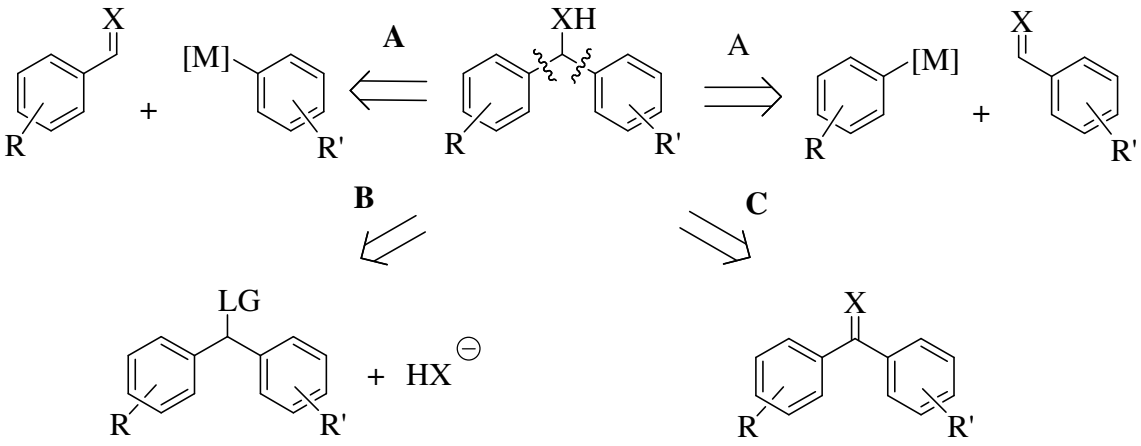
Chapter 4
Catalytic, Enantioselective Preparation of Diarylmethanols

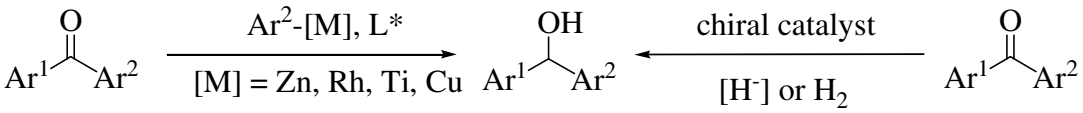
4.1. Introduction

Control of the stereochemistry in the formation of chiral diarylmethanols has attracted considerable interest over the past 20 years since enantiopure derivatives are important intermediates for the synthesis of biologically active molecules. Commonly, several routes allow access to these compounds (scheme 1):[1] i) carbon-carbon bond formation of aromatic aldehydes and the appropriate organometallic compounds (path **A**); ii) nucleophilic displacement at the benzylic position (path **B**); iii) or reduction of the C=O bond of the corresponding diarylketones (path **C**).



X = O, NR"
LG = leaving group

The catalytic asymmetric synthesis of diarylmethanols is generally achieved by one out of the two following strategies: either the addition of suitable aryl nucleophiles to aromatic aldehydes or the reduction of diarylketones (scheme below).



Addition to aldehydes **Reduction of ketones**

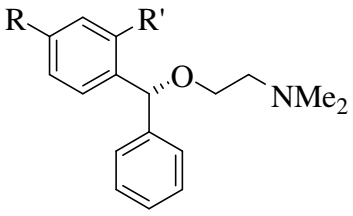
In general, asymmetric, catalytic approaches towards enantiopure diarylmethanols have become increasingly important recently, as reflected by the high number of publications on this topic during the last 10 years. Although alternative methods with stoichiometric

quantities of chiral reagents are also known ("auxiliary approach"), we will focus on the more atom-economic catalytic versions utilizing substoichiometric quantities of chiral inducers.

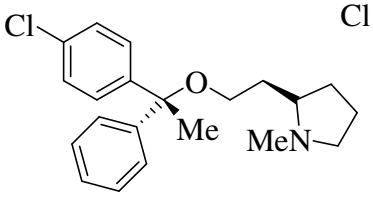
4.2. Biologically active diarylmethanols derivatives

Diarylmethanols are precursors for a number of compounds with physiologically interesting properties, which includes antihistaminic, antiarrhythmic, diuretic, antidepressive, laxative, local-anesthetic and anticholinergic activities. For example, the diphenhydramine derivatives orphenadrine (**4.1**) and neobenodine (**4.2**) show antihistaminic as well as anticholinergic activity (Figure below). Clemastine (**4.3**) was used as a first-generation histamine H_1 antagonist for the treatment of allergic diseases. Subsequently, other histamine antagonist with related structures have been discovered, for example, (*S*)-carbinoxamine (**4.4**)

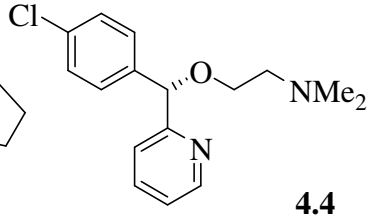
Diarylmethanols also play an important role for the synthesis of compounds with 1,1-diarylalkyl units, which are present in other antidepressants, antimuscarinics, and endothelin antagonists. For example CDP-840 (**4.5**) selectively inhibits phosphodiesterase IV.



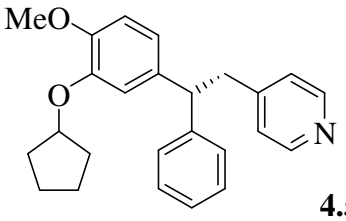
R = Me, R' = H **4.1**
R = H, R' = Me **4.2**



4.3



4.4



4.5

Molecules with this structural unit can be prepared by nucleophilic displacement at the benzylic position of activated diarylmethanols using C-nucleophiles.

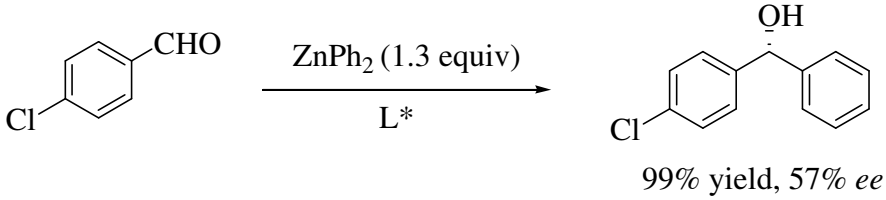
Interestingly, these transformations can be triggered to proceed with either retention or inversion of configuration at the stereogenic center. The extent of inversion at the benzhydryl center is highly dependent on the activation strategy.
It was found that the formation of the corresponding chlorides and bromides from the enantioenriched diarylmethanols led to extensive racemization. Compounds with other activating groups such as phosphates were unreactive towards displacement by C-nucleophiles. However, in situ activation by reaction with LiHMDS and Ts_2O in THF followed by a treatment with a C-nucleophile allowed the formation of the corresponding 1,1-diarylalkyl derivatives with complete inversion.

This thesis will now focus on the synthesis of enantiomerically enriched diarylmethanols obtained through path **A**, i.e. using organometallic compounds in the formation of new carbon-carbon bonds starting from the corresponding aldehydes.

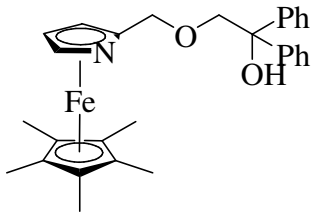
4.3. Catalytic enantioselective preparation of diarylmethanols
Nucleophilic addition of organometallic compounds to aldehydes

4.3.1. Phenyl transfer reactions to aromatic aldehydes using diphenylzinc as aryl source

In 1997, Fu reported the first enantioselective catalytic addition of diphenylzinc to aldehydes.[2] Diphenylzinc, *p*-chlorobenzaldehyde and a catalytic amount of a planar-chiral azaferrocene (**4.6**) generated the desired diarylmethanol in almost quantitative yield as illustrated in the scheme below. Although the enantiomeric excesses (57%) was rather low at this stage, the reported transformation proved most stimulating and set the basis for many subsequent studies following soon after.

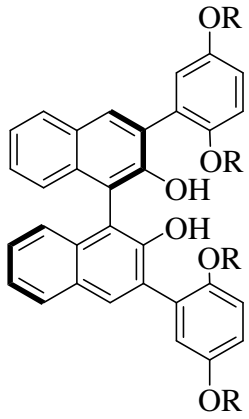


99% yield, 57% *ee*



4.6

The first highly enantioselective catalytic addition of diphenylzinc to aldehydes was described by Pu two years later.[3] In this study, *p*-chlorobenzaldehyde was reacted with diphenylzinc in the presence of (*R*)-**4.7** (20% mol) in diethyl ether at room temperature to give the desired alcohol in 86% yield with 94 % *ee*.



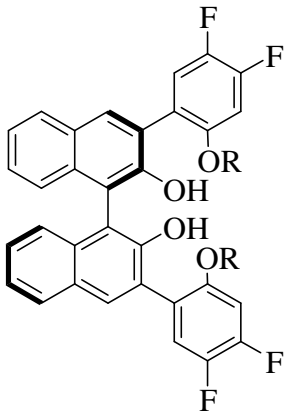
4.7

As the authors pointed out, a pre-treatment of the binaphthol derivative with 40 mol% of diethylzinc was crucial for achieving such a high enantioselectivity. An additional improvement was observed when the reaction was run at low concentration (5 mM). These results suggest that the zinc complex generated from diethylzinc and the ligand is a more selective catalyst than the one formed from the reaction of diphenylzinc and the ligand.

The formation of the (*S*)-isomer of the product indicated that the phenyl transfer occurred from the *re* face of the aldehyde. The same side selectivity has been observed in the diethylzinc addition to aromatic aldehydes. Furthermore it was shown that even in the absence of any catalyst the addition of diphenylzinc to *p*-methoxyaldehyde proceeded well to furnish racemic the diarylmethanol. This non-catalytic background reaction was suggested to be responsible for the lower enantioselectivity (77% *ee*) in the formation of the alcohol derived from *p*-methoxyaldehyde when only 5% mol of

binaphthyl derivative was used. Increasing the amount of the ligand to 20% mol and lowering the temperature to -30 °C resulted in a significantly higher enantiomeric excess of the product (84% yield, 93% *ee*).

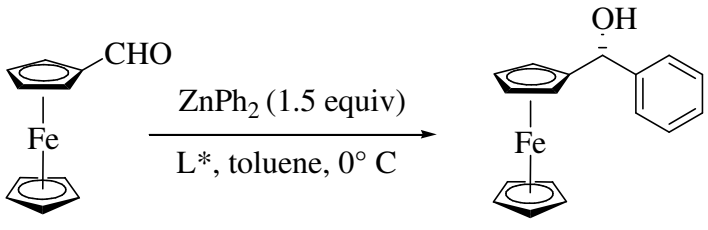
The use of fluorinated binaphthol type-compounds was reported by Pu in 2000. Of these, only ligand **4.8** , having a similar structure like **4.7**, was applied in the phenyl transfer reaction.[4]

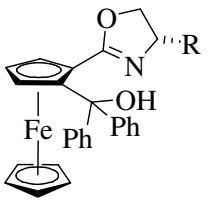


4.8

Various aromatic aldehydes were reacted with diphenylzinc in the presence of 20% mol of the fluorinated ligand in dichloromethane. After 5 h at room temperature the products were formed with good enantioselectivities (70-95% *ee*) and in high yields (86-92%).

In 1999 Bolm introduced planar-chiral ferrocene-based hydroxyl oxazolines (**4.9**) as catalysts for the addition of diphenylzinc to aldehydes.[5] Here, diphenylzinc was transferred to *p*-chlorobenzaldehyde at 0° C with a catalyst loading of 10% mol to give the product with 88% *ee* in nearly quantitative yield.





R = Ph
R = *t*-Bu
4.9

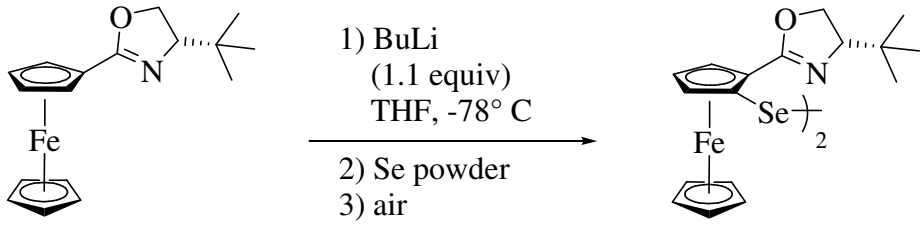
The ferrocene with R = Ph, proved to be as efficient as the one bearing R = *t*-Bu and gave identical results. A wide range of aldehydes was tested and, in all cases, the product yields were high. The enantiomeric excesses, however, depended on the substitution pattern of the aromatic aldehyde. The highest *ee* was obtained in the conversion of the ferrocenylcarbaldehyde which furnished the corresponding ferrocenylalcohol with *ee* > 96% in 89% yield.

The presence of *ortho*-substituents on the aromatic aldehyde resulted in reduced enantiomeric excesses. In the case of *o*-bromobenzaldehyde and 1-naphthaldehyde the products were formed in excellent yields (> 98%), but the enantiomeric excesses were only 31% and 28%, respectively. The aryl transfer onto the heteroaromatic 2-formylpyridine occurred with only low enantioselectivitiy (33% *ee*) due to the competitive, uncatalysed and non-selective reaction of diphenylzinc with the substrate.

The use of a modified phenylzinc reagent, formed in situ from diphenyl- and diethylzinc (in a 1:2 ratio), had two beneficial effects.[6] First, this protocol allowed the amount of diphenylzinc to be reduced to 0.65 equiv. since both phenyl groups were transferred. Second, the undesirable background reaction was suppressed, which led to a significant increase in enantioselectivity. The authors suggest that ethylphenylzinc is formed in an equilibrium with diethylzinc and diphenylzinc. Apparently, the ethyl group then behaves as a nontransferable moiety on zinc, while phenyl is transferred to the aldehyde with complete selectivity (no ethyl addition product was found). This result endorses the observation of Pu and Blacker, who had noted an improvement in the enantioselectivity by pretreatment of **4.7** with diethylzinc (see above). With Bolm's ferrocene catalyst (R = *t*-Bu) the mixed zinc species afforded for example (p-chlorophenyl)phenylmethanol with 97% *ee* compared to 88% *ee* under the original conditions. The temperature could be increased to 10° C without loss of enantioselectivity. Furthermore, with this new protocol the range of substrates was no longer limited to para-substituted aromatic

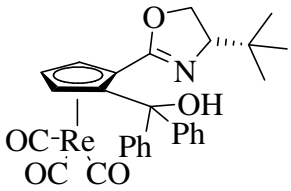
aldehydes. o-Bromobenzaldehyde afforded the desired product with an enantioselectivity of 91% *ee* compared to 31% *ee* with the original protocol.

Additionally, Bolm showed the applicability of a diferrocenyl diselenide **4.10** in the catalytic asymmetric phenyl transfer reaction to aldehydes.[7] The synthesis of this ligand was accomplished by directed ortho-lithiation of oxazolinylferrocene followed by addition of selenium powder.



4.10

After oxidation with air, diselenide **4.10** was obtained in 69% yield. Use of 5 ol% of diselenide and a 1:2 mixture of diphenyl- and diethylzinc led to the corresponding (*R*)-diarylmethanols with up to 85% *ee* in high yields (65–96%). As an extension of this chemistry the application of cyrhetrene (η^5-cyclopentadienylrhenium(I)tricarbonyl complex) **4.11** in the asymmetric addition of diphenylzinc to aldehydes was reported.

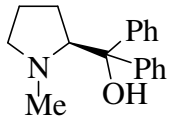


4.11

For most examples, higher enantiomeric excesses of the corresponding alcohols were obtained (up to 99% *ee*) than with the use of the ferrocene analogue.

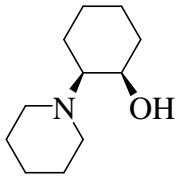
The synthesis of twelve proline derivatives and their use as catalysts in the asymmetric addition of diphenylzinc to various aromatic aldehydes was reported by Zhao in 2001.[8] In this case, the best result (89% *ee*) was achieved with 10 mol% of N-methyl-α,α-diphenylpyrrolidine methanol in toluene at -30° C (**4.12**). In THF, CH_2Cl_2 or hexane the enantioselectivities were poor. *para*-Substituted aromatic aldehydes led to the highest

enantioselectivities, whereas *ortho* and *meta*-substituted substrates afforded products with lower ee-values. Presumably steric interactions between the substrate and the catalyst were the reason for these diminished selectivities.



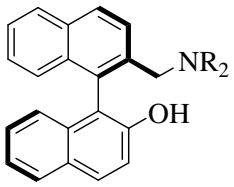
4.12

cis-Amino alcohol **4.13** has recently been applied in aryl transfer reactions by Bolm.[9] Its synthesis involved an efficient resolution of racemic N-benzylated trans-2-aminocyclohexanol followed by stereospecific functional group conversions. Use of 10 mol% of this molecule in the phenyl transfer from a diphenylzinc/diethylzinc mixture onto aromatic aldehydes afforded diarlymethanols with up to 87% *ee*.



4.13

In 2002, Ha reported the preparation of binaphthyl-based amino alcohols **4.14** and their application in the asymmetric diphenylzinc additions to aldehydes.[10]

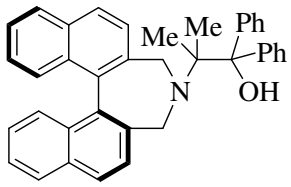


4.14

Initially, these amino alcohols were screened in the asymmetric diphenylzinc addition to *p*-methoxybenzaldehyde. The best result was obtained with 10 mol% of the ligand with NR_2 = morpholine, in toluene at 0° C. Next, the phenyl transfer onto various aromatic aldehydes was investigated leading to products with very high enantioselectivities (92–

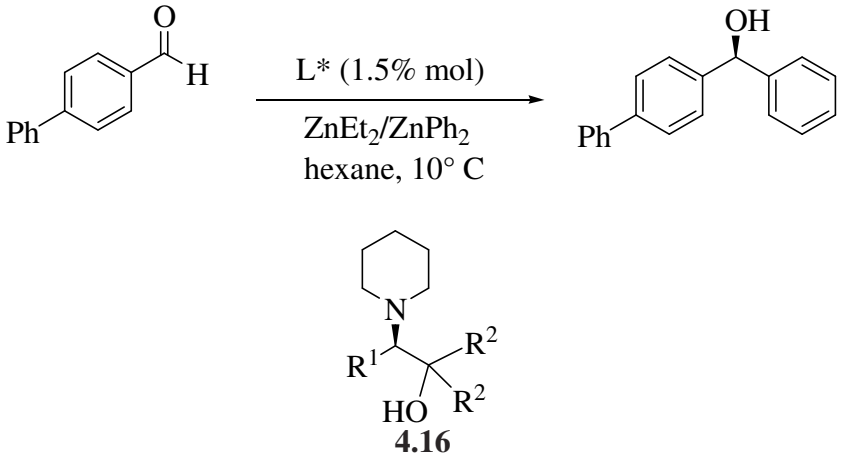
98% *ee*) in excellent yields (95–98%). Only moderate results, however, were obtained for α,β-unsaturated (75–85% *ee*) and aliphatic aldehydes (66–68% *ee*).

Superchi applied catalysts with a 1,19-binaphthylazepine skeleton, and with 10 mol% of (*S*) **4.15** the phenyl transfer reaction from diphenylzinc onto 4-chlorbenzaldehyde afforded the desired alcohol with an *ee* of 54%.[11]



4.15

In 2004 another effective catalyst for enantioselective phenyl transfer reactions to aldehydes was reported by Pericas.[12] The use of 1.5–10 mol% of 2-piperidino-1,2,2-triphenylethanol **4.16** and a mixture of diethyl- and diphenylzinc (ratio 2:1) provided the corresponding products with enantiomeric excesses of up to 99%.

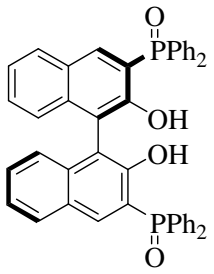


4.16

First, the addition of diphenylzinc to *p*-tolualdehyde was studied, using 10 mol% of **4.16**, which had been pretreated with an equimolar amount of diethylzinc, under high dilution conditions (10 mM) in various solvents. The best result was obtained in diethyl ether after 24 h, affording the desired product with 78% ee in 29% yield. In hexane the yield was slightly higher (57%), but the enantioselectivity decreased to 73% ee. Without pretreatment of **4.16** with diethylzinc the ee was significantly lower (48% vs 78% ee) and the conversion was usually incomplete under these high dilution conditions.

Furthermore, the effect of an excess of diethylzinc (1.32 equiv.) along with 0.64 equiv. of diphenylzinc and 10 mol% of aminoalcohol **4.16** on the phenyl transfer onto p-tolualdehyde was explored. At an aldehyde concentration of 100 mM in hexane at 0° C, the addition reaction went to completion within 2 h affording diarylmethanol with 98% *ee* in 90% yield. At room temperature the corresponding product was formed with a slightly lower enantioselectivity (97% *ee*, 94% yield). A study of the temperature/ee relationship between 0 and 25° C revealed that a maximum enantioselectivity was achieved at 10° C. Additionally, the high activity of aminoalcohol **4.16** allowed the catalyst loading to be reduced to 1.5 mol%. Under these conditions, the highest enantioselectivity (99% *ee*) was achieved with 4-phenylbenzaldehyde as substrate. The chemical behaviour, as well as results from DFT calculations suggested the intermediacy of a mixed zinc species (EtPhZn).

3,3'-Bis(diphenylphosphinoyl)-BINOL **4.17** was used in catalysed, asymmetric organozinc additions to aldehydes by Ishihara.[13]

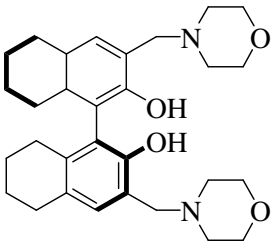


4.17

In the enantioselective phenyl transfer from diphenylzinc to a number of aromatic aldehydes in the presence of 10 mol% of diethylzinc and 10 mol% of **4.17**, the corresponding diarylmethanols were formed with good enantiomeric excesses (81–88%) in high yields (86–93%) after 24 h at room temperature.

Recently, Pu described the application of the H_8-BINOL derivative **4.18** in asymmetric phenyl transfer reactions.[14] Linear as well as α- and β-branched aliphatic substrates gave products with *ee* values in the range of 92–98%. From aromatic aldehydes diarylmethanols with up to 96% *ee* were obtained. Generally, use of 10 mol% of **4.18** led to the best results. Investigations by NMR spectroscopy as well as studies of the

relationship between the ee of the catalyst and the ee of the product suggested the intermediacy of a monomeric zinc complex.

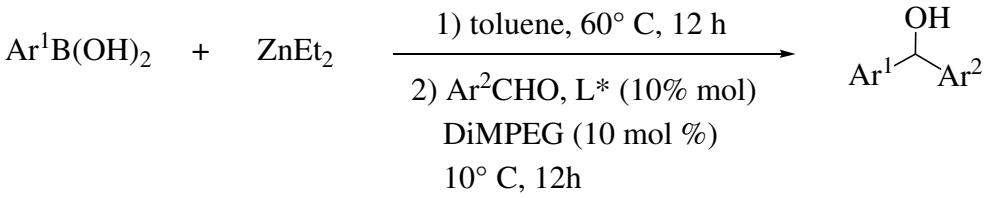


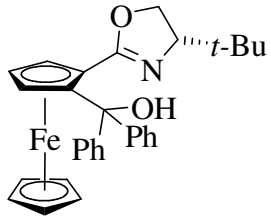
4.18

4.3.2. Other aryl sources in the aryl transfer reactions to aldehydes.

The catalysed aryl transfer reactions described above relied on the use of diphenylzinc as aryl source and consequently, they have been limited to the transfer of a phenyl group to aldehydes.

In 2002 Bolm reported the first general, catalytic asymmetric aryl transfer reaction to aldehydes using the ferrocene reported below **4.19** as catalyst and arylzinc species formed in situ from arylboronic acids and diethylzinc.[15]



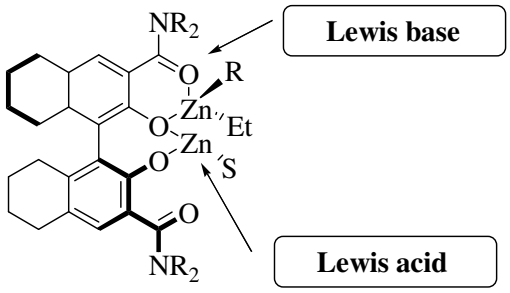


4.19

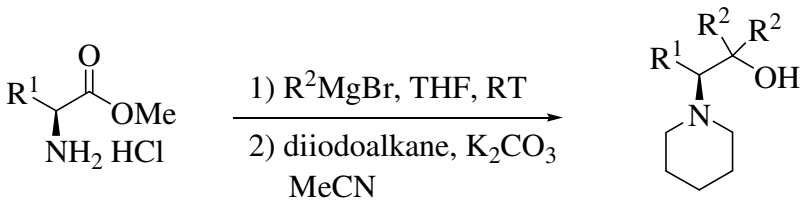
Subsequently, a multigram scale application was described. The presence of catalytic amounts of a polyether further improved the enantioselectivities of the reaction from 31–95% *ee* to 85–98% *ee*. In this new protocol, the aryl boronic acid (2.4 equiv.) was first reacted with diethylzinc (7.2 equiv.) in the presence of 10 mol% of

dimethylpolyethyleneglycol (DiMPEG, Mw = 2000 g mol^{-1}) at 60° C for 12 h. **4.19** (10 mol%) and the aldehyde were added at 10° C. One of the most significant advantages of this method is the accessibility of both enantiomers using the same catalyst by choosing the appropriate combination of boronic acid and aldehyde. For example, reaction of phenylboronic acid and p-chlorobenzaldehyde gave the (*R*)-enantiomer of the corresponding product with excellent enantioselectivity (97% *ee*) in high yield (93%). The (*S*)-enantiomer of the product was accessible by aryl transfer from *p*-chlorophenylboronic acid onto benzaldehyde. Albeit in this case the yield was only moderate, the enantioselectivity was very high again (61% yield, 97% *ee*). *ortho*-Substituted boronic acids afforded diarylmethanols with only slightly lower enantiomeric excesses and yields. For example, 1-naphthylphenylmethanol was obtained with 85% *ee* in 91% yield by a catalysed reaction of benzaldehyde and 1-naphthylboronic acid.

In 2005, Katsuki introduced binaphthol dicarboxamides as catalysts for the aryl transfer reaction onto aldehydes.[16] In relatively short reaction times (2.5 h) at 0° C diarylmethanols with up to 96% *ee* were obtained. Interestingly, the use of solvent mixtures of toluene and MTBE (methyl-*t*-butylether) (1:1) was crucial for achieving high enantioselectivities. Addition of 10 mol% of DiMPEG did not improve the enantiomeric excess of the product, but slowed down the reaction. The adduct in the picture below was formed by double deprotonation of the ligand, and it was suggested as the active catalyst. This proposal contrasts the assumed mechanism of reactions with organozincs catalysed by conventional amino alcohols:



In 2005, Braga adopted this protocol involving mixtures of boronic acids and diethylzinc as aryl source and employed catalysts based on β-amino alcohols[17] which had previously been introduced for the synthesis of diarylmethanols by Pericas.

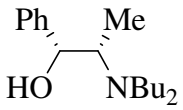


4.20

β-Amino alcohols of this type (**4.20**) are rapidly synthesised in two steps, starting from commercially available amino acid ester hydrochlorides. A double Grignard addition or hydride reduction leads to the desired amino alcohols which can further be converted into cyclic tertiary amines by treatment with diiodoalkanes and potassium carbonate in acetonitrile.

Initially the influence of the substituent R^2 was examined, while R^1 was kept constant as benzyl group. With *p*-tolualdehyde as substrate the best result was achieved with phenyl boronic acid in toluene and 20 mol% of the piperidine derivative having an ethyl group as R^2. With this catalysis the product was obtained with 92% *ee* in 97% yield. The size of the aza-ring was also of importance. When the smaller pyrrolidine derivative was used, the enantiomeric excess of alcohol derived from *p*-tolualdehyde decreased to only 65%. However, variation of R^1 to an *iso*-propyl group led to a higher enantioselectivity (*ee* = 97%). This catalyst (R^1 = *i*-Pr, R^2 = Et) was then used in the asymmetric aryl transfer to various aromatic aldehydes. The *ortho*- and *para*-tolualdehydes underwent smooth aryl addition and the products were obtained with 97% ee and in 93% and 97% yield, respectively. With *ortho*- and *para*-methoxybenzaldehyde, however, the corresponding products were obtained with enantiomeric excesses of only 81%. Furthermore, the aryl transfer of various aryl boronic acids to benzaldehyde was studied. There, use of *p*-chlorophenylboronic acid furnished the product with 94% *ee* in 97% yield.

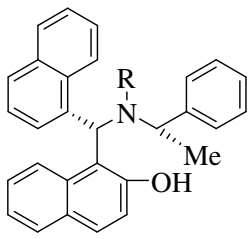
In many of the described processes high catalyst loadings (10–20 mol%) were required to achieve synthetically useful results. Since the addition of polyethylene glycol ethers (PEG) had led to beneficial effects in such reactions, Bolm studied the effect of other additivies on the catalysed aryl transfer reaction using his ferrocene ligand and (1*R*,2*S*)-DBNE (N,N-dibutylnorephedrine) **4.21** as catalysts in greater detail.[18]



4.21

It was assumed that the presence of compounds such as PEG would suppress unwanted non-asymmetric pathways by deactivating achiral, Lewis acidic species (such as zinc alkoxides as well as diphenylzinc, which adds to aldehydes even in the absence of a catalyst) and thus prevent their non-enantioselective contribution to the overall process. Confirming this hypothesis, an ‘‘MPEG effect’’ was revealed, which allowed the catalyst loading to be significantly reduced. Also other additives (such as imidazole) affected the catalysis, and a few of them enhanced the efficiency of the existing catalytic asymmetric reaction. Additionally, an automated high-throughput screening of various additives in the enantioselective phenyl transfer reaction with 2-bromobenzaldehyde in the presence of (1R,2S)-DBNE was conducted. Besides polyethyleneglycols (PEGs), also 2-propanol, TMEDA or N-methylimidazole had beneficial effects on the enantioselectivity in the formation of the product. Furthermore, addition of one equivalent of imidazole led to a reversal of the absolute configuration of the product.

In 2005 an axial chiral aminonaphthol **4.22** was introduced for the catalytic asymmetric phenyl transfer to aromatic aldehydes by Chan.[19]

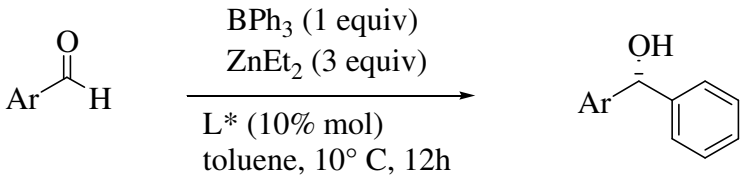


4.22

Phenylboronic acid served as (sole) aryl source in this report. Using a mixture of phenylboronic acid (2 equiv.), diethylzinc (6 equiv.), DiMPEG (10 mol%) and the (*S*,*S*)-ligand with R = Me (16 mol%) in toluene, *p*-chlorobenzaldehyde was transformed into the corresponding alcohol with 94% *ee* in 90% yield. Lowering the catalyst loading to 8 mol% had only a minor influence on the yield and enantioselectivity (89% yield, 92%

ee). Also for the preparation of many other diarylmethanols this catalyst amount was sufficient to obtain them with high enantiomeric excesses (>96% *ee*). A phenyl boronic acid/dimethylzinc combination could also be used for the generation of the phenyl transfer reagent. However in this case, lower yields and only slightly higher *ees* resulted under otherwise identical reaction conditions. In contrast to previously published results, *ortho*-substituted benzaldehydes gave products with higher enantioselectivities than other substrates. For example, 2-methylbenzaldehyde was transformed into the corresponding diarylmethanol in 94% yield with 98% *ee*.

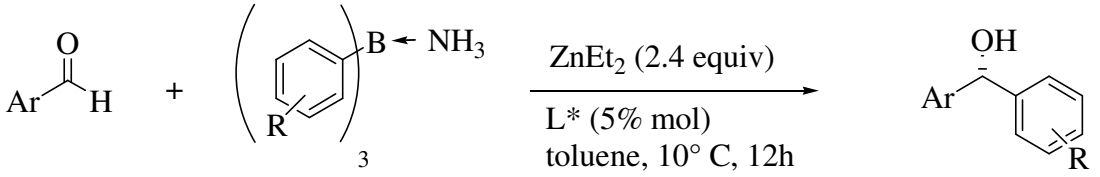
Triphenylborane was recently found to be an interesting alternative to diphenylzinc as phenyl source.[20] It is commercially available in large quantities, and rather inexpensive compared to diphenylzinc. In analogy to the other preparations, the aryl zinc reagent (presumably EtZnPh) was formed in situ using 1 equiv. of triphenylborane and 3 equiv. of diethylzinc:

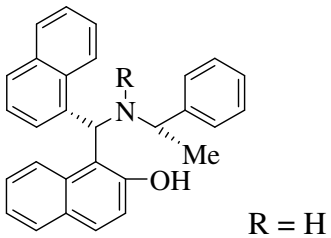


With Bolm's ferrocene **4.19**, this system was successfully applied to a wide range of *para*- and *ortho*-substituted aromatic aldehydes. In reactions with *p*-chlorobenzaldehyde, the *ee* of the product remained the same (97% *ee*), but the yield increased to 98%, compared to 95% in the original protocol. A remarkable enantioselectivity has also been achieved with 2-thiophenecarbaldehyde, which gave 9l with 91% *ee*. Aliphatic aldehydes yielded the corresponding arylalkyl alcohols with 80–97% *ee*. A slightly lower enantioselectivity was observed in the phenyl transfer onto 2-bromobenzaldehyde, which afforded the corresponding product with 87% *ee* only. Probably steric effects and a chelation to the substituent in *ortho*-position were responsible for this decrease in *ee*.

In 2005, Dahmen extended this protocol using triarylborane ammonia complexes as stable, versatile and economic precursors for zinc reagents.[21] Their applications in various aryl transfer reactions to aldehydes were investigated. In the presence of 5

mol% of aminonaphthol **4.23** and diethylzinc the best result was obtained using *p*-tolualdehyde and triphenylborane ammonia complex with R = H as aryl source, which gave diarylmethanol with 98% *ee* in 96% yield.



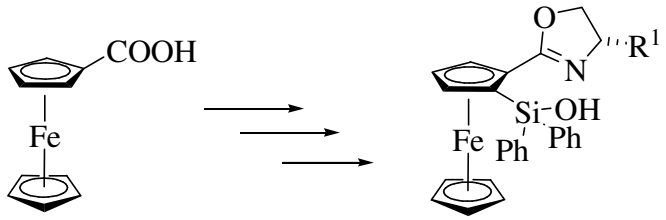


R = H

4.23

Electron-poor as well as electron rich borane complexes were applied in addition to benzaldehyde affording products with slightly lower enantiomeric excesses (94–96%) and yields (86–92%). Aliphatic aldehydes were transformed into the corresponding products with up to 71% *ee*.

Recently, Bolm reported the synthesis of ferrocene-based silanols **4.24** (sila analogues of the ferrocenes) and their application in asymmetric phenyl transfer reactions to aromatic aldehydes.[22] They can easily be prepared in four steps, starting from ferrocene carboxylic acid:



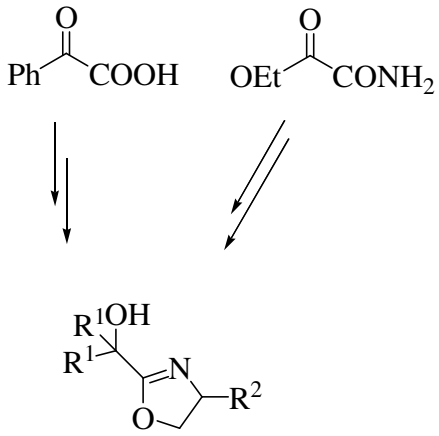
R^1 = *t*-Bu, Ph, *i*-Pr, Bn

R^2 = Me, *i*-Pr, Ph

4.24

The catalytic properties of these silanols were examined in the standard phenyl transfer reaction to p-chlorobenzaldehyde applying all three phenyl sources: (1) diphenylzinc, (2) triphenylborane and (3) phenylboronic acid. Most organosilanols showed good enantioselectivities and afforded the desired product in respectable yields. The best result was obtained with a combination of diphenylzinc and organosilanol with R^1 = *t*-Bu and R^2 = *i*-Pr, which gave (*p*-chlorophenyl)phenylmethanol with 91% *ee* in 82% yield. All other silanols led to inferior results, presumably due to an insufficient steric impact of the substituents R^1 and R^2. Other aromatic aldehydes were transformed into the corresponding diarylmethanols with 83–87% *ee* using diphenylzinc and the silanol reported above. Triphenylborane was almost as effective as diphenylzinc as aryl source. The application of phenylboronic acid in the presence of polyethyleneglycol DiMPEG as additive led to products with lower enantioselectivities and decreased yield.

In the same year, Bolm described the synthesis of new chiral hydroxy oxazolines **4.25** and their application in the catalytic asymmetric phenyl transfer reaction to aromatic aldehydes.[23] Starting from either phenylglyoxylic acid or ethyl oxamate several enantiopure α-hydroxy oxazolines were prepared by condensation with β-amino alcohols.

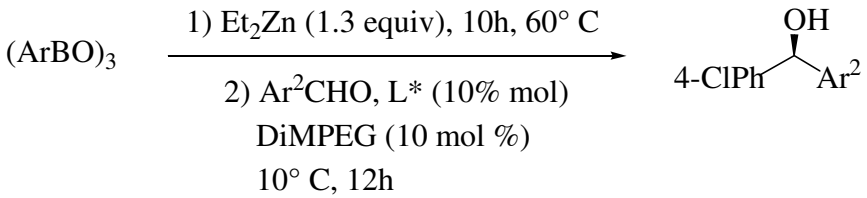


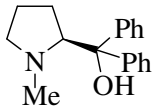
4.25

In order to study the efficacy of these oxazolines, several experiments were carried out using *p*-chlorobenzaldehyde as test substrate. A mixture of triphenylborane and diethylzinc served as phenyl source. Furthermore, the effect of DiMPEG as additive was studied. Products with up to 71% *ee* were obtained using hydroxy oxazoline in the reaction. Catalysts with more bulky aryl substituents did not lead to any improvement,

and use of α,α-dimesityl substituted hydroxy oxazoline even resulted in racemic products. Application of various aldehydes in the phenyl transfer reaction using hydroxy oxazolines allowed the synthesis of diarylmethanols with up to 81% *ee*.

In 2005 Zhao reported the use of proline-derived β-aminoalcohols in the asymmetric aryl transfer to aldehydes. Boroxines served as aryl source.[24]
Test substrates were phenylboroxine (in combination with diethylzinc) and *p*-chlorobenzaldehyde. From this experiment the aminoalcohol **4.26** proved to be the more effective affording the product with 89% *ee*.



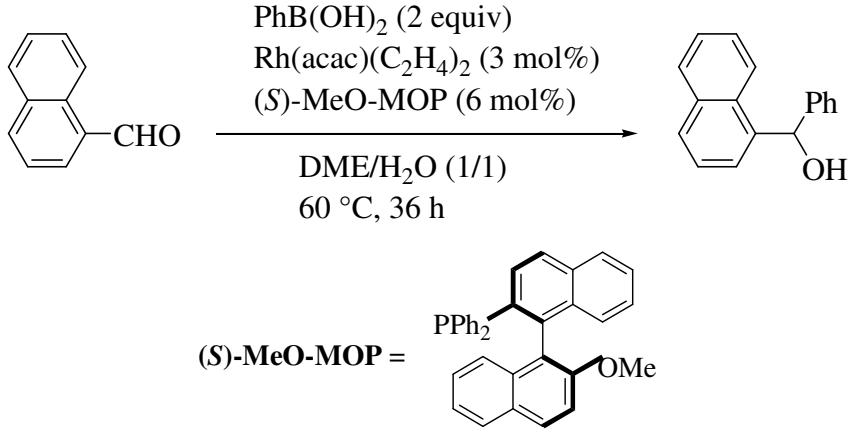


4.26

This aminoalcohol was then tested in the enantioselective phenyl transfer onto a variety of aromatic aldehydes. Herein, *para*-substituted benzaldehydes generally led to better results than *meta*- and *ortho*-substituted ones. Interestingly, the use of DiMPEG as additive resulted in a significantly decreased yield, although an increase of the enantiomeric excess was observed. For example, in the presence of DiMPEG (*p*-chlorophenyl)phenylmethanol was obtained with 96% *ee* in 37% yield. Importantly, pretreatment of the aminoalcohol with diethylzinc (as previously reported by Pu) improved the enantioselectivity significantly. Furthermore, the use of boroxines instead of boronic acids allowed the amount of diethylzinc to be reduced from 4.0 to 1.3 equiv. With this modified procedure, the enantioselectivities in the formation of the addition products were increased to 87–95% *ee*. The authors also studied the asymmetric aryl transfer reaction from other aromatic boroxines to benzaldehyde and the corresponding diarylmethanols were obtained with up to 94% *ee* in good yield. As expected, the products now had the opposite absolute configuration.

4.3.3. Rh-, Ti-, and Cu-catalysed enantioselective aryl transfer reactions

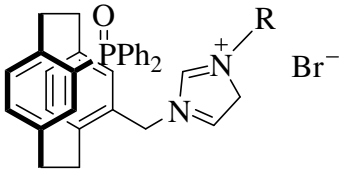
A Rhodium-catalysed asymmetric addition of an arylboronic acid to an aromatic aldehyde was first reported by Miyaura in 1998.[25] Although complexes with bidentate ligands such as dppf catalysed the reaction effectively, enantiopure diphosphines such as BINAP and DIOP gave only racemic products. However, applying monophosphine (*S*)-MeO-MOP **4.27** as ligand in the rhodium-catalysed asymmetric phenyl transfer reaction from phenylboronic acid to 1-naphthylaldehyde afforded the corresponding alcohol with 95% yield and 41% *ee* Conversions of other substrates were not reported.



4.27

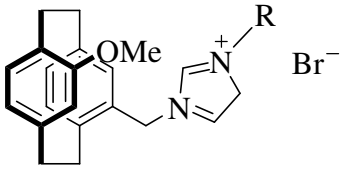
In 2005, Bolm described [2.2]paracyclophane-based imidazolium salts **4.28** and **4.29** as stable precursors for planar chiral carbenes and demonstrated their use in rhodium-catalysed asymmetric aryl transfer reactions.[26] An enatioselectivity up to 38% *ee* was obtained using **4.28** with R = (*S*)-CHMePh in combination with 1-naphthylaldehyde and phenylboronic acid as substrates.

4.28



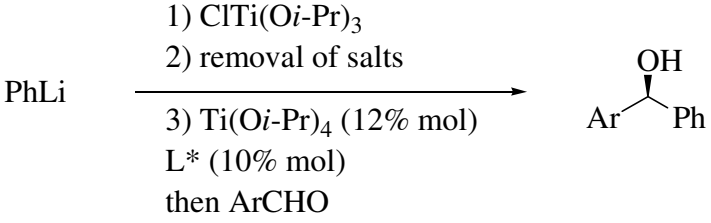
R = Me
R = (*S*)-CHMePh
R = (*R*)-CHMePh
R = Mesityl

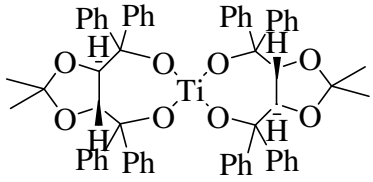
4.29



R = Me
R = (*S*)-CHMePh
R = (*R*)-CHMePh

The titanium/TADDOLate-catalysed enantioselective addition of alkyl- and aryltitanium reagents to aldehydes was reported by Seebach as early as 1994.[27] Two diarylmethanols were synthesised with up to 96% *ee* using 10 mol% of catalyst **4.30** in combination with 12 mol% of Ti(O*i*-Pr)$_4$. The phenyltitanium reagent was prepared by reaction of the corresponding organolithium or Grignard reagent with ClTi(O*i*-Pr)$_3$ in toluene. The authors noted that even the presence of traces of such salts significantly reduced the enantioselectivity in the addition reaction.

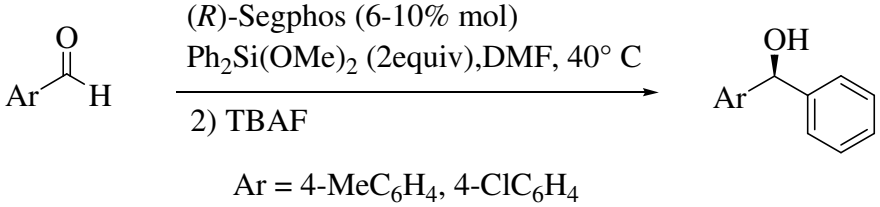




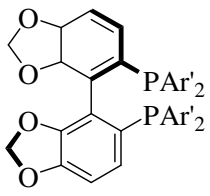
4.30

Therefore, Li^+ removal was obtained by complexation to 12-crown-4, while addition of 1,4-dioxane, followed by centrifugation, achieved complete precipitation of magnesium salts.

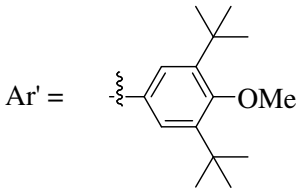
A copper-catalysed enantioselective phenyl transfer reaction to aromatic aldehydes using dimethoxydiphenylsilane as nucleophile was described by Shibasaki in 2005.[28] Using CuF_2 $2H_2O$ and (R)-DTBM-Segphos **4.31** as ligand, the synthesis of two diarylmethanols with up to 92% ee was reported . The active nucleophile is presumably a phenylcopper species generated by transmetalation from dimethoxydiphenylsilane.



Ar = 4-MeC_6H_4, 4-ClC_6H_4

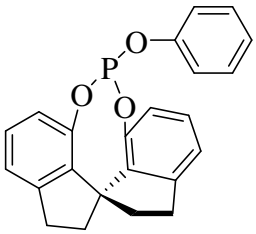


4.31



More recently, the group of Zohu reported the arylation of N-tosylarylimines in the presence of phenylboronic acids using using chiral spiro monophosphite ligands.[29]

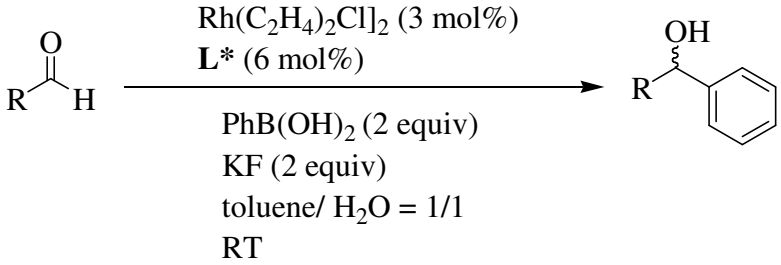
Initial studies dealt with the reaction of 1-naphthaldehyde and 2 equiv of $PhB(OH)_2$ in DME/H_2O (1:1) in the presence of 1.5 mol % of $[RhCl(CH_2CH_2)_2]_2$ and 6 mol % of **4.32**:



4.32

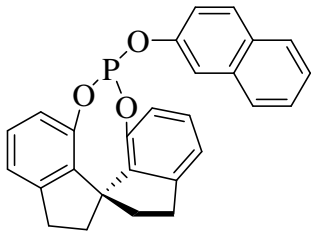
After reaction for 48 h at 60 °C, the addition product was isolated in 37% yield and 42% *ee*.

Variation of the solvent showed that the 1:1 mixture of toluene/H_2O was the best choice of solvent. It was also noticed that the addition of 2 equiv of KF as additive boosted both the yield and enantiomeric excess of addition product to 95% and 70%, respectively.



For searching more efficient chiral ligands, different spiro monophosphites were synthesized. Among them, **4.33** was found to be the best ligand which could proceed the

addition reaction smoothly even with 1 mol % of rhodium at 0 °C, giving the addition product in excellent yield (95%) and good ee value (80%).



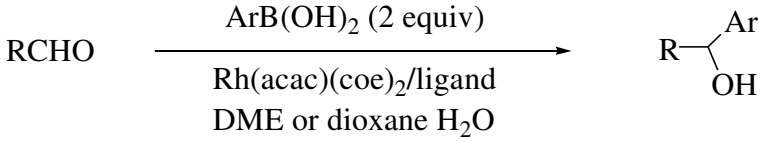
4.33

The shape of this ligand indicates that the rigid spiro phosphite moiety with a large dihedral angle benefit the formation of an effective catalyst with high activity and asymmetric induction ability.

Having optimized reaction conditions, they finally examined the reaction with various aldehydes and arylboronic acids obtaining good enantiomeric excesses up to 87%.

4.4. Rhodium-Catalysed Addition of Arylboronic Acids to Aldehydes

In 2000 Miyaura reported the significant effect of tri(*tert*-butyl)-phosphine in accelerating the addition of arylboronic acids to aldehydes:[30]



A series of rhodium(I)/phosphine complexes prepared *in situ* from $Rh(acac)(coe)_2$ (coe = cyclooctene) and the representative phosphines, revealed the effect of bidentate phosphines entries 1-8), basicity of monophosphines (entries 9-16), and stoichiometry of the ligand on the reactivity of the rhodium complexes (entries 15-17).

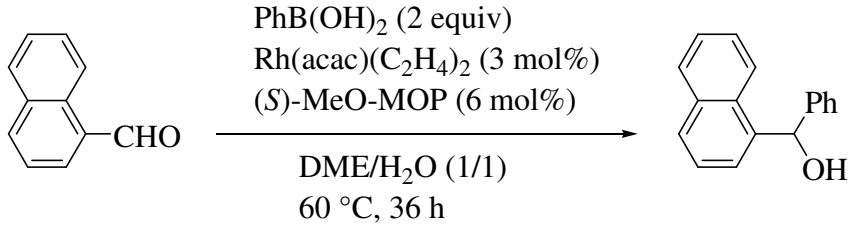
Entry	Ligand (equiv)	Yield% at 50° C	Yield% at 80° C
1	dppm (1)	-	30
2	dppe (1)	-	6
3	dppp (1)	-	71
4	dppb (1)	-	60
5	dppf (1)	20	85
6	DPEphos (1)	-	73
7	Xantphos (1)	-	0
8	DBFphos (1)	-	31
9	PPh_3 (1)	33	48
10	Me_3P (1)	24	12
11	*i*-Pr_3P (1)	88	86
12	*n*-Bu_3P (1)	-	89
13	*i*-Bu_3P (1)	75	-
14	Cy_3P (1)	50	83
15	*t*-Bu_3P (1)	99	79
16	*t*-Bu_3P (2)	67	77
17	*t*-Bu_3P (3)	57	-

A mixture of a 4-methoxybenzaldehyde (1 mmol), PhB(OH)2 (2 mmol), Rh(acac)(coe)2, (0.03 mmol) and a ligand (0.03-0.09 mmol) in DME/H2O (3/2, 5 mL) was stirred for 16 h at 50 or 80 °C.

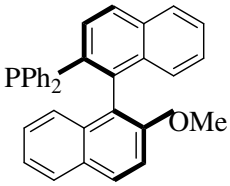
These preliminary results indicated that the reaction is accelerated by the use of bidentate phosphine complexes having a large P-Rh-P angle such as dppf, while monophosphine complexes resulted in significantly low yields when using 3 equiv of phosphine to the rhodium metal. However, a reinvestigation of the catalysts revealed a new correlation, namely, that the catalyst activity is highly dependent on both the basicity and the stoichiometry of the phosphine ligands. The effect of bidentate phosphine suggested the superiority of dppf (entry 5), but the same reaction was remarkably accelerated by bulky and donating trialkylphosphines such as tri(isopropyl)phosphine (entry 11) and tri(*tert*-butyl)phosphine (entry 15) when using 1 equiv of phosphine to the rhodium metal. The use of tri(*tert*-butyl)phosphine allowed quantitative conversion at 50 °C (entry 15). Although the addition of excess of *tert*-butylphosphine dropped the yields proportionally (entries 15-17), this effect of stoichiometry was dramatic in small trialkylphosphines; in fact, the presence of 3 equiv

of Et_3P completely stopped the reaction. In summary, the basicity and stoichiometry exhibited a more pronounced effect in modentate ligands than that of bidentate ligands.

The facile rhodium-catalysed addition of arylboronic acids to aldehydes using phosphines as ligand encouraged the same group to examine the asymmetric version of this protocol using (*S*)-MeO-MOP as monodentate chiral phosphorus ligand:[31]

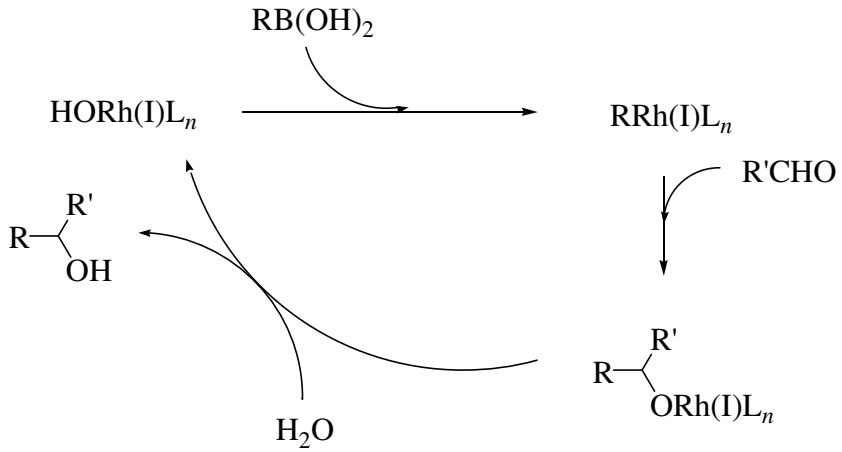


(*S*)-MeO-MOP =

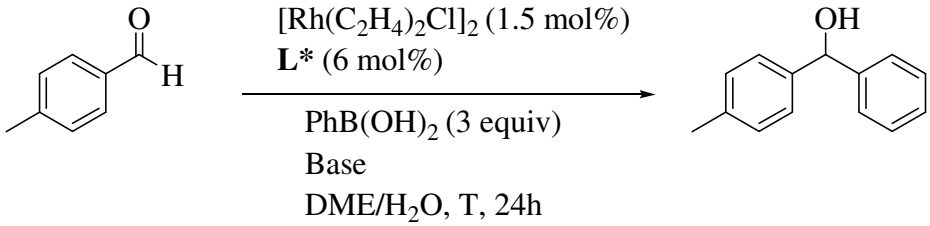


The asymmetric phenyl transfer reaction from phenylboronic acid to 1-naphthylaldehyde afforded the corresponding alcohol with 95% yield and 41% *ee*. It was also noticed that chiral bidentate ligands such as DIOP and BINAP unfortunately resulted in the formation of racemic alcohols.

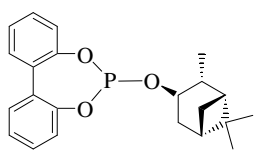
A mechanistic rationale for the reaction was also postulated: a transmetalation between arylboronic acid and the RO-Rh species (RO = acac or OH) to give an Ar-Rh^I complex is invoked as the first step, followed by the insertion of the aldehyde into the Ar-Rh bond. The arylrhodium(I) complexes are unstable such as to preclude isolation in pure form, but they have been reasonably speculated to be the key intermediates in various coupling reactions with organic halides and the addition to alkenes and alkynes. However, the insertion of aldehydes into the carbon-metal bond is very rare in transition metals except for the allylic derivatives.



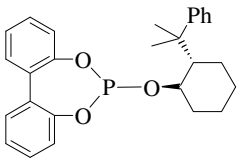
On the basis of these results we decided to test in the asymmetric rhodium-catalysed addition of arylboronic acids to aldehydes, the chiral tropos phosphorus ligands previously used by Gennari, Piarulli and co-workers (see Chapter 3). We started our screening studying the addition of phenylboronic acid to *p*-tolyldehyde, using the conditions reported by Miyaura:



The ligands that were tested in this reaction are reported in the table below:



3.27



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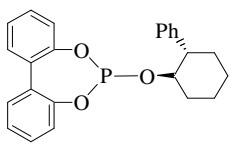

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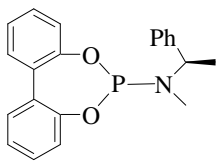


3.39

Entry	Ligand	Base	Temp. (°C)	Yield (%)	*ee* (%)
1	PPh_3	-	80°C	7	rac
2	**3.27**	-	80°C	28	7 (*S*)
3	**3.27**	KOH (2M)	80°C	68	rac
4	**3.27**	KOH (2M)	RT	46	rac
5	**3.27**	KOH (2M)	80°C	40	4 (*S*)
7	**3.30**	KOH (2M)	80°C	59	4 (*S*)
8	**3.30**	KOH (2M)	80°C	85	11 (*S*)
9	**3.30**	-	80°C	20	6 (*S*)
10	**3.30**	KOH (2M)	80°C	-	-
11	**3.39**	KOH (2M)	80°C	-	-

The reported results indicate that the reaction works better at high temperature (80° C) and in presence of a base (a solution of KOH 2 M) which boosted the yield to 68% (entry 3).

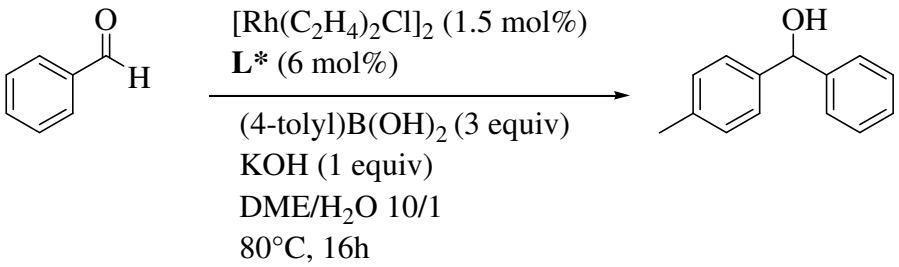
Triphenylphosphine and phospohoramidites has no positive effect as ligands, while the reaction is remarkably accelerated using phopshites.

It is also possible to underline that yields are higher using a ratio DME:H_2O = 10:1 instead of 1:1.

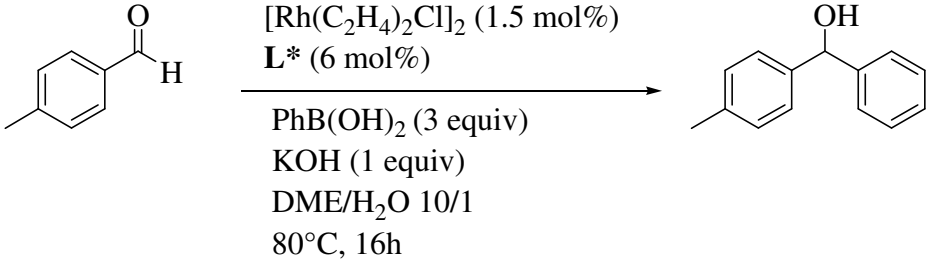
Unfortunately in each case enantiomeric excesses were not good.

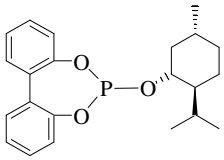
We also investigated different rhodium precursors in the addition reaction and found that all tested rhodium complexes furnished similar enantioselectivities, whereas the $[RhCl(CH_2CH_2)_2]_2$ gave the highest yield.

In order to compare yield and enantiomeric excess, we also studied the addition of p-tolylboronic acid to benzaldehyde using the best ligand **3.30**, obtaining the corresponding diarylmethanol in 85% yield and 10 % e.e. (compare the results with entry 8 in the previous table):



Having established the best reaction conditions we tested other ligands belonging to the family of phosphites and phosphoramidites:





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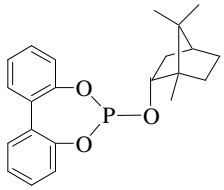

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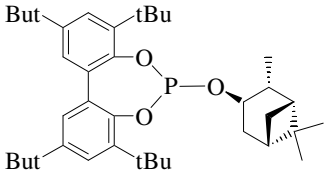

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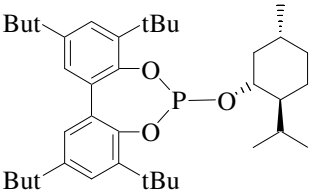

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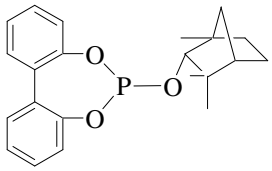

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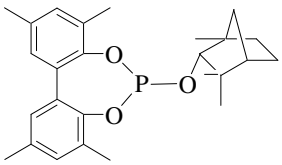

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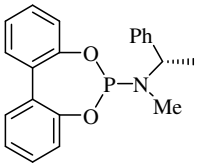

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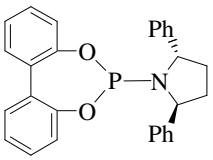

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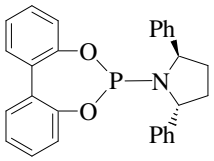


3.42

Entry	Ligand	Yield (%)	*ee* (%)
3	**3.26**	-	-
4	**3.29**	83	6 (*S*)
5	**3.31**	85	rac
6	**3.32**	92	5 (*S*)
7	**3.33**	-	-
8	**3.35**	-	-
9	**3.38**	-	-

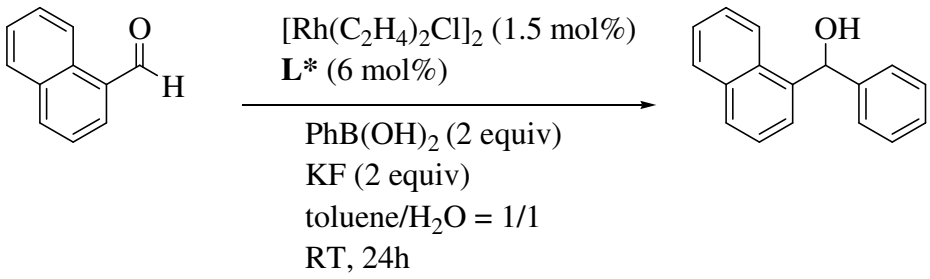
As a general comment, under these reaction conditions, only a few ligands were able to accelerate the reaction, while other phosphite ligands and especially some phosphoramidites did not show any activity, presumably also because of decomposition of the ligands in the reaction medium.

We also tested phosphites and phosphoramidites in combination in order to determine if there is any cooperative effect of the two ligands (match and mismatch):

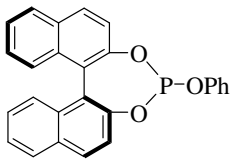
Entry	L_a	L_b	Yield (%)	*ee* (%)
10	**3.28**	**3.38**	52	rac
11	**3.28**	**3.39**	64	7 (*S*)
12	**3.30**	**3.38**	n.p.	/
13	**3.30**	**3.39**	47	2 (*S*)
14	**3.30**	**3.38**	n.p.	/
15	**3.30**	**3.39**	n.p.	/

As discussed above, Zhou and co-workers reported very recently that sterically hindered monodentate phosphite ligands were particularly effective in promoting the addition of phenylboronic acid to arylaldehyde, such as 1-naphthaldehyde, especially if the reaction was conducted in a 1:1 mixture of toluene/H_2O with the addition of 2 equiv of KF as an

additive. On the basis of these new results we decided to test our ligands using the reaction conditions reported by the group of Zhou. Several aldehydes were reacted with ligand **3.27** revealing that 1-naphthaldehyde afforded the arylation product with the highest yield.



Since ligands characterized by sterically hindered substituents apparently afforded the product in the highest enantiomeric excesses, we synthesised a a few binaphtholic phosphites and phosphoramidites and tested them in the addition to 1-naphthaldehyde. The results are summarized in the table below:



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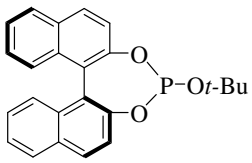
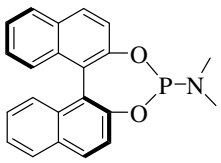


3.45



3.46

Entry	L*	Yield (%)	*ee* (%)
1	**3.27**	41	7 (*S*)
2	**3.30**	37	4 (*S*)
3	**3.44**	89	56 (*S*)
4	**3.45**	80	27 (*S*)
5	**3.46**	75	22 (*S*)

Binaphtholic phosphites and phosphoramidites afforded the product with increased yields and enantiomeric excesses (Entry 3-5), albeit the latter are still moderate at best.

We also evaluated some combinations of binaphtholic/biphenolic ligands and binaphtholic/binaphtholic ligands:

Entry	L_a	L_b	Yield (%)	*ee* (%)
7	**3.44**	**3.36**	17	25 (*S*)
8	**3.44**	**3.35**	-	-
9	**3.44**	**3.33**	9	27 (*S*)
10	**3.44**	**3.34**	62	26 (*S*)
11	**3.44**	**3.39**	50	43 (*S*)
12	**3.44**	**3.40**	65	28 (*R*)
13	**3.44**	**3.46**	50	27 (*S*)
14	**3.45**	**3.46**	75	22 (*S*)
15	**3.30**	**3.46**	57	19 (*S*)

Unfortunately, no cooperative effect could be highlighted using ligand combinations, since both reduced yields and ee's are obtained in all the tested combinations. In conclusion, these ligands are not selective enough in this transformation and only moderate reactivity and enantiomeric excesses were obtained.

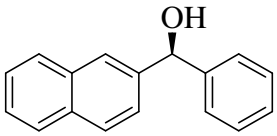
4.5. Experimental section

General procedure for the arylation of aldehydes

In a flame dried Schlenk tube flushed with nitrogen, 1.2 mg (3.09 μmol, 1.5 mol%) of $[Rh(C_2H_4)_2Cl]_2$ and ($1.23 \cdot 10^{-2}$ mmol, 6 mol%) of the ligand were dissolved in dry toluene (1 mL). After stirring for 30 min at room temperature, arylboronic acid (0.4 mmol), KF (0.4 mmol), H_2O (1 mL) and the aldehyde (0.2 mmol) were added. The resulting mixture was stirred at 25 °C for 24 h, quenched with water (3 mL) and extracted with CH_2Cl_2 (3 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was purified by flash chromatography on silica gel with a mixture of *n*-hexane/EtOAc affording the *N*-tosyl-diarylmethylamine as a white solid.

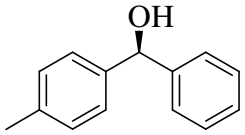
Both the *ee*'s and the absolute configurations of diarylmethanols were determined by HPLC using a Chiralcel OD-H or OD column.[29,32]

(*S*)-(1-Naphthyl)phenylmethanol.



$[\alpha]_D^{20}$ = +32 (*c* 1.46, EtOH), [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 80/20, 1.0 ml/min, 254 nm UV detector, t_R = 8.50 min for (*S*) and t_R = 17.32 min for (*R*)]. ^{1}H NMR δ 8.04 (d, *J* = 7.0 Hz, 1H, Ar-H), 7.88-7.81 (m, 2H, Ar-H), 7.64 (d, *J* = 7.0 Hz, 1H, Ar-H), 7.51-7.40 (m, 5H, Ar-H), 7.35-7.22 (m, 3H, Ar-H), 6.54 (s, 1H, CH), 2.39 (s, 1H, OH).

(*S*)-(4-Methylphenyl)phenylmethanol



$[\alpha]_D^{20}$ = +5.2 (*c* 0.92, $CHCl_3$), [HPLC condition: Chiralcel OD-H column, *n*-hexane/2-propanol = 95/5, 1.0 ml/min, 254 nm UV detector, t_R = 13.50 min for (*S*) and t_R = 15.32 min for (*R*)]. ^{1}H NMR δ 7.38-7.27 (m, 5H, Ar-H), 7.26 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.14 (d, *J* = 7.9 Hz, 2H, Ar-H), 5.98 (brs, 1H, CH), 2.36 (s, 3H, CH_3), 2.17 (brs, 1 H, OH),.

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