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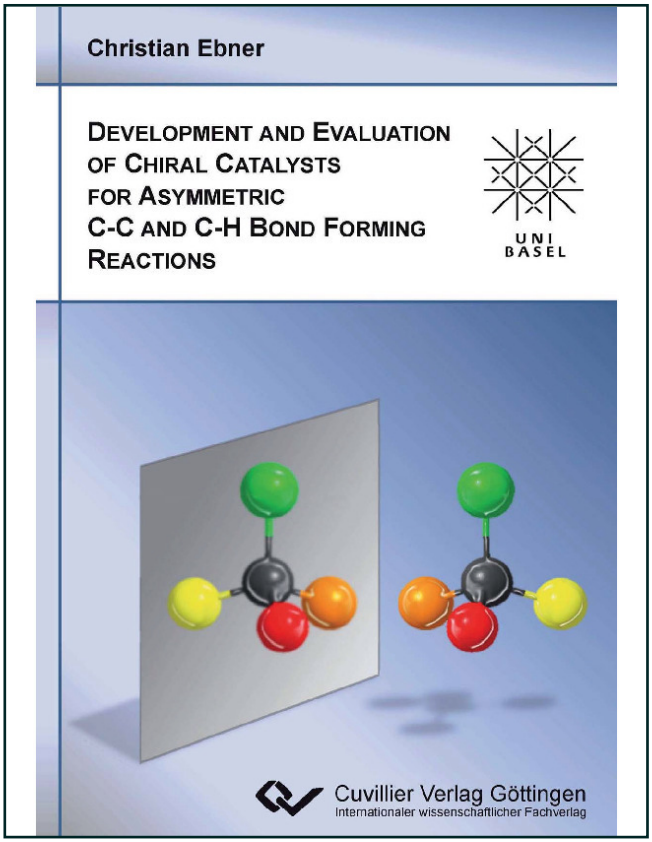
Development and Evaluation of Chiral Catalysts for Asymmetric C-C and C-H Bond forming Reactions



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Chapter 1

ESI-MS Screening of Racemic Catalyst Mixtures

1.1 Introduction

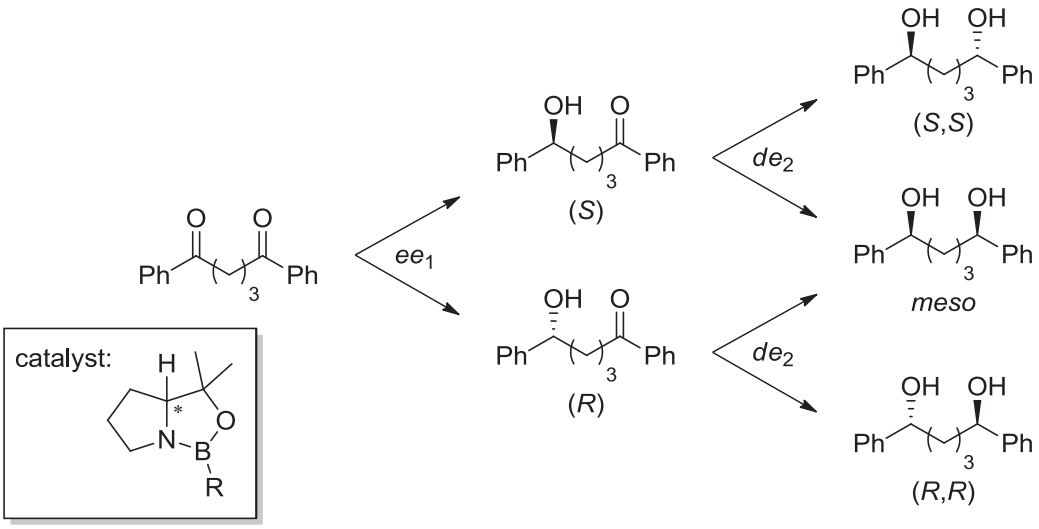
The field of asymmetric catalysis is one of the most important areas in modern organic synthesis and its relevance has been illustrated when the Nobel Prize in 2001 was given to KNOWLES, NOYORI and SHARPLESS for their work in this field.[1] Although many chiral catalysts have been already designed, there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

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

1.1.1 Previously Reported Approaches Towards Selectivity Determination by Testing Racemates

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

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

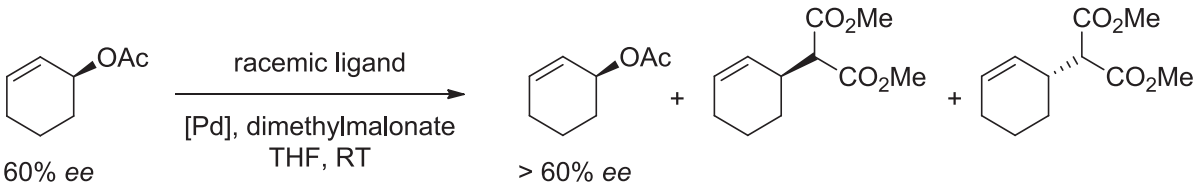


Scheme 1. *Testing racemic chiral catalysts in the enantioselective borane reduction of ketones according to* KAGAN *and co-workers.*[3]

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

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

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



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

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

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

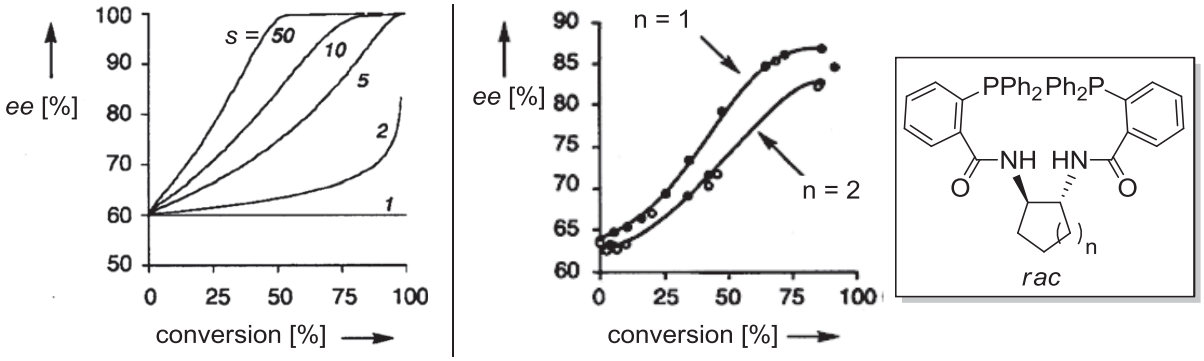
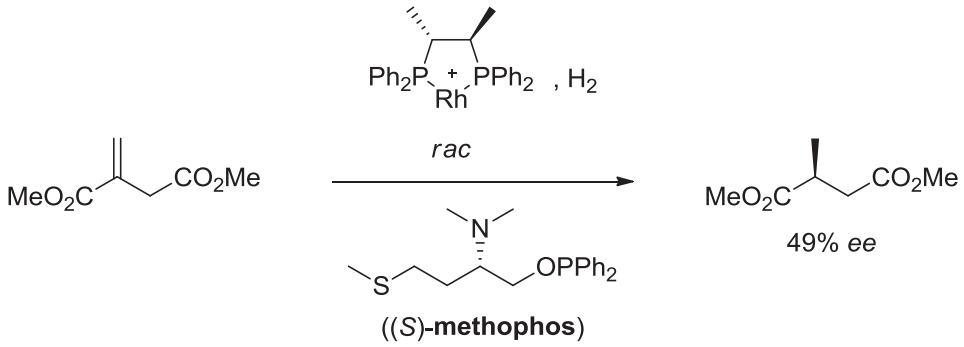


Figure 1. *Evolution of the substrate ee upon proceeding conversion. Left: calculated graphs for different catalyst selectivities; right: experimental data from testing racemic* TROST*-ligands.*[4]

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

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



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

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

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

1.1.2 ESI-MS Screening of Enantiopure Catalysts

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

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

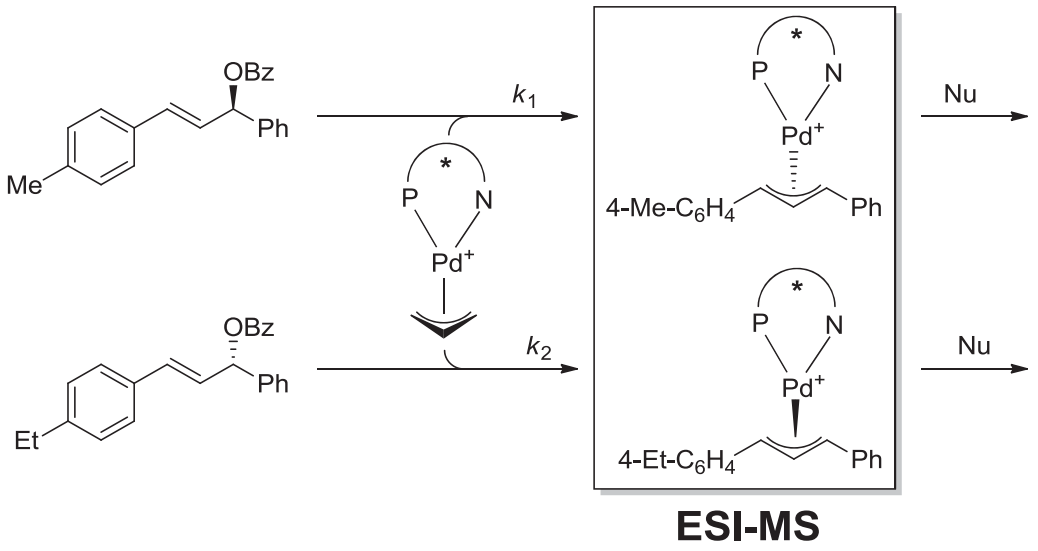
In 1968 DOLE and co-workers reported the possibility of generating gas-phase ions by electrospraying of a polymer solution into an evaporation chamber.[10] The method was then significantly improved by YAMASHITA and FENN which were able to combine electrospray

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

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

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

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



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

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

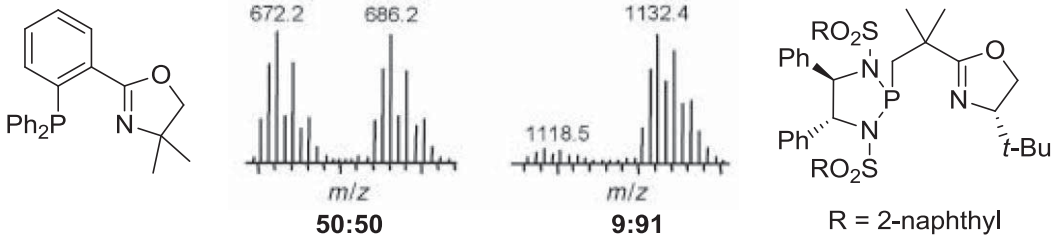
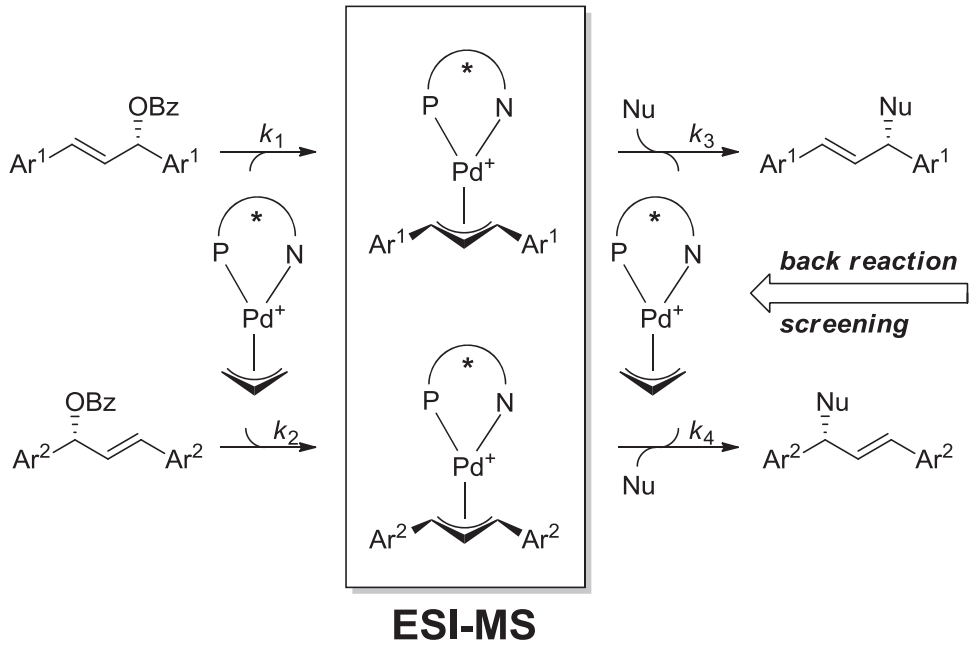


Figure 2. *Selectivity determination by ESI-MS screening of different catalyst. Left: an achiral ligand leads to an unselective catalyst (intermediates formed in a 50:50 ratio, s = 1); right: a chiral ligand leads to a selective catalyst (intermediates formed in a 9:91 ratio, s = 10).*[19]

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

1.1.2.3 ESI-MS Screening in the Palladium Catalyzed Allylic Alkylation

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



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

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

1.1.2.4 Simultaneous Screening of Catalyst Libraries by ESI-MS

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

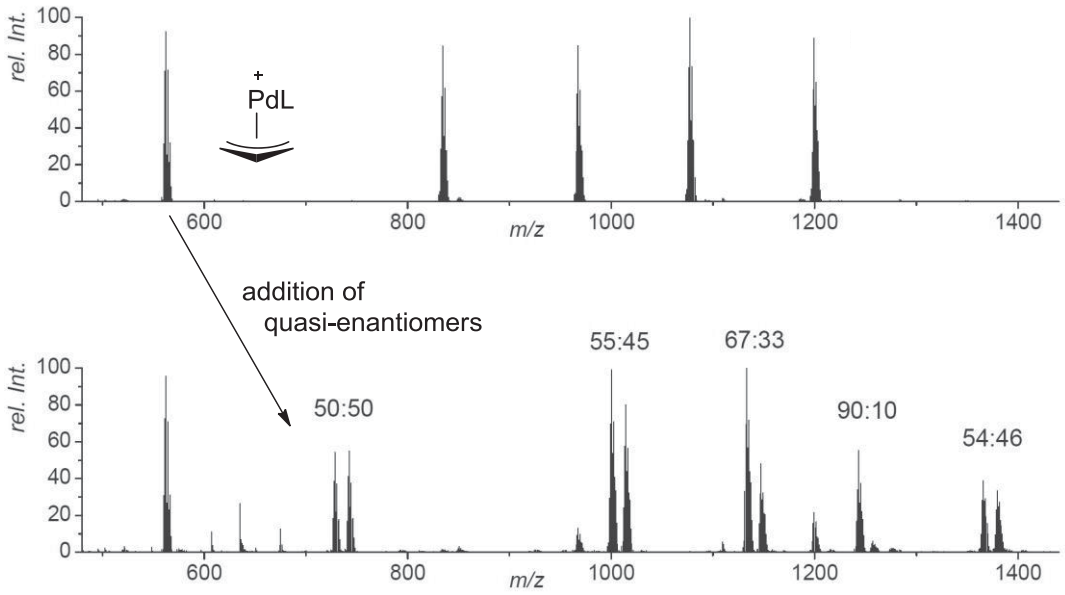


Figure 3. *Simultaneous ESI-MS screening of catalyst of different mass (top: set of 5 different precatalysts; bottom: formation of 5 different intermediate pairs after quasi-enantiomer addition).*[8]

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

1.1.3 Objectives of This Work

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

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

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

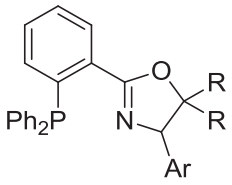
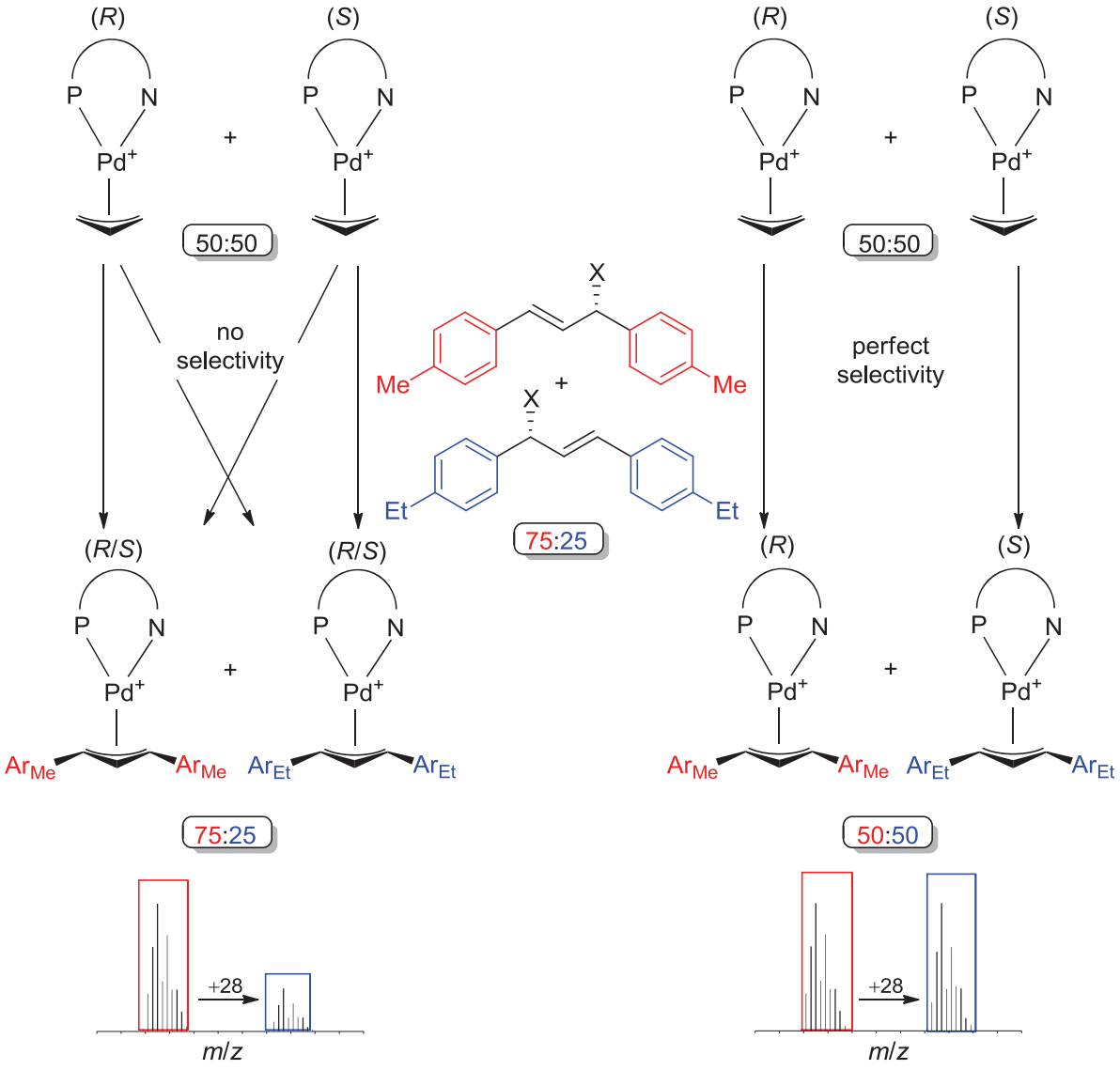


Figure 4. *Aryl-PHOX ligands to be synthesized and evaluated in the allylic substitution reaction in their racemic forms.*

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

1.2.1 Relation Between Catalyst Selectivity and Detected Intermediate Ratio

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



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

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

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

1.2.2 Sensitivity of the Method and Choice of Substrate Ratio

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

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

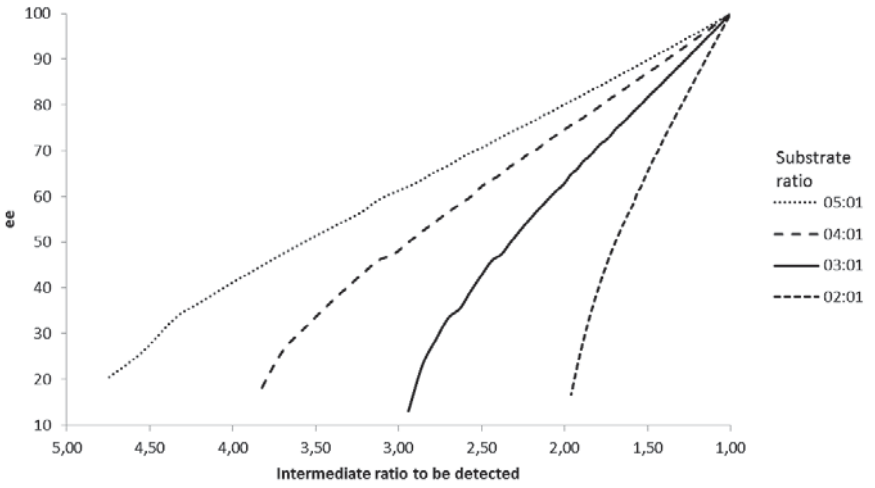


Figure 5. *Dependency of the enantiomeric excess/intermediate ratio on the substrate ratio which was applied (calculated graphs).*

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