.

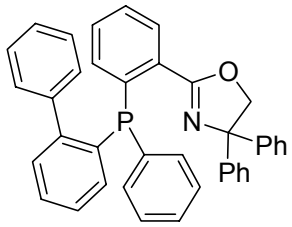
$^{31}P\{^1H\}$ NMR (162 MHz, CD_2Cl_2): δ = –30.7 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 3058m, 2968m, 2909m, 1956w, 1816w, 1735w, 1709w, 1650s, 1586m, 1461s, 1353m, 1310m, 1209m, 1163w, 1089w, 1038m, 1005m, 963m, 902w, 745s, 693s, 674w cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 388 (9, $[M+K]^+$), 350 (100, $[M+H]^+$), 294 (53), 240 (32), 122 (54).

Elemental analysis calcd. (%) for $C_{21}H_{20}NO_2P$: C 72.20, H 5.77, N 4.01; found: C 72.55, H 5.99, N 3.68.

4,4-Diphenyl-2-[2'-(2''-biphenylyl-phenylphosphino)-phenyl]-4,5-dihydrooxazole (190)



190

The ligand synthesis was accomplished in analogy to the preparation of **180** using phenyloxazoline **176** (130 mg, 0.434 mmol), TMEDA (60.7 mg, 0.522 mmol), *s*BuLi in cyclohexane (1.3 M, 400 µL, 0.520 mmol), chlorophosphine **170** (176 mg, 0.593 mmol) in abs. pentane (6.0 mL). Purification of the crude product by column chromatography (silica gel, 3 cm × 15 cm, pentane/Et_2O/NEt_3 5:1:0.5, F6-19) under argon gave ligand **190** as colourless solid (34.2 mg, 14%).

$C_{39}H_{30}NOP$ (559.63 g*mol^{-1}):

R_f = 0.38 (pentane/Et_2O 2:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 4.59 (d, *J*(H,H) = 8.4 Hz, 1 H, Ox-5-H), 4.66 (d, *J*(H,H) = 8.4 Hz, 1 H, Ox-5-H), 6.94-7.63 (m, 26 H, Ar-H), 7.82 (dd, *J*(H,H) = 7.7 Hz, *J*(P,H) = 4.0 Hz, 1 H, Ar-H), 8.08 (d, *J*(H,H) = 8.5 Hz, 1 H, Ar-6'-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ = 79.6 (s, Ox-CH_2), 125.4-130.1 (diverse Ar-CH), 130.6 (Ar-C), 131.6 (Ar-C), 132.6 (d, *J*(C,P) = 9 Hz, Ar-CH), 133.4 (d, *J*(C,P) = 12 Hz, Ar-C), 140.5 (Ar-C), 146.1 (Ar-C), 146.3 (Ar-C), 146.5 (Ar-C) ppm; despite prolonged data acquisition time the signal for Ox-2-C was not detected.

^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ = –14.4 (s) ppm.

IR (KBr): $\tilde{\nu}$ = 3053m, 2960m, 1953w, 1645s, 1488s, 1442s, 1354m, 1296m, 1185m, 1105m, 1059m, 1026m, 901w, 750s, 696s, 617m, 537s cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 559 (6, M^+), 395 (28), 378 (100), 362 (19), 302 (18), 165 (26).

7.9 Evaluation of Chiral Ligands by ESI-MS and Preparative Catalyses

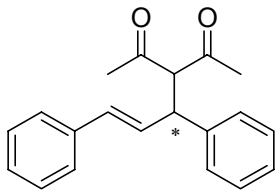
7.9.1 General Procedure for ESI-MS Screenings

In the glovebox a solution of the precatalyst under investigation was prepared by stirring stoichiometric quantities of $[Pd(C_3H_5)(MeCN)_2]OTf$ and the respective chiral ligand in abs. toluene (c_{cat} = 2.50 mM) at r.t. for 30 min. Furthermore equimolar amounts of the methyl- and ethyl-labelled quasienantiomers were dissolved in abs. toluene (c_s = 62.5 mM each) and a solution of [Na([15]crown-5)]$CEt(CO_2Et)_2$ in abs. toluene (c_{nu} = 10.0 mM) was freshly prepared.[1] All stock solutions were then filtered through syringe filters. In a typical ESI-MS screening experiment the precatalyst solution (50.0 µL) was treated with the solution of quasienantiomers (50.0 µL, 2 × 25.0 equiv. substrate per Pd) and the catalysis was initiated by the addition of the nucleophile (50.0 µL, 4 equiv. per Pd). The reaction was carried out in an oven-dried 2 mL screw-thread-vial with septum and cut-out top cap under nitrogen and the stock solutions were transferred with Hamilton 1700RN syringes.

After the mixture had been stirred for 30 s at r.t., an aliquot was taken (ca. 4 µL), diluted to 10^{-5} M (1.0 mL abs. CH_2Cl_2) and directly analysed by ESI-MS using mild desolvation conditions. The mass spectra were acquired in the centroid mode and the selectivities were calculated from the ratios of the peak heights of the two signal clusters.

[1] For the back reaction screening using carbocyclic substrates (*R*,*R*)-**90a** and (*S*,*S*)-**90b** the precatalyst and substrate solutions were prepared in abs. DMF under elsewise identical conditions.

7.9.2 General Procedure for Preparative Allylic Alkylations of 1,3-Diphenyl-2-propen-1-yl benzoate



24

In a Young tube a solution of $[Pd(C_3H_5)(MeCN)_2]OTf$ (2.00 mg, 5.28 μmol) and the respective chiral ligand (5.28 μmol) in abs. toluene (2.0 mL) was degassed by three freeze-pump-thaw cycles and stirred for 60 min at r.t. In a second Young tube benzoate **21** (83.0 mg, 0.264 mmol) in abs. toluene (1.3 mL) was subsequently treated with acetyl acetone (79.3 mg, 0.792 mmol), BSA (161 mg, 0.792 mmol) and catalytic amounts of dried KOAc (ca. 2.00 mg). After three freeze-pump-thaw cycles the catalyst solution was added and the resulting mixture stirred at r.t., until all starting material was consumed according to TLC analysis. The reaction was diluted with Et_2O (30 mL) and ice-cold saturated aqueous NH_4Cl solution (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc/NEt_3 18:1:1, F14-20) afforded the product **24** as colourless solid, whose enantiomeric excess was determined by HPLC analysis.

$C_{20}H_{20}O_2$ (292.37 g*mol^{-1}):

m.p. 76 °C.

R_f = 0.42 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 4.31 (dd, *J*(H,H) = 11.6, 8.5 Hz, 1 H, C*H*CH($COCH_3$)$_2$), 4.39 (d, *J*(H,H) = 11.6 Hz, 1 H, CHC*H*($COCH_3$)$_2$), 6.22 (dd, *J*(H,H) = 15.7, 8.2 Hz, 1 H, PhCHC*H*), 6.44 (d, *J*(H,H) = 15.7 Hz, 1 H, PhC*H*CH), 7.16-7.38 (m, 10 H, Ph-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 29.9 (CH_3), 30.1 (CH_3), 49.3 (*C*HCH($COCH_3$)$_2$), 74.0 (CH*C*H($COCH_3$)$_2$), 126.3 (Ph-CH), 127.2 (CH), 127.7 (CH), 128.0 (Ph -CH), 128.5 (Ph-CH), 128.9 (Ph-CH), 129.6 (CH), 131.5 (CH), 136.7 (3-Ph-*i*-C), 140.5 (1-Ph-*i*-C), 202.3 (*C*OCH_3), 202.4 (*C*OCH_3) ppm.

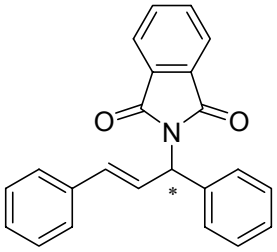
IR (KBr): $\tilde{\nu}$ = 3059w, 3024w, 2925w, 1723s, 1492m, 1417m, 1369s, 1273m, 1175m, 970s, 743s, 697s cm^{-1}.

MS (FAB, NBA+KCl): *m/z* (%) = 331 (28, $[M+K]^+$), 274 (26), 249 (27, $[M–COCH_3]^+$), 193 (100, $[M–C_5H_7O_2]^+$), 115 (23).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 97:3, 0.9 mL*min^{-1}, 20 °C, 254 nm): t_R = 16.3 (*R*), 17.9 (*S*) min.

Elemental analysis calcd. (%) for $C_{20}H_{20}O_2$ (292.37): C 82.16, H 6.89; found: C 81.82, H 7.01.

7.9.3 General Procedure for Preparative Allylic Aminations of 1,3-Diphenyl-2-propen-1-yl benzoate



25

In a Young tube a solution of $[Pd(C_3H_5)Cl]_2$ (1.00 mg, 2.74 μmol) and the respective chiral ligand (5.48 μmol) in CH_2Cl_2 (0.6 mL) was degassed by three freeze-pump-thaw cycles. The ampoule was sealed at 0.01 mbar and the solution stirred at 50 °C for 2 h. After the mixture had been cooled to r.t. the catalyst was added to a degassed solution of benzoate **21** (85.9 mg, 0.273 mmol) and potassium phthalimide (60.7 mg, 0.328 mmol) in CH_2Cl_2 (1.0 mL) in a Young tube. The resulting mixture was stirred at r.t. under argon, until all starting material was consumed according to TLC analysis. The reaction was diluted with Et_2O (30 mL) and ice-cold saturated aqueous NH_4Cl solution (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc/NEt_3 18:1:1, F18-30) afforded **25** as colourless solid, whose enantiomeric excess was determined by HPLC analysis.

$C_{23}H_{17}NO_2$ (339.39 g*mol^{-1}):

m.p. 118-119 °C.

$\boldsymbol{R_f}$ = 0.22 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.13 (d, *J*(H,H) = 8.8 Hz, 1 H, CHN), 6.72 (d, *J*(H,H) = 16.0 Hz, 1 H, PhC*H*CH), 7.07 (dd, *J*(H,H) = 16.0, 8.8 Hz, 1 H, PhCHC*H*), 7.20-7.39 (m, 6 H, Ph-H), 7.41-7.52 (m, 4 H, Ph-H), 7.71 (m_c, 2 H, Phth-H), 7.85 (m_c, 2 H, Phth-H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 56.6 (CHN), 123.5 (Ar-CH), 125.4 (C*H*CH), 126.9 (Ar-CH), 127.6 (Ar-CH), 127.9 (Ar-CH), 128.2 (Ar-CH), 128.7 (Ar-CH), 128.8 (Ar-CH), 132.1 (Ptht-C), 134.2 (Ar-CH), 134.5 (CHC*H*), 136.4 (3-Ph-*i*-C), 139.0 (1-Ph-*i*-C), 167.9 (CON) ppm.

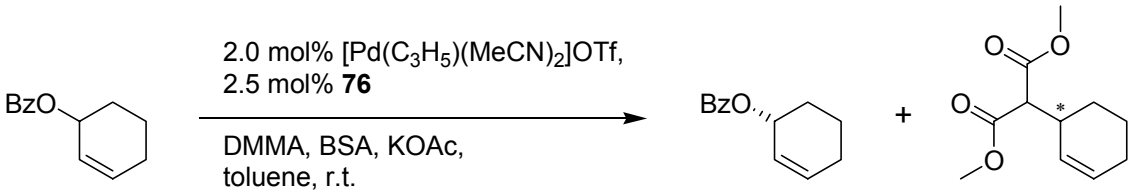
IR (KBr): $\tilde{\nu}$ = 3064w, 1713s, 1644m, 1492m, 1451m, 1382s, 1114m, 971m, 763s, 718m cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 339 (10, M^+), 321 (7), 193 (100, $[M–C_8H_4NO_2]^+$), 115 (14).

HPLC (Daicel Chiracel OD-H, heptane/*i*PrOH 99:1, 0.5 mL*min^{-1}, 20 °C, 254 nm): t_R = 37.6 (*S*), 51.8 (*R*) min.

7.9.4 Analyses of Preparative Kinetic Resolutions

Ligand 76



77 (*R*)-**77** **78**

In a Young tube a solution of $[Pd(C_3H_5)(MeCN)_2]OTf$ (7.40 mg, 19.6 μmol) and ligand **76** (19.3 mg, 23.5 μmol) in abs. toluene (4.0 mL) was stirred for 3 h at r.t. In a second Young tube benzoate **77** (194 mg, 0.958 mmol) and catalytic amounts of dried KOAc (ca. 2.00 mg) in abs. toluene (2.0 mL) were treated with dimethyl malonate (378 mg, 2.86 mmol) and BSA (582 mg, 2.86 mmol) in abs. toluene (2.0 mL) and the reaction was immediately started by the addition of the catalyst (t = 0 min). The resulting mixture was stirred at r.t., while the reaction course was analysed by taking small aliquots of 100 μL. The respective sample was poured into brine (4.0 mL) and the resulting mixture extracted with hexanes/EtOAc (2:1, 2 × 4.0 mL). The combined organic phases were dried over $MgSO_4$ and filtered over a pad of silica gel (0.5 × 4 cm). After evaporation of the solvent the residue was re-dissolved in heptane (1.0 mL). The enantiomeric excess of each sample was determined by HPLC analysis on a chiral column (Daicel Chiracel AD-H, heptane/isopropanol 99.8:0.2, 0.5 mL*min^{-1},

20 °C, 220 nm: t_R = 18.0 ((*R*)-**77**), 20.0 ((*S*)-**77** min). The conversions were measured by GC analysis (Restek Rtx-1701, 110/0/1/180/0/20/250): t_R= 39.0 (**78**), 54.2 (**77**) min and calculated with the help of Equation **[4]**.

$$conversion\,[\%] = catalyst\ loading\,[\%] + 100 \cdot \left[\frac{A(product) \cdot Q}{A(product) \cdot Q + A(substrate)} \right] \qquad \textbf{[4]}$$

The conversion was corrected for the catalyst loading of 2 mol% (Chapter 3.1.4). A Q factor of 0.834 was calculated by GC analysis of several known product substrate mixtures and the correlation of the given ratios with the respective peak areas.

$$\frac{n(product)}{n(substrate)} = \frac{A(product)}{A(substrate)} \cdot Q \qquad \textbf{[5]}$$

The kinetic analysis of the resolution using ligand **76** was repeated with consistent results and both sets of data points were analysed in one diagram (Chapter 3.1.4).

1. Series of measurements

Time *t* [min]	Area (**78**) [%]	Area (**77**) [%]	Conv. corr. [%]	*ee* (**77**) [%]
0.5	0.00	100.00	2.00	0.72
1.0	1.41	98.86	2.95	0.86
1.3	2.29	97.61	3.99	2.04
2.3	3.59	96.41	5.01	3.28
3.3	5.49	94.51	6.62	4.42
4.2	6.78	93.22	7.72	5.12
5.0	7.94	92.06	8.71	5.94
6.0	11.90	88.10	12.13	7.72
7.3	12.79	87.21	12.89	9.28
9.0	15.67	84.33	15.41	10.40
10.0	17.69	82.31	17.20	11.74
11.0	19.02	80.98	18.39	12.50
12.0	21.06	78.94	20.20	12.89
13.0	23.00	77.00	21.94	14.96
14.0	25.01	74.99	23.75	16.80
15.0	27.36	72.63	25.91	16.52
16.0	29.89	70.11	28.23	17.76
17.0	32.28	67.72	32.05	23.00
22.0	43.56	57.44	40.19	28.76
25.0	49.07	50.93	46.56	24.78
27.0	54.65	45.35	52.04	28.20
30.0	59.82	40.18	57.39	28.22
38.0	72.78	27.20	71.06	31.78
41.0	78.76	21.77	77.11	33.02

2. Series of measurements

Time *t* [min]	Area (**78**) [%]	Area (**77**) [%]	Conv. corr. [%]	*ee* (**77**) [%]
0.5	0.00	100.00	2.00	1.50
1.3	4.19	95.81	5.52	3.90
2.5	5.82	94.18	6.89	4.76
4.0	8.27	91.73	8.99	5.42
5.0	9.86	90.14	10.36	6.78
6.0	11.01	88.99	11.35	9.18
8.0	14.96	85.04	14.79	8.08
10.0	17.81	82.19	17.31	12.36
12.0	20.82	79.18	19.98	15.58
14.0	23.13	76.87	22.07	16.88
18.0	28.88	71.12	27.30	20.66
20.0	31.07	68.93	29.32	20.36
22.0	33.19	66.81	31.29	22.96
24.0	36.04	63.96	33.97	23.60
26.0	37.71	62.29	35.54	20.66
30.0	42.14	57.86	39.78	26.68
32.0	44.74	55.26	42.31	29.54
35.0	47.11	52.89	44.63	34.04
37.0	48.71	51.29	46.14	33.38
39.0	50.74	49.26	48.21	33.82
42.0	52.81	47.18	50.28	39.12

The enantiomeric excess was plotted against the corrected conversion and a *s* factor of 3.50 ± 0.08 was calculated with Equation **[2]** using the least squares method.

$$conversion\,[\%] = 100 \cdot \left[1 - \frac{\left(1 - \frac{ee_{Substrate}}{100} \right)^{1/s-1}}{\left(1 + \frac{ee_{Substrate}}{100} \right)^{s/s-1}} \right] \qquad \textbf{[2]}$$

Ligand 59

The kinetic resolution of benzoate **77** (194 mg, 0.958 mmol) using ligand **59** (15.5 mg, 23.5 μmol) was performed under identical conditions with $[Pd(C_3H_5)(MeCN)_2]OTf$ (7.40 mg, 19.6 μmol), dimethyl malonate (378 mg, 2.86 mmol), BSA (582 mg, 2.86 mmol) and dried KOAc (ca. 2.00 mg) in abs. toluene (8.0 mL). The reaction was repeated with consistent results and both sets of data points were analysed in one diagram. As described in Chapter

3.1.4 it is not possible to fit these data using Equation **[2]** and the *s* factor was calculated from single point measurements.

1. Series of measurements

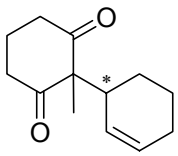
Time *t* [min]	Area (**78**) [%]	Area (**77**) [%]	Conv. corr. [%]	*ee* (**77**) [%]
0.5	0.00	100.00	2.00	2.01
3.0	0.00	100.00	2.00	0.54
6.0	0.00	100.00	2.00	1.80
10.0	0.51	99.41	2.42	2.60
16.0	2.21	97.79	3.85	4.80
31.0	8.07	91.93	8.82	11.60
60.0	27.53	72.47	26.06	43.80
85.0	52.75	47.25	50.22	71.08
105.0	65.75	34.25	63.55	82.80

2. Series of measurements

Time *t* [min]	Area (**78**) [%]	Area (**77**) [%]	Conv. corr. [%]	*ee* (**77**) [%]
1.0	0.00	100.00	2.00	0.60
3.0	0.00	100.00	2.00	1.00
5.0	0.00	100.00	2.00	1.12
11.0	0.00	100.00	2.00	3.10
16.0	0.75	99.25	2.63	4.14
20.0	1.57	98.43	3.31	4.90
25.0	3.84	96.16	5.22	6.34
31.0	7.81	92.19	8.59	14.80
35.0	12.93	87.07	13.02	20.42
40.0	17.62	82.38	17.14	25.94
45.0	23.40	76.60	22.31	33.60
51.0	32.36	67.64	30.52	43.28
59.0	47.04	52.96	44.56	62.06
65.0	55.89	44.11	53.38	74.90
70.0	65.18	34.82	62.96	79.02
75.0	75.24	24.76	73.71	87.34

7.9.5 General Procedure for Preparative Allylic Alkylations of Cyclohex-2-enyl benzoate

2-(Cyclohex-2'-enyl)-2-methylcyclohexane-1,3-dione (94)



94

In a Young tube a solution of $[Pd(C_3H_5)Cl]_2$ (1.08 mg, 2.97 μmol) and the respective chiral ligand (5.94 μmol) was stirred in abs. DMF (1.0 mL) at r.t. for 2 h. NaH (18.5 mg, 0.772 mmol) was suspended in a second Young tube in abs. DMF (2.0 mL) and treated with 2-methylcyclohexane-1,3-dione (135 mg, 1.07 mmol). After 15 min at r.t. benzoate **77** (60.0 mg, 0.297 mmol) was added followed by the catalyst solution and the resulting mixture was stirred at r.t., until all starting material was consumed according to TLC analysis. The reaction was diluted with Et_2O (20 mL) and ice-cold saturated aqueous NH_4Cl solution (20 mL) was added. The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc 4:1) afforded **94** as colourless solid, whose enantiomeric excess was determined by HPLC analysis.

$C_{13}H_{18}O_2$ (206.28 g*mol^{-1}):

m.p. 77-78 °C.

$\boldsymbol{R_f}$ = 0.50 (hexanes/EtOAc 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 3 H, CH_3), 1.28 (m_c, 1 H), 1.41-1.56 (m, 2 H), 1.67 (m_c, 1 H), 1.79 (m_c, 1 H), 1.95 (m_c, 2 H), 2.11 (m_c, 1 H), 2.57 (m_c, 2 H), 2.76 (dt, *J*(H,H) = 14.3, 6.4 Hz, 1 H), 2.89 (dt, *J*(H,H) = 14.3, 6.6 Hz, 1 H), 2.97 (m_c, 1 H), 5.23 (d, *J*(H,H) = 10.0 Hz, 1 H, C*H*CH), 5.81 (m_c, 1 H, CHC*H*) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 10.8 (CH_3), 18.5 (5'-CH_2), 22.3 (5-CH_2), 24.2 (6-CH_2), 24.7 (4-CH_2), 37.7 (4'-CH_2), 38.1 (6'-CH_2), 42.4 (1'-CH), 71.0 (2-C), 124.7 (3-CH), 130.9 (2-CH), 209.0 (CO), 209.5 (CO) ppm.

IR (KBr): $\tilde{\nu}$ = 3024w, 2952m, 2900m, 1722s, 1689s, 1432s, 1371w, 1320s, 1266m, 1225m, 1141w, 1094m, 1064m, 1024s, 986w, 884m, 844m, 808m, 719m, 628m, 564m, 473w cm^{-1}.

MS (EI. 70 eV): *m/z* (%) = 206 (18, M^+), 178 (33), 150 (98), 135 (82), 122 (42), 81 (100, $C_6H_9^+$).

HPLC (Daicel Chiracel AD-H, heptane/isopropanol 98:2, 0.8 mL*min^{-1}, 30 °C, 254 nm): t_R = 11.1 (*S*), 13.5 (*R*) min.

7.9.6 Ligand Evaluation by Conventional Preparative Allylic Alkylations

A solution of $[Pd(C_3H_5)Cl]_2$ (0.01 equiv.) and the respective chiral ligand (0.025 equiv.) in CH_2Cl_2 (1.2 mL/mmol substrate) in a Young tube was degassed by three freeze-pump-thaw cycles. The ampoule was sealed at 0.01 mbar and the mixture stirred at 50 °C for 2 h. The substrate (1.00 equiv.) in CH_2Cl_2 (4.0 mL/mmol substrate) was treated with dimethyl malonate (3.00 equiv.), BSA (3.00 equiv.) and catalytic amounts of dried KOAc. After three freeze-pump-thaw cycles the catalyst solution was added and the resulting mixture stirred at r.t., while the course of the transformation was analysed by TLC. The reaction was diluted with Et_2O (100 mL/mmol substrate) and ice-cold saturated aqueous NH_4Cl solution (100 mL/mmol substrate) was added. The aqueous phase was extracted with Et_2O (2 × 100 mL/mmol substrate) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent column chromatography (silica gel, 3 × 20 cm, hexanes/EtOAc/NEt_3 18:1:1) afforded the product. The enantiomeric excesses were determined on chiral HPLC or GC columns and the spectroscopic properties of all products were in agreement with published data.[150]

7.10 Iridium-Catalysed Asymmetric Allylic Substitutions

7.10.1 Mass Spectrometric Analysis of Allylic Aminations[131, 140]

In a Young Tube $[Ir(COD)Cl]_2$ (4.50 mg, 6.70 μmol) and (*R*,*R*,*R*)-**195** (7.20 mg, 13.4 μmol) in abs. THF (200 μL) and propylamine (30 μL, 0.365 mmol) were heated to 50 °C. After 20 min and 2 h respectively aliquots (ca. 6 μL) were taken and diluted with MeOH (1.0 mL) using oven-dried 2 mL glass screw-thread-vials with septum cut-out top caps. The samples were filtered through syringe filters and directly analysed by ESI-MS using mild desolvation conditions. Afterwards all volatiles were removed under reduced pressure and the yellow residue was re-dissolved in THF (400 μL). Carbonate **197** (123 mg, 0.639 mmol) and aniline

(77.0 mg, 0.827 mmol) were added and the resulting mixture was stirred at r.t. After 5 min and 30 min respectively the reaction was analysed by ESI-MS as described above.

7.10.2 General Procedures for Screening Allylic Substitutions using Quasienantiomeric Substrates

The activated catalyst **194** was prepared by heating a solution of $[Ir(COD)Cl]_2$ (1.06 mg, 1.57 μmol) and **195** (1.69 mg, 3.15 μmol) and lithium phenolate **199** (20.5 mg, 0.157 mmol) in abs. THF (200 μL) at 50 °C for 4 h. After the catalyst solution had been cooled to r.t. quasienantiomeric phenolates (*R*)-**127a** and (*S*)-**127b** (or benzoates (*R*)-**126a** and (*S*)-**126a**) (78.7 μmol each) in abs. THF (100 μL) were added and the resulting mixture was stirred at r.t. After 5 min and 30 min respectively aliquots (ca. 6 μL) were taken, diluted with MeOH (1.0 mL) and analysed by ESI-MS as described in Section 7.10.1.

7.10.3 Investigation of Allylic Aminations using ESI-MS and NMR Analysis[140]

In a Young tube $[Ir(COD)Cl]_2$ (4.00 mg, 5.98 μmol) and (*S*,*S*,*S*)-**195** (12.8 mg, 23.9 μmol) were dissolved in abs. THF-d_8 (800 μL) and propylamine (75 μL, 0.912 mmol). After this solution had been heated at 50 °C for 60 min, an aliquot was taken (sample A) and analysed by NMR (140 μL diluted with 560 μL THF-d_8) and ESI-MS (20 μL diluted with 1.0 mL MeOH). After the reaction mixture had been stirred for another 50 min at 50 °C, all volatiles were removed in high vacuum. The yellow solid was re-dissolved in THF-d_8 (600 μL) and the solution transferred to a NMR tube. Carbonate **197** (4.30 mg, 22.4 μmol) was added and the reaction mixture analysed by NMR (sample B). An aliquot was taken (10 μL diluted with 0.5 mL MeOH) and analysed by ESI-MS as well. After 60 min at r.t. additional $[Ir(COD)Cl]_2$ (2.50 mg, 3.73 μmol) was added and the resulting solution (sample C) analysed by NMR and ESI-MS (10 μL diluted with 0.5 mL MeOH). After 3.5 h aniline (3.00 μL, 32.9 μmol) was added and the reaction immediately analysed by NMR and ESI-MS (10 μL diluted with 0.5 mL MeOH), once again.

Sample A:

ESI-MS (100 °C, MeOH): *m/z* = 898 (15, $[\mathbf{196}+Na]^+$), 1379 (100, $[\mathbf{194}+H]^+$).

$^{31}P\{^{1}H\}$ NMR (202 MHz, THF-d_8): δ = 116.0 (s, **196**), 128.9 (d, *J*(P,P) = 46 Hz, **194**), 153.9 (d, *J*(P,P) = 46 Hz, **194**) ppm.

Sample B:

ESI-MS (100 °C, MeOH): *m/z* = 956 (100, **198**), 1379 (4, [**194**+H]$^+$).

$^{31}P\{^{1}H\}$ NMR (202 MHz, THF-d_8): δ = 116.0 (s, **196**), 128.9 (d, *J*(P,P) = 46 Hz, **194**), 153.9 (d, *J*(P,P) = 46 Hz, **194**) ppm.

Sample C:

ESI-MS (100 °C, MeOH): *m/z* = 956 (100, **198**).

$^{31}P\{^{1}H\}$ NMR (202 MHz, THF-d_8): δ = 103.9 (s), 116.0 (s, **196**) ppm.

Sample D:

ESI-MS (100 °C, MeOH): *m/z* = 956 (100, **198**).

$^{31}P\{^{1}H\}$ NMR (202 MHz, THF-d_8): δ = 103.9 (s), 116.0 (s, **196**) ppm.

CHAPTER 8

APPENDIX

8 Appendix

8.1 X-Ray Crystal Structures

X-ray data analyses were carried out and crystal structures were solved by Markus Neuburger and Dr. Sylvia Schaffner at the Department of Chemistry of the University of Basel. Data collection was performed with a Nonius KappaCCD diffractometer. Measurements were recorded at 173 K. The structure was solved with SIR92[151] or SIR97[152] and refined with crystals.[153] Chebychev polynomial weights were used to complete the refinement.[154] Hydrogen atoms were calculated and refined as rigidifying atoms. The absolute configuration and enantiopurity was determined by refinement of the flack parameter.[155]

	(+)-(*R*)-**159a**	(–)-(*S*)-**159a**
molecular formula	$C_{18}H_{20}NOPS$	$C_{18}H_{20}NOPS$
molecular weight	329.40	329.40
shape	plate	block
colour	colourless	colourless
temperature [K]	173	173
radiation	$Mo_{K\alpha}$	$Mo_{K\alpha}$
wavelength [Å]	0.71073	0.71073
crystal size [mm^3]	0.14 · 0.17 · 0.27	0.16 · 0.20 · 0.20
crystal system	trigonal	trigonal
space group	P 3_2	P 3_1
a [Å]	9.13950(10)	9.13950(10)
b [Å]	9.13950(10)	9.13950(10)
c [Å]	17.4359(3)	17.4359(3)
α [°]	90	90
β [°]	90	90
γ [°]	120	120
unit cell volume [$Å^3$]	1261.30(3)	1260.44(3)
Z	3	3
calcd. density [$g*cm^{-3}$]	1.301	1.302
adsorption coeff. μ [mm^{-1}]	0.289	0.289
F(000)	522	522
Θ range for data collection	2.573-30.053	2.574-30.012
collected reflections	10735	13665
independent reflections	4910 (R_{int} = 0.056)	4886 (R_{int} = 0.146)
observed reflections	3707	3306
refinded parameters	200	200
R	0.0321	0.0299
R_w	0.0486	0.0484
goodness of fit	1.1054	1.1199
Flack parameter	0.07(6)	0.03(6)

	(–)-(*R*)-**160a**	(+)-(*S*)-**160a**
molecular formula	$C_{16}H_{24}NOPS$	$C_{16}H_{24}NOPS$
molecular weight	309.41	309.41
shape	plate	plate
colour	colourless	colourless
temperature [K]	173	173
radiation	$Mo_{K\alpha}$	$Mo_{K\alpha}$
wavelength [Å]	0.71073	0.71073
crystal size [mm^3]	0.08 · 0.09 · 0.19	0.08 · 0.12 · 0.32
crystal system	monoclinic	monoclinic
space group	P 1 2_1 1	P 2_1
a [Å]	8.80250(10)	8.80020(10)
b [Å]	10.3357(2)	10.32970(10)
c [Å]	9.37570(10)	9.37770(10)
α [°]	90	90
β [°]	92.2969(10)	92.3064(7)
γ [°]	90	90
unit cell volume [$Å^3$]	852.32(2)	851.775(16)
Z	2	2
calcd. density [$g*cm^{-3}$]	1.206	1.206
adsorption coeff. μ [mm^{-1}]	0.280	0.280
F(000)	332.000	332.00
Θ range for data collection [°]	2.174-30.006	2.173-30.043
collected reflections	9136	9368
independent reflections	4976 (R_{int} = 0.110)	4923 (R_{int} = 0.028)
observed reflections	4250	4398
refinded parameters	183	183
R	0.0287	0.0318
R_w	0.0368	0.0484
goodness of fit	1.1183	1.0034
Flack parameter	0.00(5)	0.03(5)

	(+)-(*S*)-**162a**
molecular formula	$C_{20}H_{24}NOPS$
molecular weight	325.28
shape	plate
colour	colourless
temperature [K]	173
radiation	$Mo_{K\alpha}$
wavelength [Å]	0.71073
crystal size [mm^3]	0.02 · 0.12 · 0.20
crystal system	orthorhombic
space group	P 2_1 2_1 2_1
a [Å]	8.2162(2)
b [Å]	12.3226(3)
c [Å]	19.0837(5)
α [°]	90
β [°]	90
γ [°]	90
unit cell volume [$Å^3$]	1932.13
Z	4
calcd. density [$g*cm^{-3}$]	1.229
adsorption coeff. μ [mm^{-1}]	0.257
F(000)	760
Θ range for data collection [°]	1.967-27.169
collected reflections	15624
independent reflections	4259 (R_{int} =0.039)
observed reflections	2551
refinded parameters	218
R	0.0256
R_w	0.0512
goodness of fit	1.0037
Flack parameter	0.01(8)

8.2 List of Abbreviations

Å	Ångström (10^{-10} m)
abs.	absolute
Ac	acetyl
acac	acetyl acetone
An	anisyl
Ar	aryl
aq.	aqueous
BINOL	2,2'-dihydroxy-1,1'-binaphtyl
Bn	benzyl
Bp	biphenyl
b.p.	boiling point
bpy	bipyridyl
BSA	*N*,*O*-bis(trimethylsilyl)-acetamide
*n*Bu	1-butyl
*s*Bu	*sec*-butyl, 2-butyl
*t*Bu	*tert*-butyl, 2-methyl-2-propyl
Bz	benzoyl
c	concentration
calcd.	calculated
cat.	catalytic
CID	collision induced dissociation
COD	1,5-cyclooctadiene
conv.	conversion
COSY	correlation spectroscopy (NMR)
Cy	cyclohexyl
δ	chemical shift
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEPT	distortionless enhancement by polarisation transfer (NMR)
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMMA	dimethyl malonate
DMSO	dimethyl sulfoxide
DPPBA	diphenylphosphino benzoic acid
EDC	*N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide
ee	enantiomeric excess
EI	electron impact
ent	enantiomer
ESI	electrospray ionisation
Et	ethyl
equiv.	equivalent
F	fraction
FAB	fast atom bombardement
Fu	furyl
GC	gas chromatograpy
HMBC	heteronuclear multiple bond correlation (NMR)
HMQC	heteronuclear multiple quantum coherence (NMR)
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
Hz	Hertz
i	*ipso*
init	initial
I_{rel}	relative intensity
J	coupling constant
k	rate constant
L	ligand
m	*meta*
M	metal

M	molar [mol*L^{-1}]
Me	methyl
MS	mass spectrometry
m/z	mass-to-charge ratio
NMR	nuclear magnetic resonance
Np	naphtyl
Nu	nucleophile
o	*ortho*
Ox	oxazolinyl
p	*para*
Piv	pivaloyl
Ph	phenyl
Phim	phosphinoimidazoline
Phox	phosphinooxazoline
Phth	phthalimide
ppm	parts per million (10^{-6})
*i*Pr	isopropyl, 2-propyl
quant.	quantitative
rac	racemic
R_f	retention factor
r.t.	room temperature
s	selectivity factor
sec	secondary
t	time
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
tert	tertiary
Tf	trifluoromethanesulfonyl
THAB	tetrahexylammonium bromide
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*',*N*'-tetramethyl-ethylenediamine
TMS	trimethylsilyl
Tol	tolyl
t_R	retention time
Ts	tosyl, 4-toluenesulfonyl
Xyl	xylyl

Chapter 9

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9 References

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Eidesstattliche Erklärung

Ich erkläre, dass ich die Dissertation „Mass Spectrometric Screening of Chiral Catalysts by Monitoring the Back Reaction: Palladium-Catalysed Allylic Substitution“ nur mit der darin angegebene Hilfe verfasst und bei keiner anderen Universität und bei keiner anderen Fakultät der Universität Basel eingereicht habe.

Basel, 01.04.2008 Constanze A. Müller