Catalytic asymmetric approaches towards enantiomerically enriched diarylmethanols and diarylmethylamines

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Enantiopure diarylmethanols and diarylmethylamines are important intermediates for the synthesis of pharmaceutically relevant products with antihistaminic, antiarrhythmic, diuretic, antidepressive, laxative, local-anesthetic and anticholinergic properties. Furthermore, they have been used as precursors for 1,1-diarylalkyl moieties, which occur in other antidepressants as well as in antimuscarinics and endothelin antagonists. In this *critical review* catalytic strategies towards enantioenriched diarylmethanols and diarylmethylamines are discussed, including methods for asymmetric carbon–carbon bond formations by aryl transfer reactions to aldehydes and arylimines, respectively, and enantioselective reductions of diarylketones.

1 Introduction

Control of stereochemistry in the formation of chiral diarylmethanols and diarylmethylamines 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). They can be synthesised by carbon–carbon bond formation of aromatic aldehydes or arylimines and the appropriate organometallic compounds (path **A**), by nucleophilic displacement at the benzylic position (path **B**), or by reduction of the C=O or C=N bonds of the corresponding diarylketones and diarylketimines, respectively (path **C**).

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Catalytic, asymmetric syntheses of diarylmethanols commonly involve one out of two strategies: either the addition of suitable aryl nucleophiles to aromatic aldehydes or the reduction of diarylketones (Scheme 2). In the case of diarylmethylamines efficient catalytic asymmetric reductions of the corresponding diarylimines are still lacking and only enantioselective aryl transfer reactions to aldimines have been developed. Usually, those involve chiral rhodium complexes, or, alternatively, are catalysed by chirally modified lithium or zinc reagents.

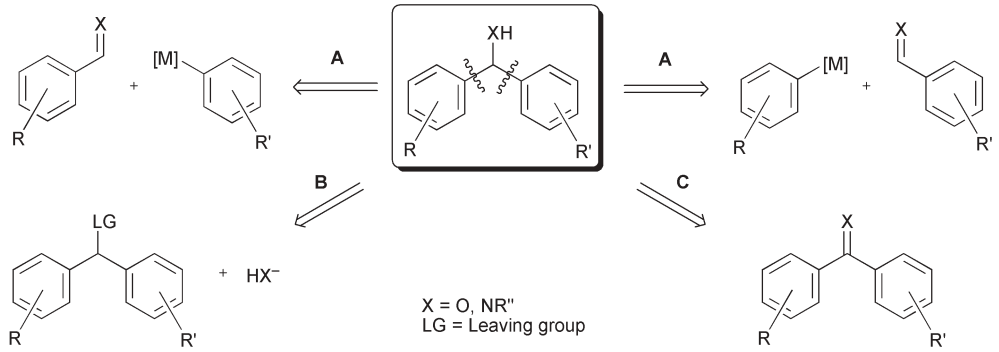
In general, asymmetric, catalytic approaches towards enantiopure diarylmethanols and diarylmethylamines have become increasingly important recently, as reflected by the high number of publications on this topic during the last 10 years. Although alternative methods with stoichiometric quantities of chiral reagents are also known (''auxiliary approach''), this review will focus on the more atom-economic *catalytic* versions utilizing substoichiometric quantities of chiral inducers.

Frank Schmidt

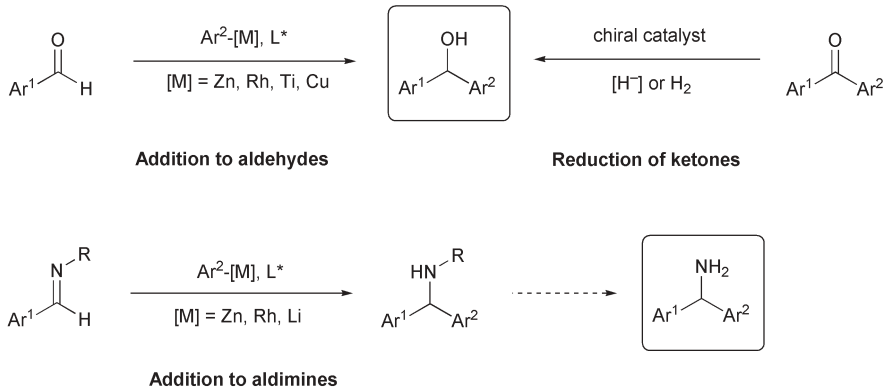
Frank Schmidt was born in 1978 in Oberhausen (Germany). He studied chemistry at the Philipps-University of Marburg (Germany). During his studies he spent 6 months at the Heriot-Watt University in Edinburgh (Scotland) as a Socrates exchange student working in the group of Professor Welch. After finishing his diploma thesis with Professor Hilt he received his Diploma in Chemistry in 2003. Currently he is working as a PhD student with Professor Bolm at the RWTH Aachen University (Germany) focusing on asymmetric aryl transfer reactions to aldehydes.

René T. Stemmler

René T. Stemmler was born in Frankfurt (Main), Germany, in 1976. He studied chemistry at the University of Freiburg and the University of North Carolina, Chapel Hill, USA. In 2003 he completed his diploma thesis under the supervision of Professor Breit. Currently, he is doctoral student in the group of Professor Bolm at the RWTH Aachen University, Germany. His project is focused on the development of new ligands for metal-catalysed asymmetric reactions.



Scheme 1 General synthetic approaches towards diarylmethanols and diarylmethylamines.



Scheme 2 Catalytic approaches towards diarylmethanols and diarylmethylamines.

Jens Rudolph

Jens Rudolph was born in Hagen (Germany). He studied chemistry at the RWTH Aachen University (Germany) and performed research as a DaimlerChrysler fellow under the supervision of Professor Michl at the University of Colorado at Boulder (USA). In 2004 he finished his doctoral work, which he jointly carried out in the group of Professor Bolm in Aachen (Germany) and in the group of Professor Norrby at the Danish Technical University (Denmark). His doctoral thesis was entitled "Asymmetric aryl transfer, experimental and theoretical methods". In 2004 he joined BASF's Chemicals Research & Engineering platform as a lab leader, where he pursues research projects oriented towards improved raw material utilisation by employing homogeneous and asymmetric catalysis. He was awarded with the Eli Lilly diploma thesis award, and he will receive the Borchers Medal from RWTH Aachen University for his PhD thesis.

Carsten Bolm

Carsten Bolm studied chemistry at the TU Braunschweig in Germany and at the University of Wisconsin in Madison (USA). In 1987 he finished his doctoral work with Professor Reetz in Marburg (Germany). After postdoctoral studies at MIT, Cambridge (USA), with Professor Sharpless, Carsten Bolm began to work on his habilitation in Basel (Switzerland) in the group of Professor Giese. In 1993 he became Professor of Organic Chemistry at the University of Marburg (Germany), and has since 1996 been a full professor for Organic Chemistry at the RWTH Aachen University (Germany). He has held visiting professorships at the universities in Madison, Wisconsin (USA), Paris (France), Florence (Italy), Milan (Italy), and Namur (Belgium). His list of awards include the Heinz-Maier-Leibnitz prize, the ADUC-Jahrespreis for habilitands, the annual prize for Chemistry of the Akademie der Wissenschaften zu Göttingen, the Otto-Klung prize, the Otto-Bayer award, and a fellowship of the Japan Society for the Promotion of Science.

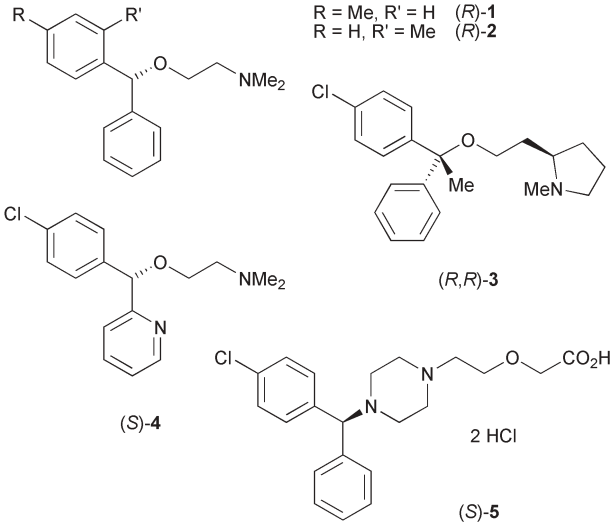


Fig. 1 Examples of physiologically active compounds derived from diarylmethanols and diarylmethylamines.

2 Biologically active diarylmethanol and diarylmethylamine derivatives

Diarylmethanols and -methylamines are precursors for a number of compounds with physiologically interesting properties, which include antihistaminic, antiarrhythmic, diuretic, antidepressive, laxative, local-anesthetic and anticholinergic activities.[1] For example, the diphenhydramine derivatives orphenadrine (**1**) and neobenodine (**2**)[2] show anthistaminic as well as anticholinergic activity (Fig. 1). Clemastine (**3**)[3] was used as a first-generation histamine H_1 antagonist for the treatment of allergic diseases. Subsequently, other histamine H_1 antagonists with related structures have been discovered, for example, (*S*)-carbinoxamine (**4**)[4] and, in particular, the second-generation antagonist cetirizine hydrochloride (**5**, Zyrtec®), which is more selective towards H_1-receptors.[5] Significantly, only the (*S*)-enantiomer of the latter compound is biologically active,[6] and it has therefore been marketed in enantiopure form since the beginning of 2002 (Levocetirizine, Xyzall®).

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.[7] For example, CDP-840 (**6**, Fig. 2) selectively inhibits phosphodiesterase IV.

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

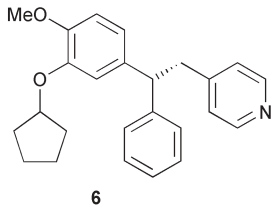


Fig. 2 Phosphodiesterase IV inhibitor CDP-840 (**6**).

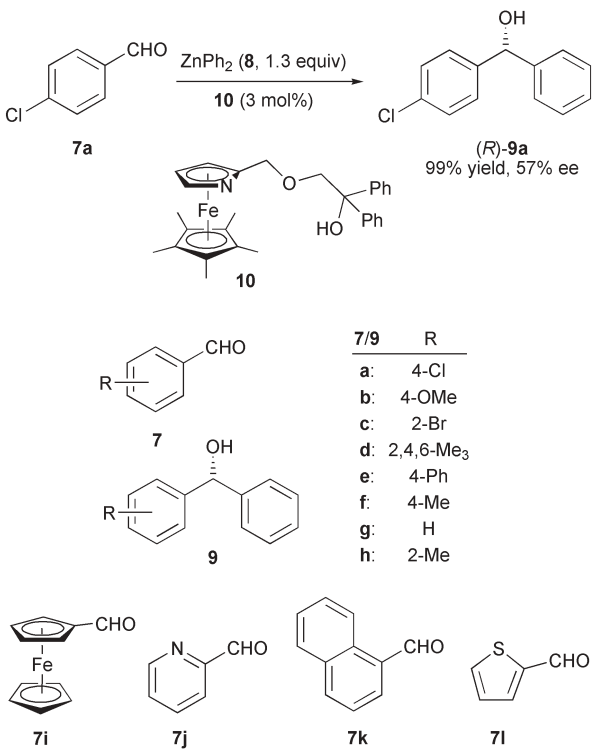
retention[8] (for the synthesis of (*S*)-ceterizine, **5**) or inversion[7] (CDP-840) of configuration at the stereogenic center. The extent of inversion at the benzhydryl center is highly dependent on the activation strategy. Thus, it was found that the formation of the corresponding chlorides and bromides from the enantioenriched diarylmethanols led to extensive racemisation. 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 treatment with a C-nucleophile allowed the formation of the corresponding 1,1-diarylalkyl derivatives with complete inversion.[9]

3 Catalytic, enantioselective preparation of diarylmethanols

3.1 Nucleophilic addition of organometallic compounds to aldehydes

3.1.1 Phenyl transfer reactions to aromatic aldehydes using diphenylzinc as aryl source. In 1997, Fu reported the first enantioselective catalytic addition of diphenylzinc (**8**) to aldehydes.[10] Diphenylzinc, *p*-chlorobenzaldehyde (**7a**) and a catalytic amount of planar-chiral azaferrocene **10** generated the desired diarylmethanol **9a** in almost quantitative yield (Scheme 3). Although the enantioselectivity (57% ee) was rather low at this stage, the reported transformation proved most stimulating and set the basis for many subsequent studies following soon after.

The first highly enantioselective catalytic addition of diphenylzinc to aldehydes was described by Pu two years



Scheme 3 First use of diphenylzinc in the catalytic, asymmetric phenyl transfer reaction to an aromatic aldehyde.

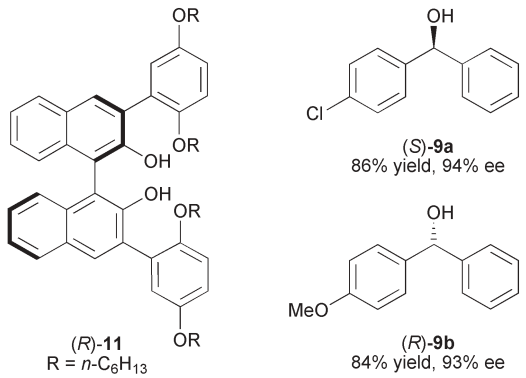


Fig. 3 Use of binaphthyl derivative (*R*)-**11** in the catalysed enantioselective phenyl transfer to aldehydes.

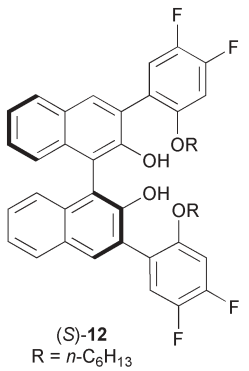


Fig. 4 Fluorinated BINOL derivative for the asymmetric phenyl transfer reaction to aldehydes.

later.[11] In that study, *p*-chlorobenzaldehyde (**7a**) was reacted with diphenylzinc (**8**) in the presence of (*R*)-**11** (20 mol%) in diethyl ether at room temperature to give (*S*)-**9a** in 86% yield with 94% ee (Fig. 3). As the authors pointed out, a pretreatment 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 (*R*)-**11** is a more selective catalyst than the one formed from the reaction of diphenylzinc and (*R*)-**11**.

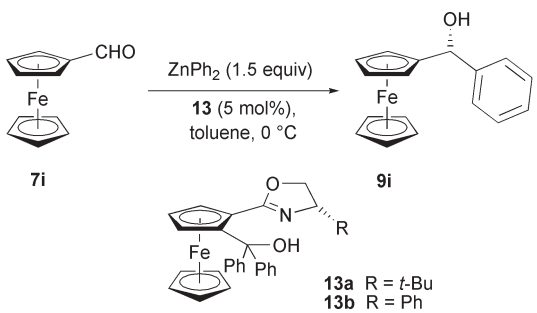
The formation of the (*S*)-isomer of **9a** indicated that the phenyl transfer occurred from the *re* face of the aldehyde. The same side selectivity had been observed in the diethylzinc addition to aromatic aldehydes.[12] Furthermore it was shown that even in the absence of any catalyst the addition of diphenylzinc to *p*-methoxybenzaldehyde (**7b**) proceeded well to furnish racemic diarylmethanol **9b**. This non-catalytic background reaction was suggested to be responsible for the lower enantioselectivity (77% ee) in the formation of **9b** when only 5 mol% of binaphthyl derivative (*R*)-**11** and 10 mol% of diethylzinc were used. Increasing the amount of (*R*)-**11** to 20 mol% and lowering the temperature to –30 °C resulted in a significantly higher enantiomeric excess of **9b** (84% yield, 93% ee).

The use of fluorinated binaphthol-type compounds were reported by Pu in 2000. Of these, only (*S*)-**12**, having a similar structure like **11**, was applied in the phenyl transfer reaction (Fig. 4).[13] Various aromatic aldehydes were reacted with diphenylzinc in the presence of 20 mol% of (*S*)-**12** in dichloromethane. After 5 h at room temperature the products were formed with good enantioselectivities (70–95% ee) in high yields (86–92%).

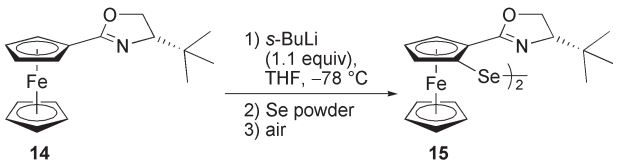
In 1999 Bolm introduced planar-chiral ferrocene-based hydroxy oxazolines **13** as catalysts for the addition of diphenylzinc (**8**) to aldehydes (Scheme 4).[14] Here, diphenylzinc was transferred to *p*-chlorobenzaldehyde (**7a**) at 0 °C with a catalyst loading of 10 mol% of **13a** to give **9a** with 88% ee in nearly quantitative yield. Ferrocene **13b** proved to be as efficient as **13a** 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 ferrocenylcarbaldehyde (**7i**), which furnished the corresponding ferrocenylalcohol (**9i**) with an enantioselectivity of ⩾96% ee in 89% yield.

The presence of *ortho*-substituents on the aromatic aldehyde resulted in reduced enantioselectivities. In the case of *o*-bromobenzaldehyde (**7c**) and 1-naphthaldehyde (**7k**) 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 (**7j**) occurred with only low enantioselectivity (to give **9j** with 3% 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:[15] 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. This result endorses the observation of Pu[13] and Blacker,[16] who had noted an improvement in the enantioselectivity by pretreatment of **11** with diethylzinc (see above). With Bolm's catalyst **13a** the mixed zinc species afforded (*p*-chlorophenyl)phenylmethanol (**9a**) with 97% ee compared to 88% ee under the original conditions.[14] 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 (**7c**) afforded the desired product with an enantioselectivity of 91% ee compared to 31% ee with the original protocol.[14]



Scheme 4 Ferrocene-based hydroxy oxazolines in catalytic asymmetric phenyl transfer reactions to aldehydes.



Scheme 5 Synthesis of a diferrocenyl diselenide.

Additionally, Bolm showed the applicability of a diferrocenyl diselenide **15** in the catalytic asymmetric phenyl transfer reaction to aldehydes.[17] The synthesis of **15** was accomplished by directed *ortho*-lithiation of oxazolinylferrocene **14** followed by addition of selenium powder. After oxidation with air, diselenide **15** was obtained in 69% yield (Scheme 5).

Use of 5 mol% of diselenide **15** 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) **16** in the asymmetric addition of diphenylzinc to aldehydes was reported (Fig. 5).[18] For most examples, higher enantiomeric excesses of the corresponding alcohols were obtained (up to 99% ee) than with the use of the ferrocene analogue **13a**. Even the *ortho*-disubstituted aromatic aldehyde 2,4,6-trimethylbenzaldehyde (**7d**) was tolerated furnishing the corresponding diarylmethanol **9d** with 98% ee in >80% yield.

The synthesis of twelve proline derivatives and their use as catalysts in the asymmetric addition of diphenylzinc (**8**) to various aromatic aldehydes was reported by Zhao in 2001 (Fig. 6).[19] In this case, the best result (89% ee) was achieved with 10 mol% of *N*-methyl-α,α-diphenylpyrrolidine methanol (**17a**) in toluene at −30 °C. 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.

cis-Amino alcohol **17b** has recently been applied in aryl transfer reactions by Bolm (Fig. 6).[20] Its synthesis involved an efficient resolution of racemic *N*-benzylated *trans*-2-aminocyclohexanol followed by stereospecific functional group

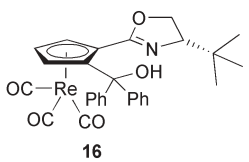


Fig. 5 A planar-chiral η^5-cyclopentadienylrhenium(I)tricarbonyl complex for the asymmetric phenyl transfer reaction.

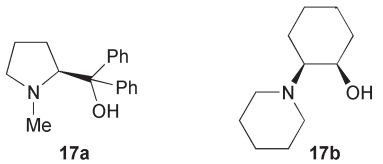


Fig. 6 Amino alcohols used in asymmetric phenyl transfer reactions.

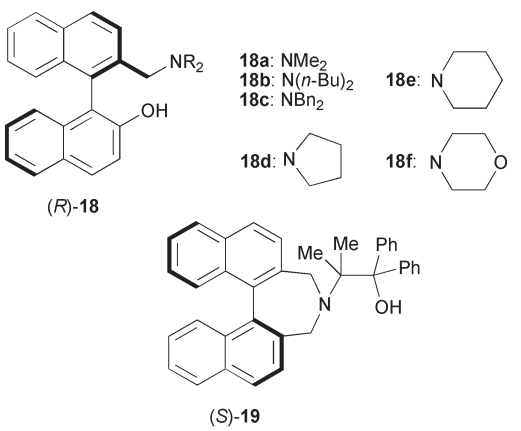


Fig. 7 Binaphthyl-based amino alcohols.

conversions. Use of 10 mol% of **17b** in the phenyl transfer from a diphenylzinc/diethylzinc mixture onto aromatic aldehydes afforded diarlymethanols with up to 87% ee.

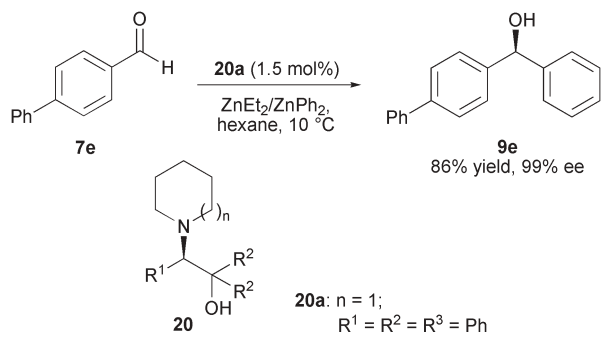
In 2002, Ha reported the preparation of binaphthyl-based amino alcohols (*R*)-**18** and their application in the asymmetric diphenylzinc additions to aldehydes (Fig. 7).[21]

Initially, amino alcohols **18** were screened in the asymmetric diphenylzinc addition to *p*-methoxybenzaldehyde (**7b**). The best result was obtained with 10 mol% of **18f** 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 1,1′-binaphthylazepine skeleton (Fig. 7), and with 10 mol% of (*S*)-**19** alcohol (*S*)-**9a** was obtained with an ee of 54% in the phenyl transfer reaction from diphenylzinc onto 4-chlorbenzaldehyde (**7a**).[22]

In 2004 another effective catalyst for enantioselective phenyl transfer reactions to aldehydes was reported by Pericàs.[23] The use of 1.5–10 mol% of 2-piperidino-1,2,2-triphenylethanol (**20a**) and a mixture of diethyl- and diphenylzinc (ratio 2 : 1) provided the corresponding products with enantiomeric excesses of up to 99% (Scheme 6).

First, the addition of diphenylzinc to *p*-tolualdehyde (**7f**) was studied. Using 10 mol% of **20a**, which had been pretreated with an equimolar amount of diethylzinc, the catalyses were



Scheme 6 Aminoalcohol **20a** as catalyst for the enantioselective phenyl transfer reaction onto aromatic aldehyde **7e**.

performed under high dilution conditions (10 mM) in various solvents. The best result was obtained after 24 h in diethyl ether affording **9f** with 78% ee in 29% yield. In hexane the yield was slightly higher (57%), but the enantioselectivity decreased to 73% ee. Without pretreatment of **20a** 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 **20a** on the phenyl transfer onto *p*-tolualdehyde (**7f**) 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 **9f** 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 **20a** allowed the catalyst loading to be reduced to 1.5 mol%. Under those conditions, the highest enantioselectivity (99% ee) was achieved with 4-phenylbenzaldehyde (**7e**) as substrate (Scheme 6). The chemical behaviour as well as results from DFT calculations suggested the intermediacy of a mixed zinc species (EtPhZn). 3,3′-Bis(diphenylphosphinoyl)-BINOL **21** was used in catalysed, asymmetric organozinc additions to aldehydes by Ishihara (Fig. 8).[24]

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 **21**, the corresponding diarylmethanols **9** were formed with good enantioselectivities (81–88%) in high yields (86–93%) after 24 h at room temperature.

Recently, Pu described the application of H_8-BINOL derivative **22** in asymmetric phenyl transfer reactions.[25] 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 **22** 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.

3.1.2 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 *phenyl* transfers to aldehydes. In 2002 Bolm reported the first general, catalytic asymmetric *aryl*

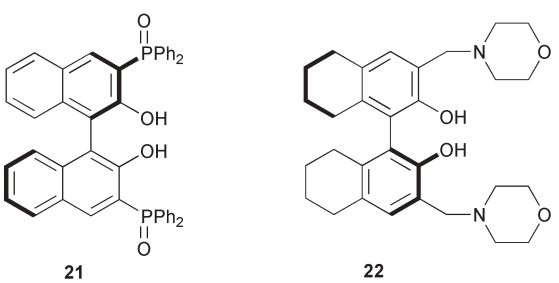
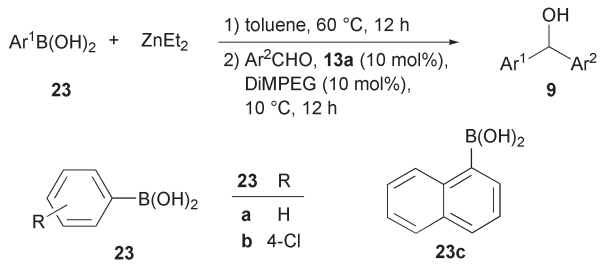


Fig. 8 BINOL-derived chiral ligands.



Scheme 7 Use of boronic acids as aryl source in the asymmetric aryl transfer reaction.

transfer reaction to aldehydes using ferrocene **13a** as catalyst and arylzinc species formed *in situ* from arylboronic acids and diethylzinc (Scheme 7).[26] Subsequently, a multigram scale application was described.[27] 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 (**23**, 2.4 equiv.) was first reacted with diethylzinc (7.2 equiv.) in the presence of 10 mol% of dimethylpolyethyleneglycol (DiMPEG, M_w = 2000 g mol^{-1}) at 60 °C for 12 h. Then ferrocene **13a** (10 mol%) and the aldehyde **7** 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 (**23a**) and *p*-chlorobenzaldehyde (**7a**) gave the (*R*)-enantiomer of the corresponding product **9a** with excellent enantioselectivity (97% ee) in high yield (93%). The (*S*)-enantiomer of **9a** was accessible by aryl transfer from *p*-chlorophenylboronic acid (**23b**) onto benzaldehyde (**7g**). 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 (**9k**) was obtained with 85% ee in 91% yield by a catalysed reaction of benzaldehyde (**7g**) and 1-naphthyl boronic acid (**23c**) (Scheme 7).

In 2005, Katsuki introduced binaphthol dicarboxamides as catalysts for the aryl transfer reaction onto aldehydes.[28] 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 TBME (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. Adduct **24**, formed by double deprotonation of the ligand, was suggested as the active catalyst (Fig. 9). This proposal contrasts the assumed mechanism of reactions with organozincs catalysed by conventional amino alcohols.[29]

In 2005, Braga adopted this protocol involving mixtures of boronic acids and diethylzinc as aryl source and employed catalysts based on β-amino alcohols **20**,[30] which had previously been introduced for the synthesis of diarylmethanols by Pericàs.[23] β-Amino alcohols of this type are rapidly synthesised in two steps, starting from commercially available amino acid ester hydrochlorides **25**. A double Grignard addition or hydride reduction leads to the desired amino

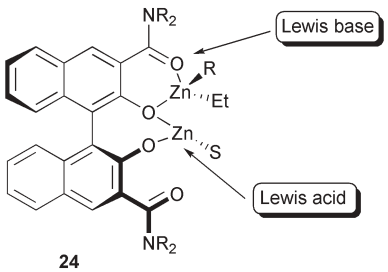


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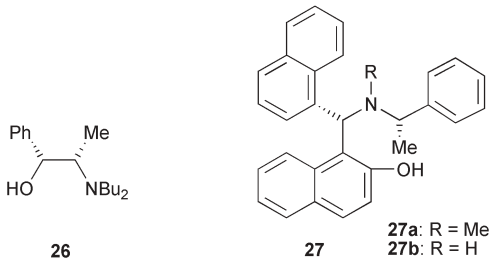
Fig. 9 Suggested structure of the active catalyst obtained from binaphthol dicarboxamides.



26 **27**

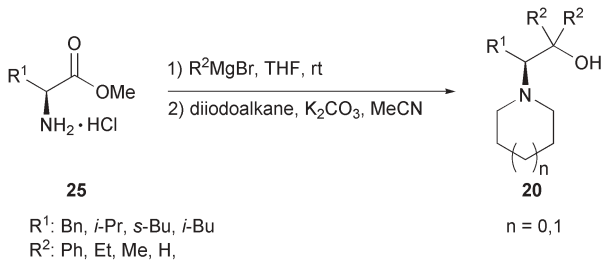
27a: R = Me
27b: R = H

Fig. 10 Aminoalcohols used in asymmetric phenyl transfer reactions.

alcohols which can further be converted into cyclic tertiary amines by treatment with diiodoalkanes and potassium carbonate in acetonitrile (Scheme 8).

Initially the influence of the substituent R^2 was examined while R^1 was kept constant as benzyl group. With *p*-tolualdehyde (**7f**) as substrate the best result was achieved with phenyl boronic acid (**23a**) in toluene and 20 mol% of the piperidine derivative of **20** (n = 1) having an ethyl group as R^2. From this catalysis **9f** 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 (**20** with n = 0), the enantiomeric excess of alcohol **9f** 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 **7h** and **7f** underwent smooth aryl addition and the products (**9h** and **9f**) 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 (**7g**) was studied. There, use of *p*-chlorophenylboronic acid (**23b**) furnished product **9a** with 94% ee in 97% yield. Recently, Braga extended these studies and reported the application of **17a** and related prolinols in combination with arylboronic acids and diethylzinc.[31]

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,[26] Bolm studied the effect of other additivies on the catalysed aryl transfer reaction using ferrocene **13a** and (1*R*,2*S*)-DBNE (*N*,*N*-dibutyl norephedrine, **26**, Fig. 10) as catalysts in greater detail.[32] It was



25 **20**

R^1: Bn, *i*-Pr, *s*-Bu, *i*-Bu
R^2: Ph, Et, Me, H,

n = 0,1

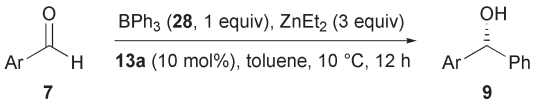
Scheme 8 Synthesis of chiral amino alcohols from amino acid ester hydrochlorides.

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 (**7c**) in the presence of (1*R*,2*S*)-DBNE (**26**) was conducted.[33] Besides polyethyleneglycols (PEGs), also 2-propanol, TMEDA or *N*-methylimidazole had beneficial effects on the enantioselectivity in the formation of **9c**. Furthermore, addition of one equivalent of imidazole led to a reversal of the absolute configuration of the product.

In 2005 axial chiral aminonaphthol **27a** was introduced for the catalytic asymmetric phenyl transfer to aromatic aldehydes by Chan (Fig. 10).[34] Phenylboronic acid (**23a**) served as (sole) aryl source in this report.

Using a mixture of phenylboronic acid (**23a**, 2 equiv.), diethylzinc (6 equiv.), DiMPEG (10 mol%) and (*S*,*S*)-**27a** (16 mol%) in toluene, *p*-chlorobenzaldehyde (**7a**) was transformed into the corresponding alcohol **9a** 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/di*methyl*zinc 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 (**7h**) was transformed into the corresponding diarylmethanol **9h** in 94% yield with 98% ee.

Triphenylborane (**28**) was recently found to be an interesting alternative to diphenylzinc (**8**) as phenyl source.[35] 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 **28** and 3 equiv. of diethylzinc (Scheme 9). With ferrocene **13a**, this system was successfully

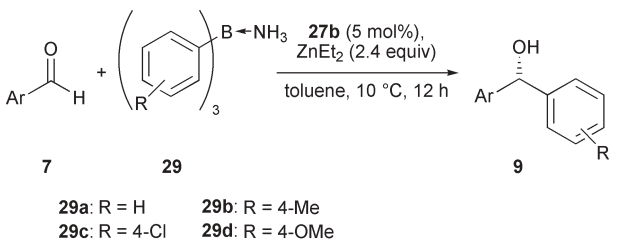


Scheme 9 Triphenylborane as phenyl source.

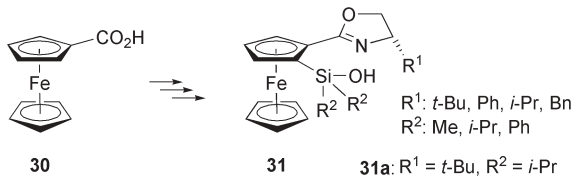
applied to a wide range of *para*- and *ortho*-substituted aromatic aldehydes. In reactions with *p*-chlorobenzaldehyde (**7a**), the ee of **9a** remained the same (97% ee), but the yield increased to 98%, compared to 95% in the original protocol.[15] A remarkable enantioselectivity has also been achieved with 2-thiophenecarbaldehyde (**7l**), 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 (**7c**), which afforded the corresponding product **9c** 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 **29** as (air) stable, versatile and economic precursors for zinc reagents. Their applications in various aryl transfer reactions to aldehydes were investigated.[36] In the presence of 5 mol% of aminonaphthol **27b** and diethylzinc the best result was obtained using *p*-tolualdehyde (**7f**) and triphenylborane ammonia complex **29a** as aryl source, which gave diarylmethanol **9f** with 98% ee in 96% yield. Electron poor as well as electron rich borane complexes **29b–d** were applied in addition to benzaldehyde (**7g**) affording products with slightly lower enantioselectivities (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 **31** (sila analogues of ferrocenes **13**) and their application in asymmetric phenyl transfer reactions to aromatic aldehydes (Scheme 11).[37] They can easily be prepared in four steps, starting from ferrocene carboxylic acid (**30**). The



Scheme 10 Triarylborane ammonia complexes as arylsource.



Scheme 11 Organosilanols used as catalysts in asymmetric aryl transfer reactions.

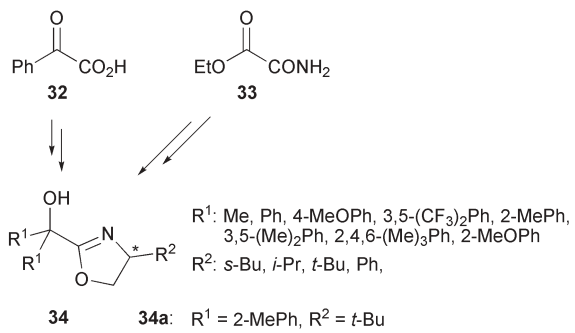
catalytic properties of **31** were examined in the standard phenyl transfer reaction to *p*-chlorobenzaldehyde (**7a**) applying all three phenyl sources: (1) diphenylzinc, (2) triphenylborane and (3) phenylboronic acid. Most organosilanols showed good enantioselectivities and afforded the desired product in respectable yields. The best result was obtained with a combination of diphenylzinc and organosilanol **31a**, which gave (*p*-chlorophenyl)phenylmethanol (**9a**) with 91% ee in 82% yield. All other silanols led to inferior results, presumably due 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 (**8**) and silanol **31a**. Triphenylborane (**28**) was almost as effective as diphenylzinc (**8**) as aryl source. The application of phenylboronic acid in the presence of polyethyleneglycol DiMPEG as additive led to products **9** with lower enantioselectivities and decreased yield.

In the same year, Bolm described the synthesis of new chiral hydroxy oxazolines and their application in the catalytic asymmetric phenyl transfer reaction to aromatic aldehydes.[38] Starting from either benzoylformic acid (**32**) or ethyl oxamate (**33**) several enantiopure α-hydroxy oxazolines **34** were prepared by condensation with β-amino alcohols (Scheme 12).

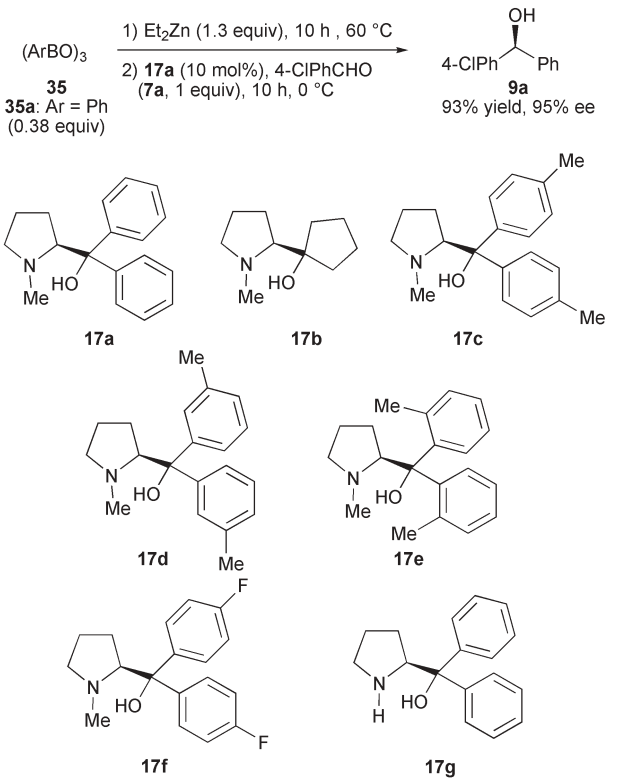
In order to study the efficacy of **34**, several experiments were carried out using *p*-chlorobenzaldehyde (**7a**) as test substrate. A mixture of triphenylborane and diethylzinc served as phenyl source. Furthermore, the effect of DiMPEG as additive was studied. Products with up to 71% ee were obtained using hydroxy oxazoline **34a** 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 oxazoline **34a** allowed the synthesis of diarylmethanols with up to 81% ee.

In 2005 Zhao reported the use of proline-derived β-aminoalcohols **17** in the asymmetric aryl transfer to aldehydes. Boroxines **35** served as aryl source (Scheme 13).[39]

Test substrates were phenylboroxine (**35a**) (in combination with diethylzinc) and *p*-chlorobenzaldehyde (**7a**). All aminoalcohols **17** performed similarly, affording **9a** with 81–89% ee. Only in catalyses with **17b** and **17g** the ee-values were significantly lower (33% and 35% ee, respectively). Aminoalcohol **17a** was the most effective. Subsequently, **17a** was tested in the enantioselective phenyl transfer onto a variety of aromatic aldehydes. Herein, *para*-substituted benzaldehydes generally



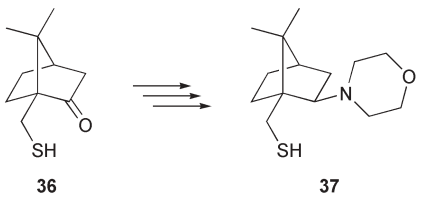
Scheme 12 Chiral α-hydroxy oxazolines.



Scheme 13 Proline-derived β-aminoalcohols for the aryl transfer reaction.

led to better results than *meta*- and *ortho*-substituted ones. Interestingly, the use of DiMPEG as additive[32] 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 (**9a**) was obtained with 96% ee in 37% yield. Importantly, pretreatment of **17a** with diethylzinc (as previously reported by Pu[11]) improved the enantioselectivity significantly. Furthermore, the use of boroxines **35** 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 (Scheme 13). The authors also studied the asymmetric aryl transfer reaction from other aromatic boroxines to benzaldehyde (**7g**) and the corresponding diarylmethanols **9** were obtained with up to 94% ee in good yield. As expected, the products now had the opposite absolute configuration.

Recently, Uang prepared camphor-derived γ-amino thiol **37**, which was synthesised from 10-mercapto-bornan-2-one (**36**) in a 5 step procedure (Scheme 14).[40] Its application was studied in the reaction of a 1 : 3 mixture of phenylboronic acid and diethylzinc with various aromatic aldehydes in the presence of 10 mol% of **37** for 48 h at −35 °C, which furnished the corresponding diarylmethanols **9** with excellent enantiomeric excesses (95–99.5% ee) in high yields. Noteworthy, the presence of DiMPEG as additive (10 mol%)[32,33] had no influence on the enantioselectivity (as observed by Katsuki[28]), but reduced the yield.



Scheme 14 Camphor-derived γ-amino thiol **37** used in the asymmetric aryl transfer of arylboronic acids.

3.1.3 Recyclable catalyst systems. Since chiral catalysts are commonly expensive, their easy recovery and reusability are highly desirable attributes. Polymer-bound systems simplify both the recycling of the catalyst and the purification of the products. For the enantioselective diphenylzinc addition to aldehydes Pu introduced binaphthyl-based polymeric catalysts **38**,[41] which were structurally similar to their low-molecular counterparts **11** published earlier by the same group.[11] In the presence of 40 mol% of (*R*)-**38** (M_w = 25800 g mol^{-1}, Fig. 11), 3.2 equiv. of diethylzinc and 1 equiv. of diphenylzinc, *p*-anisaldehyde (**7b**) reacted well to give diarylmethanol **9b** with 92% ee in 72% yield.

Noteworthy, the catalyst loading was relatively high and the reaction had to be carried out at −30 °C. Furthermore, the substrates had to be added over 20 h using a syringe pump (double slow addition technique). In the reduction of acetophenone by catecholborane and diethylzinc it was shown that polymer **38** was recyclable and could be applied three times without significant loss of enantioselectivity.

In 2002, Bolm described the preparation of a MPEG-supported ferrocenyl oxazoline **39** and its application in the catalytic addition of diphenylzinc to aromatic aldehydes (Fig. 12).[42] An excellent enantioselectivity (97% ee) was achieved in the reaction between a mixture of diphenyl- and diethylzinc (1 : 3.2) and *p*-chlorobenzaldehyde (**7a**). This enantiomeric excess was as high as the one obtained with low molecular weight ferrocenyl oxazoline **13a**.[15] MPEG-supported **39** was easily recovered by precipitation upon addition

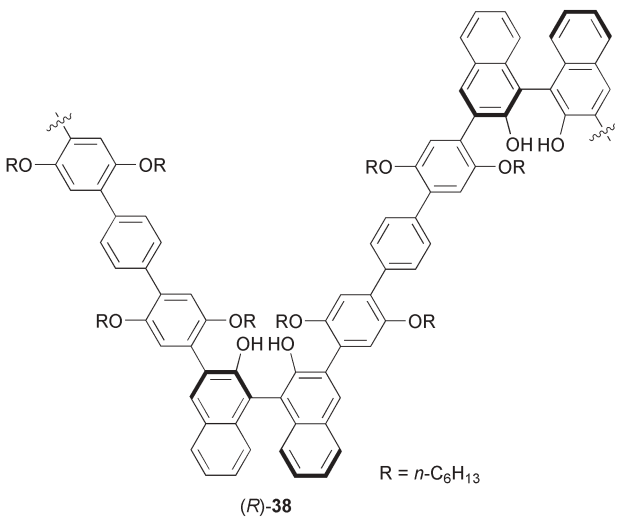
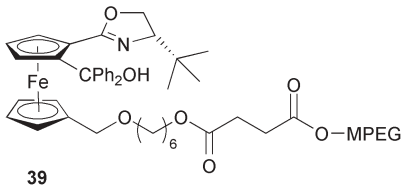


Fig. 11 Binaphthyl-based polymeric catalysts used in the aryl transfer reactions.



39

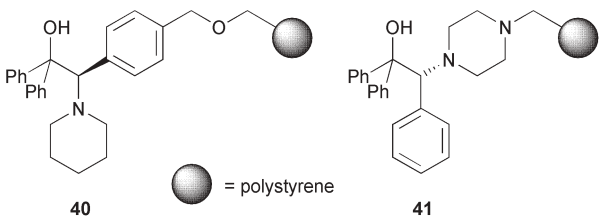
Fig. 12 MPEG-supported ferrocenyl oxazoline.

of diethyl ether and could be reused several times. Even after five catalytic cycles, the product of the phenyl transfer reaction to *p*-chlorobenzaldehyde (**7a**) had 95% ee. Attempts to use a catalyst bound to an insoluble support (starting from trityl chloride resin) failed and led to racemic products in the aryl transfer catalysis only.

The use of polystyrene supported amino alcohols **40** and **41** in enantioselective phenyl transfer reactions was reported by Pericàs in 2005 (Fig. 13).[43] Both catalysts led to diarylmethanols with high enantiomeric excesses (up to >99% ee) if they were used in quantities of 10 mol%. Mixtures of diphenylzinc and diethylzinc served as phenyl source.

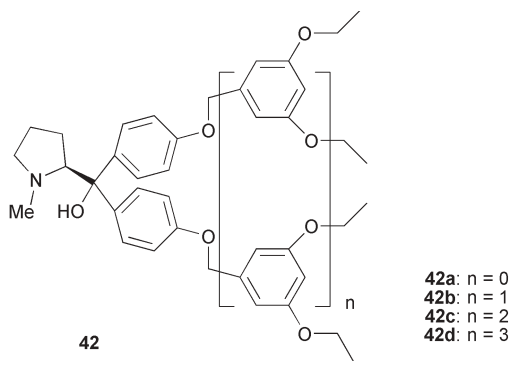
Highly effective and recyclable proline-derived dendrimers **42** were recently described by Zhao (Fig. 14).[44] Clearly, the core structure of **42** is reminiscent to the low molecular weight prolinol derivatives **17**, that the author had reported earlier.[39] For the enantioselective aryl transfer reaction to aromatic aldehydes either arylboronic acids or boroxines in combination with diethylzinc were used as aryl source.

Using 20 mol% of dendrimers **42** with phenylboronic acid as aryl source at −15 °C,[44] according to Bolm's protocol,[26] led to the phenyl transfer onto **7a** affording (4-chlorophenyl)phenylmethanol (**9a**) with 88–93% ee in >90% yield. Among all dendrimers, **42c** performed best in terms of both enantioselectivity and yield (93% ee, 98% yield). Interestingly, when the



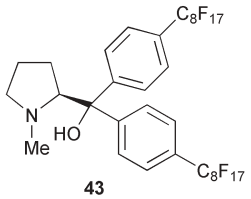
40 41

Fig. 13 Polystyrene supported amino alcohols.



42

Fig. 14 Proline-derived dendrimers.



43

Fig. 15 A perfluorinated proline derivative for the asymmetric phenyl transfer reaction.

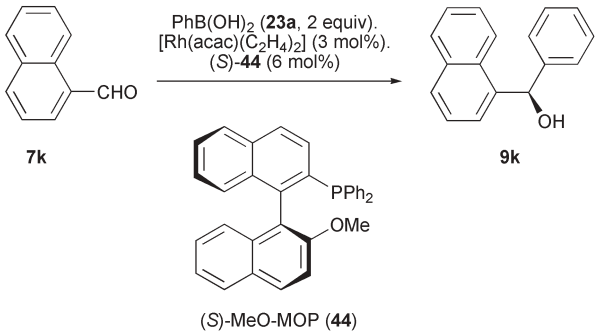
reaction was conducted with phenylboroxine [$(PhBO)_3$ (**35a**)] instead of phenylboronic acid (**23a**), a slightly higher enantioselectivity was achieved. Furthermore, the reaction time could be shortened from 12 to 4 h and it was possible to reduce the amount of diethylzinc from 7.2 to 4.5 equiv. Using 20 mol% of dendrimer **42c** under those conditions, (*S*)-(4-chlorophenyl)phenylmethanol (**9a**) was formed with remarkable 98% ee in 98% yield. Other aromatic aldehydes gave the corresponding products **9** with up to 98% ee in up to 98% yield. By precipitation with MeOH after the aryl transfer reaction the dendrimer was easily recovered and could be reused with little loss of activity and enantioselectivity ($\geqslant$95% ee and >91% yield after five cycles).

In 2005 an alternative approach for catalyst recycling was reported by Bolm and Kim.[45] They used proline derivative **43** containing "perfluoro ponytails" in a fluorous organic biphasic system (FBS) for the asymmetric phenyl transfer addition (from a Et_2Zn/Ph_2Zn mixture) to aldehydes (Fig. 15). In terms of catalyst structure, this work was related to the studies by Zhao, who employed non-fluorinated proline derivative **17a** as catalyst.[39,44] Reaction of a diphenylzinc/diethylzinc mixture with *p*-chlorobenzaldehyde (**7a**) in the presence of 10 mol% of **43** in the biphasic solvent system consisting of FC-72 (perfluorohexane) and hexane afforded diarylmethanol **9a** with 88% ee in 30 min. The recyclability of **43** by simple phase separation was demonstrated in the Et_2Zn addition to benzaldehyde. Noteworthy, even after six reaction cycles, no significant loss of enantioselectivity was observed.

3.1.4 Rhodium-, titanium- and copper-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.[46] Although complexes with bidentate ligands such as dppf catalysed the reaction effectively, enantiopure diphosphines such as BINAP and DIOP gave only racemic products.[47] However, applying monophosphine (*S*)-MeO-MOP (**44**) as ligand in the rhodium-catalysed asymmetric phenyl transfer reaction from **23a** to 1-naphthaldehyde (**7k**) afforded **9k** with 41% ee (Scheme 15). Conversions of other substrates were not reported.

Later, attempts were made by Fürstner,[48] and Frost,[49] who applied chiral *N*-heterocyclic carbenes in combination with $[Rh(acac)(coe)_2]$ and sparteine or bisoxazolines in conjunction with $[RhCl(cod)]_2$ as catalysts, respectively. While the catalytic activity of these systems was satisfactory, the enantiomeric excesses were low (<10% ee).

In 2005, Bolm described [2.2]paracyclophane-based imidazolium salts **45** and **46** as stable precursors for planar chiral



Scheme 15 First rhodium-catalysed asymmetric aryl transfer reaction.

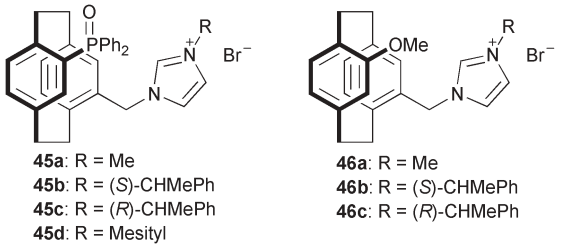
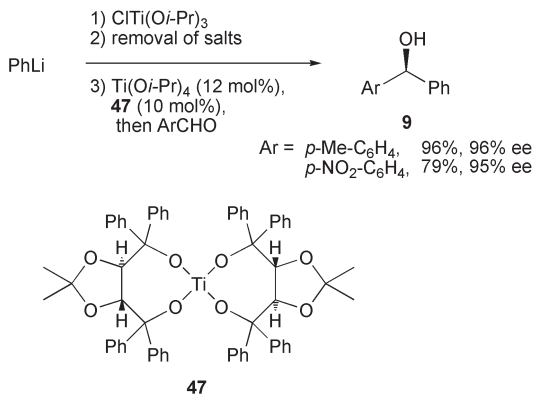


Fig. 16 [2.2]Paracyclophane-based imidazolium salts as stable precursors for planar-chiral carbenes to be used in rhodium-catalysed aryl transfer reactions.

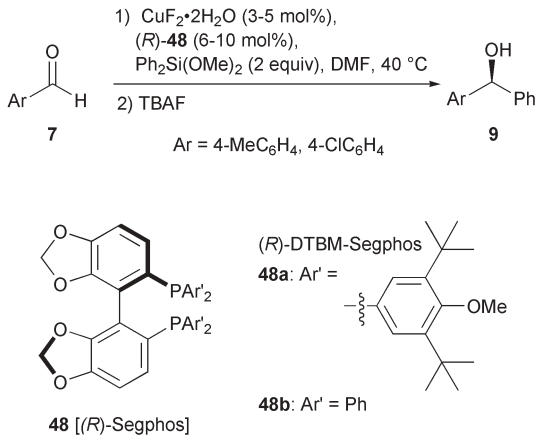
carbenes (Fig. 16)[50] and demonstrated their use in rhodium-catalysed asymmetric aryl transfer reactions. An enantioselectivity of up to 38% ee was obtained using **45b** in combination with 1-naphthaldehyde (**7k**) and phenylboronic acid (**23a**) as substrates.

The titanium/TADDOLate-catalysed enantioselective addition of alkyl- and aryltitanium reagents to aldehydes was reported by Seebach as early as 1994.[51] Two diarylmethanols were synthesised with up to 96% ee using 10 mol% of catalyst **47** in combination with 12 mol% of $Ti(O\textit{i}\text{-}Pr)_4$ (Scheme 16).

The phenyltitanium reagent was prepared by reaction of the corresponding organolithium or Grignard reagent with $ClTi(O\textit{i}\text{-}Pr)_3$ in toluene followed by removal of the precipitated lithium or magnesium salts by centrifugation. The authors noted that even the presence of traces of such salts significantly reduced the enantioselectivity in the addition reaction.



Scheme 16 Ti-TADDOLate-catalysed addition of organotitanium reagents to aldehydes.



Scheme 17 Copper-catalysed phenyl transfer reaction.

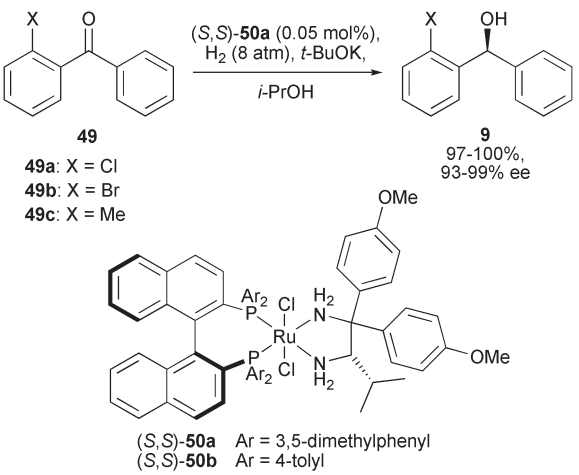
Therefore, they had to be removed by addition of 1,4-dioxane to achieve complete precipitation (for magnesium salts) or deactivated by complexation to 12-crown-4 (for lithium cations).

A copper-catalysed enantioselective phenyl transfer reaction to aromatic aldehydes using dimethoxydiphenylsilane as nucleophile was described by Shibasaki in 2005.[52] Using $CuF_2{\cdot}2H_2O$ and (*R*)-DTBM-Segphos (**48a**) as ligand, the synthesis of two diarylmethanols with up to 92% ee was reported (Scheme 17). The active nucleophile is presumably a phenylcopper species generated by transmetalation from dimethoxydiphenylsilane.

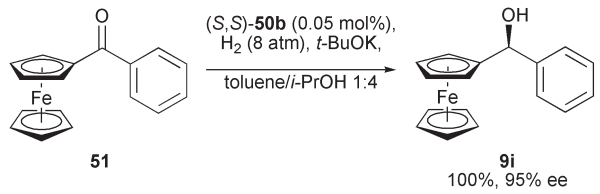
3.2 Catalysed asymmetric diarylketone hydrogenations

In 1988, Noyori extended the use of chiral BINAP-Ru(II) complexes to the asymmetric hydrogenation of ketones.[53] However, it took 12 years until the first application of this system to unsymmetrical benzophenone derivatives was reported (Scheme 18).[54]

Using 0.05 mol% of the chiral ruthenium complex (*S*,*S*)-**50a** in the presence of *t*-BuOK and applying 8 atm of hydrogen gas at room temperature, several *ortho*-substituted diarylmethanols **9** were obtained from the corresponding ketones **49** with



Scheme 18 Asymmetric hydrogenation of *ortho*-substituted diarylketones.

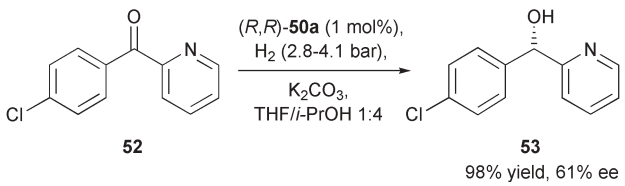


Scheme 19 Asymmetric hydrogenation of benzoylferrocene.

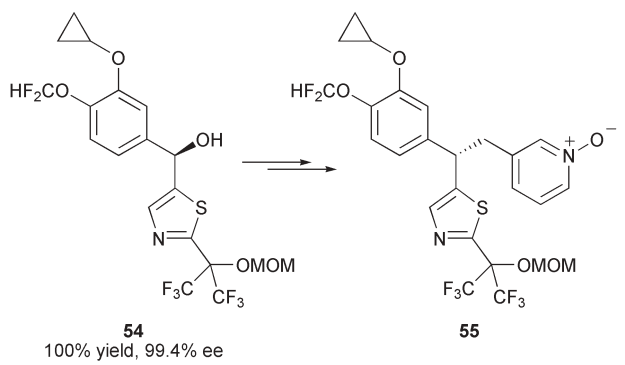
high enantioselectivities (up to 99% ee). Even a catalyst loading of 0.005 mol% in a 100 g scale conversion of *o*-chlorobenzophenone (**49a**) was sufficient to give the corresponding diarylmethanol in almost enantiomerically pure form (97% ee; 99% yield). At this stage, the scope of the reaction was limited to *ortho*-substituted benzophenones, and *meta*- and *para*-substituted derivatives resulted in highly diminished enantioselectivities (8–47% ee). Surprisingly, benzoylferrocene (**51**) was quantitatively reduced to give **9i** with remarkable 95% ee. In this case, a slightly modified catalyst [(*S*,*S*)-**50b**] was required for achieving this high catalyst efficiency (Scheme 19).

In 2003, ruthenium complex (*R*,*R*)-**50a** was used by Chen for the asymmetric reduction of aromatic/heteroaromatic and bisheteroaromatic ketones (Scheme 20).[55] In most cases, high enantioselectivities (57–99.5% ee) and excellent yields (87–100%) were achieved. Unfortunately, the reduction of ketone **52** gave the corresponding aryl/heteroarylmethanol **53** with only moderate ee (61%). This result was significant, since **53** is a relevant precursor of the histamine H_1 antagonist (*S*)-carbinoxamine (**4**).

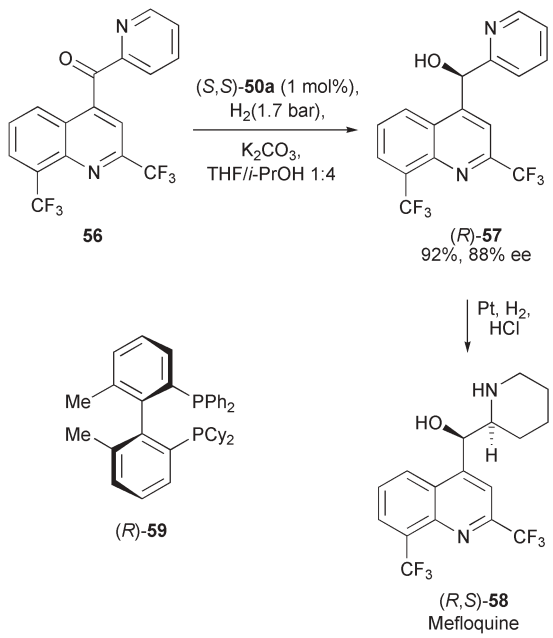
The reaction conditions were then optimized for the synthesis of aryl/heteroarylmethanol **54**, which is a precursor of the potent PDE-IV inhibitor **55**. Finally, diarylmethanol **54** was quantitatively obtained with outstanding 99.4% ee (Scheme 21).



Scheme 20 Asymmetric reduction of an aromatic/heteroaromatic ketone.



Scheme 21 Synthetic strategy towards a PDE-IV inhibitor.



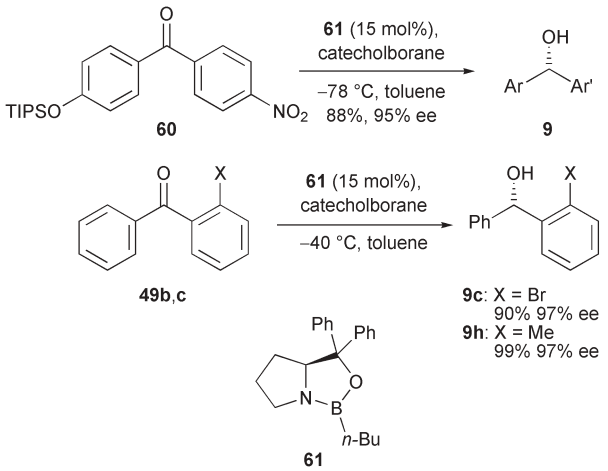
Scheme 22 Synthesis of an antimalarial drug.

In the course of the synthesis of Mefloquine [(*R*,*S*)-**58**], an antimalarial drug developed by Roche, diheteroarylketone **56** was reacted under similar conditions affording the diarylmethanol **57** with 88% ee in 92% yield (Scheme 22).[54] Interestingly, this very ketone had already been employed by Schmid in a rhodium(I)-catalysed asymmetric hydrogenation with unsymmetrical biphenyl diphosphine (*R*)-**59** as ligand several years before. There, diarylmethanol **57** was obtained with a slightly higher ee (92%).[56]

3.3 Reduction of diarylketones using boranes [Corey–Bakshi–Shibata protocol (CBS)[57]]

The asymmetric reduction of ketones using chiral oxazaborolidine catalysts and boranes, discovered by Itsuno[58] in 1981 and subsequently developed by Corey,[57] provides also a useful access for the highly enantioselective synthesis of diarylmethanols. Both electronic and steric effects determine the degree of enantiofacial discrimination. For example, use of oxazaborolidine **61** in the reduction of (electronically dissymmetric) diarylketone **60**, having an electron donor substituent on one aromatic ring and an acceptor group on the other, resulted in the formation of the corresponding diarylmethanol **9** with excellent 95% ee (Scheme 23).[59] Steric effects are reflected in the reductions of **49b** and **49c** to give high yields of **9c** and **9h**, respectively. There, the presence of an *ortho*-substituent on one of the aryl groups is sufficient for leading to high enantiocontrol, and thus **9c** and **9h** are both obtained with 97% ee (Scheme 23).[8]

Diarylketones bearing transition metal π-complexes are also applicable in this reaction. For example, substrates with chromium tricarbonyl fragments,[5] ferrocene-type π-complexes[60] and cyrhetrene derivatives[61] afforded the corresponding diarylmethanols **62**, **9i** and **63** with 95–98% ee, when subjected to the CBS-reduction conditions (Fig. 17).



Scheme 23 CBS-reduction of unsymmetrical diarylketones.

Biologically active compounds derived from diarylmethanols, such as (*S*)-carbinoxamine[8] (**4**) and cetirizine hydrochloride[5] (**5**) have been synthesised by employing the CBS methodology in the key step. The C–N bond of the latter compound was subsequently formed in a $Cr(CO)_3$-assisted replacement of the alcohol moiety by an amino group, which proceeded with complete retention of configuration at the stereogenic center.

3.4 Asymmetric hydrosilylation of diarylketones

Rhodium-catalysed asymmetric hydrosilylations of unsymmetrically substituted ketones affording optically active alcohols were first reported by Kagan in 1980.[62] Several acetophenone derivatives and *para*-substituted benzophenones were employed in this reaction. A number of mono- and bidentate phosphines and phosphites were tested as ligands and various silanes were employed as reductands. The best result (26% ee) was obtained with *p*-methoxybenzophenone (**64**) as substrate in combination with 1-naphthylphenylsilane (**65**) and 0.2 mol% of a rhodium(I)complex bearing DIOP as ligand (Scheme 24).

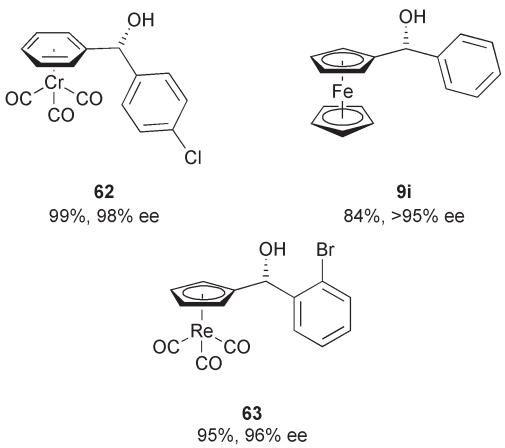
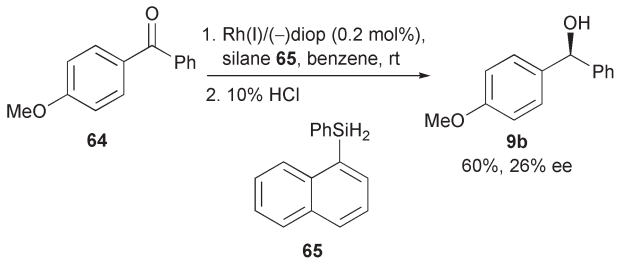
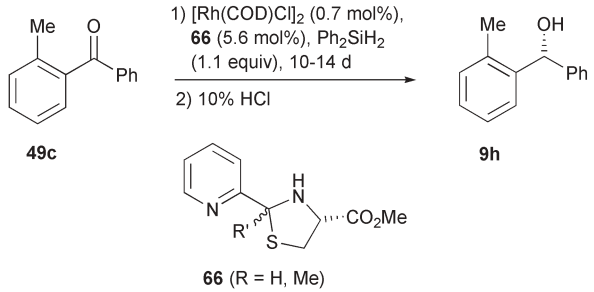


Fig. 17 Transition metal π-complex-containing diarylmethanols obtained by asymmetric ketone reduction under CBS conditions.



Scheme 24 Rhodium-catalysed asymmetric hydrosilylations of unsymmetrically substituted ketones.



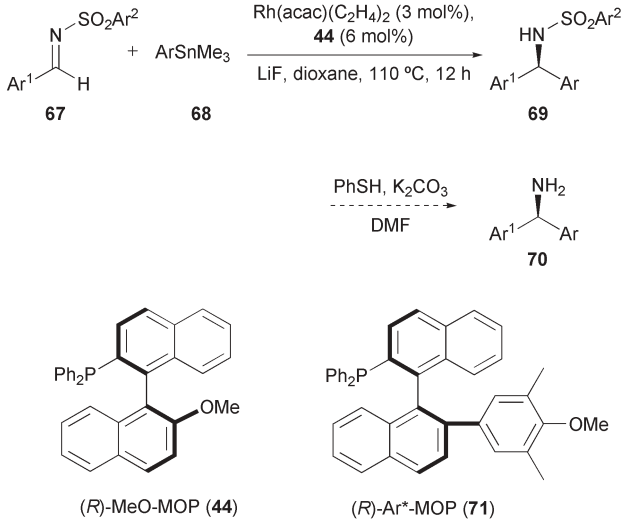
Scheme 25 Hydrosilylation reactions catalysed by rhodium pyridinethiazolidine complexes.

In 1988 Brunner reported phosphine-free hydrosilylation reactions catalysed by *in situ* generated $[Rh(COD)Cl]_2$/pyridinethiazolidine complexes (Scheme 25).[63] Among other ketones, diaryl-substituted ones were used as substrates. For example, 2-methylbenzophenone (**49c**) afforded reduction product **9h** with 25% ee. Compared to other ketones, those with two aryl groups reacted more slowly (75% conversion after 10–14 days) and the enantiomeric excesses were significantly lower. Interestingly, the pyridinethiazolidines **66** could also be applied as diastereomeric mixtures, which undergo rapid rhodium-catalysed epimerisation at the benzylic position.

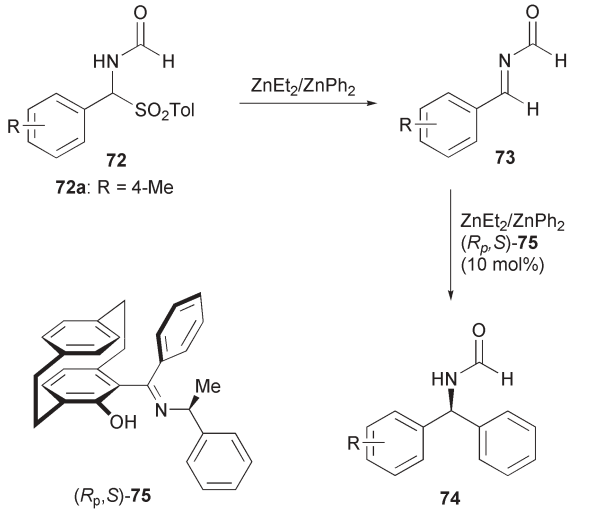
4 Asymmetric aryl transfer onto imines for the synthesis of diarylmethylamines

Enantiopure diarylmethylamines **70** are important intermediates for the synthesis of biologically active compounds (Fig. 1). The first catalysed asymmetric aryl transfer reaction onto imines resulting in the formation of optically active diarylmethylamines with high enantiomeric excesses was reported by Hayashi in 2000.[64] *N*-Alkylidenesulfonimines **67** served as starting materials in a rhodium(I)-catalysed process with arylstannanes **68** as aryl source. Monodentate phosphines (*R*)-MeO-MOP, **44**, or (*R*)-Ar*-MOP, **71**, were the most effective ligands (Scheme 26).

The substituent in the *para*-position of the sulfonyl arene (Ar^2) determined the reactivity of the aryl-accepting imines **67**. The presence of more electron-withdrawing substituents (for example a NO_2 group) led to higher enantiomeric excesses and better yields of the resulting diarylmethylsulfonamides **69**. Furthermore, Ar^1 of **67** played an important role. Aryl transfer onto electron poor imines (Ar^1 = *p*-F_3CPh, *p*-MeO_2CPh,



Scheme 26 Rhodium-catalysed asymmetric aryl transfer reaction onto imines with organostannanes.



Scheme 27 Catalytic asymmetric phenyl transfer reaction onto *N*-formylimines.

p-ClPh and *p*-FPh) furnished the products with excellent enantioselectivities ($\geqslant$96%) in very high yields ($\geqslant$90%). In contrast, the unsubstituted imine, derived from benzaldehyde (**67** with Ar^1 = Ph), gave the products with (only) up to 92% ee in 86% yield. Also, the type of phosphine ligand was crucial in this reaction. When chelating bisphosphines such as BINAP and DIOP were used, the reaction was very slow and the product could at best be isolated in only 10% yield having 6% ee. Compared to catalyses with rhodium complexes bearing MeO-MOP **44** as ligand, improved enantioselectivities and higher yields were achieved in reactions with the slightly modified phosphine **71**. Synthetically important is the fact that products stemming from substrates **69** with *N*-nosyl groups (SO_2Ar^2 = Ns) easily afforded primary amines **70** in good yields upon removal of the protecting group by reaction with benzenethiol and K_2CO_3 in DMF (Scheme 26).

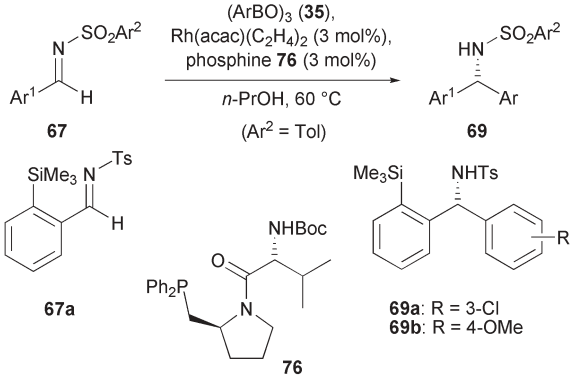
An alternative approach for asymmetric phenyl transfer reactions onto imines was described by Bolm and Bräse in 2002. There, *in situ* formed *N*-formylimines **73** accepted aryl groups from mixtures of diphenyl- and diethylzinc.[65] After screening several catalysts based on ferrocene **13a**, cyrhetrene **16** and other *N*,*O*-chelates having [2.2]paracyclophane backbones, (R_p,*S*)-**75** was identified as the most effective catalyst for this reaction (Scheme 27). The substrates, *N*-formylimines **73**, were formed *in situ* by deprotonation of amides **72** and subsequent elimination of sulfinate.

The best result was obtained with *p*-tolylamide **72a** in combination with 10 mol% of (R_p,*S*)-**75** in toluene at -20 °C, which led to **74** (with R = 4-Me) with 97% ee in 98% yield. Various electronic and steric modifications of the aryl acceptors were tolerated. Compounds with electron rich, electron poor and bulky substituents on the aromatic ring gave excellent results with enantioselectivities up to 95% ee. However, *meta*-substituted substrates resulted in slightly lower enantioselectivities.

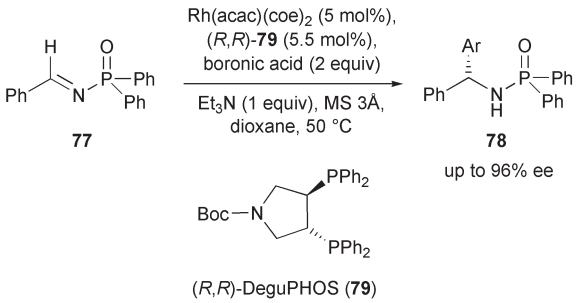
In 2004, Tomioka reported the catalytic asymmetric aryl transfer reaction onto *N*-tosylarylimines **67** (with SO_2Ar^2 = Ts) with arylboroxines **35** as aryl sources.[66] The reaction was catalysed by a rhodium(I) complex bearing the L-valine-derived amidomonophosphane **76** as chiral ligand (Scheme 28).

The enantiomeric excesses of the resulting tosylamines **69** were found to be dependent on the substitution pattern of Ar^1. The best result (94% ee, 99% yield) was achieved in the formation of amine **69a**. In this catalysis, trimethylsilyl-substituted arylimine **67a** served as starting material, which reacted with *m*-chlorophenylboroxine (**35** with Ar = 3-ClPh) in *n*-propanol at 60 °C. Also, an electron rich boroxine [(*p*-MeOPhBO)$_3$] was successfully applied in this addition reaction forming **69b** with 90% ee in 87% yield.

Recently, a rhodium-catalysed, asymmetric addition reaction of arylboronic acids to *N*-diphenylphosphinoyl aldimines **77** was described by Ellman (Scheme 29).[67] This study also included a diastereoselective variant of this reaction using a chiral auxiliary. After screening of several diphosphines, (*R*,*R*)-DeguPHOS (**79**)[68] was found to be the most effective ligand, giving phosphinic amides **78** with up to 96% ee in high yield. Interestingly, acceptable conversions of **77** were only observed with diphosphine ligands having a two-atom spacer between the two diphenylphosphino substituents or a binaphthyl backbone. Other ligands such as Josiphos, Walphos[69] and DIOP[47] gave very low conversions.



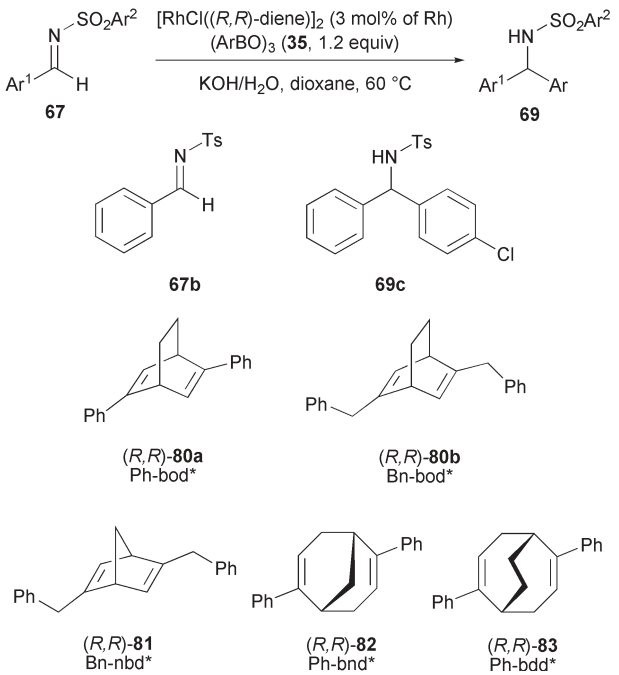
Scheme 28 Asymmetric aryl transfer reaction onto *N*-tosylarylimines with arylboroxines.



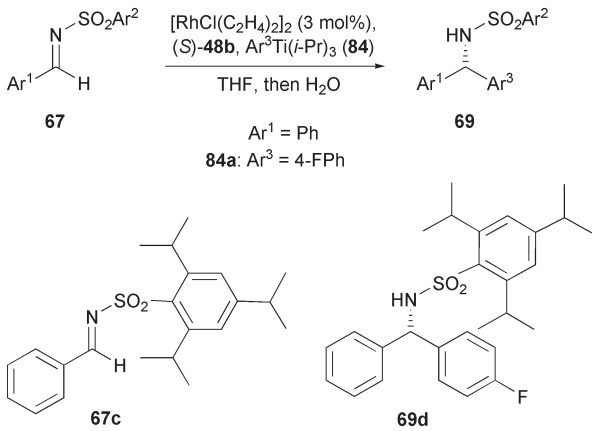
Scheme 29 Rhodium-catalysed aryl transfer reaction onto *N*-diphenylphosphinoyl aldimines.

A similar, phosphine-free rhodium catalysis was reported by Hayashi in 2004.[70] With C_2-symmetric bicyclo[2.2.2]octadienes **80** (bod*) or bicyclo[2.2.1]heptadiene **81** (Bn-nbd*) as ligands the asymmetric aryl transfer reaction between *N*-tosylarylimines **67** (with Ar^2 = Tol) and arylboroxines **35** proceeded smoothly within 6 h at 60 °C (Scheme 30). The catalyst was generated from $[RhCl(C_2H_4)_2]_2$ (3 mol% of Rh), aqueous KOH (20 mol%) and the chiral diene (3 mol%) in dioxane. Using *p*-chlorophenylboroxine (**35** with Ar = 4-ClPh) as the aryl source and *N*-tosylphenylimine (**67b**) as aryl acceptor, the rhodium catalyst generated from **80a** led to amine **69c** with excellent ee (99%) in very high yield (99%).

In subsequent studies, Hayashi described the use of 2,6-diphenylbicyclo[3.3.1]nona-2,6-diene (**82**, Ph-bnd*) and 2,6-diphenylbicylco[3.3.2]deca-2,6-diene (**83**, Ph-bdd*) in this rhodium-catalysed aryl transfer reaction.[71,72] In this case, *N*-nosyl-protected arylimines (**67** with Ar^2 = $C_6H_4(NO_2)$) could also be applied, giving the corresponding products with up to 99% ee in almost quantitative yield. The catalyst with Ph-bnd* **82** as ligand showed the highest enantioselectivity for



Scheme 30 C_2-symmetric bicyclic dienes as chiral ligands in the rhodium-catalysed aryl transfer reaction to arylimines.

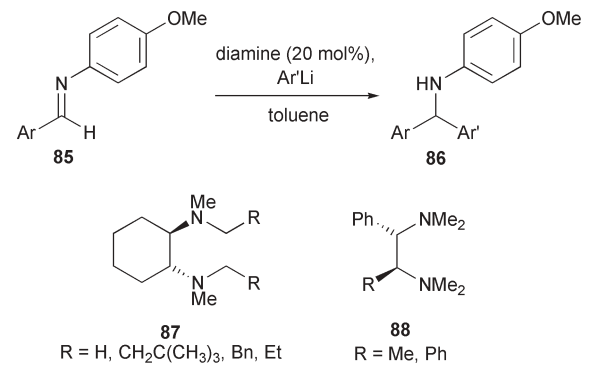


Scheme 31 Use of aryltitanium reagents in asymmetric aryl transfer reactions onto sulfonylimines.

both nosyl and tosyl protected imines. In general, all rhodium complexes with diene ligands showed higher activities than those bearing phosphines as ligands.

In 2004, Hayashi demonstrated rhodium-catalysed diarylmethylamine formations with titanium reagents as aryl sources. There, complexes with Segphos (**48b**) as ligand were applied, and *N*-alkylidene sulfonylimines such as **67** (with Ar^1 = Ph) and aryltitaniumtriisopropoxides **84** served as starting materials (Scheme 31).[73] The latter are highly reactive towards transmetalation and form aryl rhodium species, which are capable of transferring the aryl group to the imine in an enantioselective fashion. Sterically demanding sulfonylaryl groups having three isopropyl substituents on the aromatic ring were essential for achieving high enantioselectivities. A wide range of neutral, electron rich and electron poor imines as well as a variety of titanium reagents proved applicable. For example, reaction of phenylsulfonylimine **67c** with titanium reagent **84a** furnished sulfonamide **69d** with 93% ee in 96% yield (Scheme 31).

Recently, asymmetric additions of aryllithium reagents to aromatic imines **85** in the presence of C_2-symmetric diamines such as **87** and **88** have been described (Scheme 32).[74] Although in some cases an excess of the ligands was required, their amount could often be reduced to substoichiometric quantities (20 mol%) without significant loss of enantioselectivity.[75] Several diamines were tested and products **86** with up



Scheme 32 Lithium reagents in the asymmetric aryl transfer reaction onto aromatic imines.

to 84% ee (at 19% conversion) were obtained using 20 mol% of *N*,*N*,*N*′,*N*′-tetramethylcyclohexyl-1,2-diamine (**87** with R = H) in toluene at −78 °C.[76]

5 Summary and outlook

This review describes the currently available catalytic asymmetric syntheses of enantiomerically enriched diarylmethanols and diarylmethylamines. Generally, two approaches can be distinguished: First, aryl transfer reactions onto aromatic aldehydes and arylimines, and second, asymmetric reductions of C=O and C=N double bonds of diarylketones and diarylketimines. Whereas several examples have been reported for the first three transformations, the latter still lacks advances.

In order to devise successful catalysts, various ligands of diverse structures have been developed, and in a few cases excellent enantioselectivities and high yields have been achieved. Some processes are so advanced that in the future the use of aryl transfer reactions to aldehydes and imines might become test reactions in the search of highly active and fully enantioselective catalysts. Due to the importance of enantiopure diarylmethanols and diarylmethylamines as precursors for pharmaceutically relevant products, we predict the development of many more catalytic asymmetric approaches towards these important classes of chiral molecules in the near future.

Acknowledgements

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