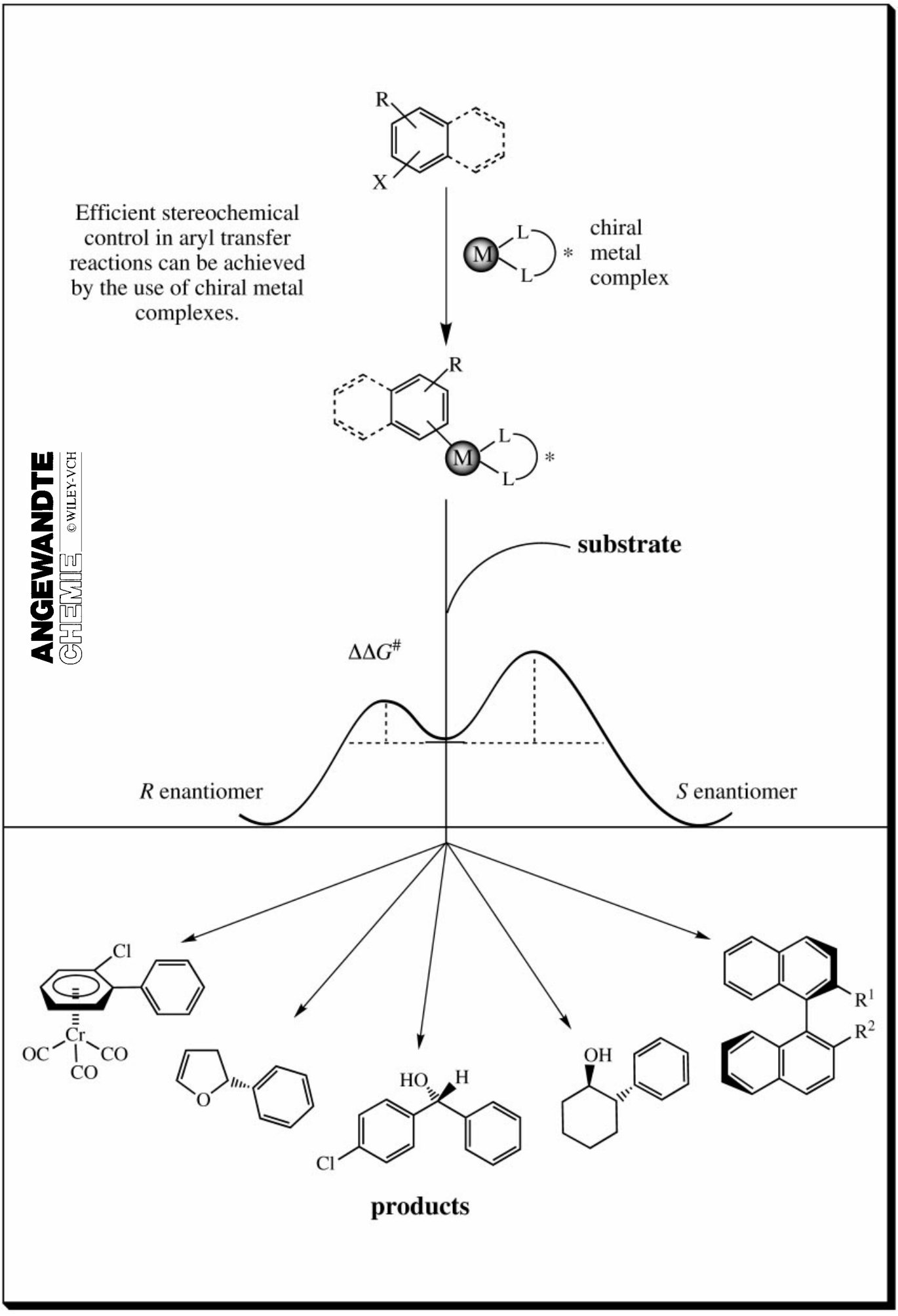

Catalyzed Asymmetric Arylation Reactions

Carsten Bolm,* Jens P. Hildebrand, Kilian Muñiz, and Nina Hermanns

Dedicated to Professor K. Barry Sharpless on the occasion of his 60th birthday

Addition and substitution reactions with carbon nucleophiles are fundamental processes in organic synthesis, and the development of general catalytic asymmetric variants thereof is still a major challenge today. In contrast to enantioselective alkyl transfer reactions, the corresponding arylations have not yet reached a high level of maturity. The existing protocols are either of no general applicability or are limited in terms of selectivity. This article summarizes established routes for catalytic asymmetric aryl transfer together with the latest developments in this area. The scope and limitations of this reaction are discussed.

Keywords: arylation · asymmetric synthesis · homogeneous catalysis · transition metals

1. Introduction

The demand of chiral compounds for both pharmaceutical and agrochemical purposes has increased dramatically during the past decade.[1] Although several approaches to enantiomerically pure chemicals exist—such as resolution or use of chiral auxiliaries—catalytic methods are by far the prefered choice, and they are also often regarded as being the most economical.[2] Asymmetric catalysis involving chiral metal complexes plays a dominant role in this area, and hence many new and promising enantioselective processes utilizing main group or transition metals have been developed in recent years.[3] Furthermore, significant progress with respect to selectivity and substrate scope has been achieved for both catalytic carbon–carbon and carbon–heteroatom bond formations. Within this context, enantioselective alkylations such as the asymmetric addition of dialkylzinc reagents to aldehydes[4] and the palladium-catalyzed allylic alkylation[5] belong to the most prominent examples, which have even reached the status of test reactions for novel ligand designs. In light of these impressive achievements and considering the fact that nonasymmetric metal-catalyzed cross-coupling reactions[6, 7] are on the verge of becoming truly general processes, it is rather surprising that the catalytic, asymmetric transfer of sp^2- and sp-hybridized carbon atoms has attracted much less attention.[8] There are numerous reasons for the lack of asymmetric versions of these synthetically highly useful processes. For example, the synthesis of suitable transfer reagents is often difficult or coherent with insufficient functional group tolerance. Furthermore, the reactivity of many reagents is not suitable to allow for additional Lewis acid catalysis. Often, low temperatures are required for high enantioselectivity, but achieving efficient transmetalation under these conditions can be problematic.

Finally, the existing protocols for the identification of novel, highly enantioselective metal catalysts are still in their infancy. Thus, most of the known catalysts for the asymmetric transfer of sp^2- and sp-hybridized carbon atoms rely on classical axial- or planar-chiral ligands such as BINAP or ferrocenes, respectively (abbreviations used in this review are explained in the appendix). Promising high-throughput screening (HTS) methods are being developed, but at the present stage they do not as yet offer general solutions.[9, 10]

One of the key issues in *aryl* transfer reactions is the selective formation of an appropriate aryl–metal intermediate. In general, three major routes[11] towards such species can be distinguished mechanistically depending on the type of aryl precursor (Scheme 1).

1) Generation of an aryl–metal compound by (formal) metal insertion into a C_{aryl}–X bond (X = halogen, alkoxy, carboxy, etc.). Such a process has the advantage that the

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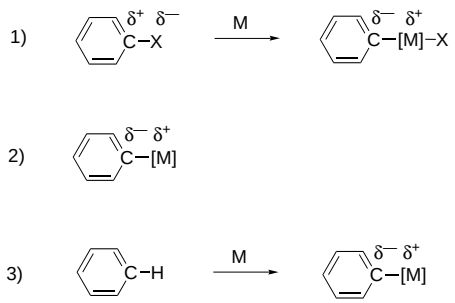

Scheme 1. Mechanistically different routes towards aryl–metal intermediates capable of aryl transfer. For further information see the text.

fragment which is to be transferred is derived from common starting materials (for example, aryl halides) which often are commercially available or readily synthesized. The major mechanistic implication is that the metal catalyst participates in two steps: first, in an umpolung of the carbon atom which is to be transferred, and second, in the subsequent coupling with the other reactant.

2) Use of a preformed aryl–metal compound which is either the reactive species itself or serves as the precursor of another metal-containing compound obtained by transmetalation. In this case, the aryl precursor already contains a nucleophilic carbon atom and no umpolung is required. Examples of such a reaction type involve starting materials such as diarylzincs, aryltrialkylstannanes, and Grignard reagents which are transmetalated to palladium during the catalytic aryl transfer.
3) The formation of aryl–metal compounds by C_{aryl}–H activation. Although such functionalizations have been known for some time,[11, 12] important advances have only recently been achieved.[13] At present, only a single application in asymmetric catalysis is known, in which an unactivated arene has been used in a reaction sequence involving a direct C_{aryl}–H activation (see Section 2.2).[14]

Asymmetric aryl transfer reactions have been known since the early 1970s when Consiglio and Botteghi,[15] and Kumada and co-workers[16] reported enantioselective Grignard cross-coupling reactions. Substantial advances involving other


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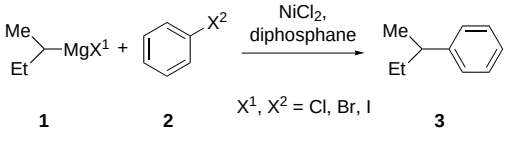
important transformations, such as 1,2- and 1,4-additions or asymmetric ring openings of *meso*-epoxides, have only recently been made (see Sections 2.5, 4, 6). This article intends to highlight the most significant achievements in the development of catalytic asymmetric arylations.

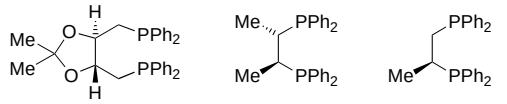
2. Asymmetric Aryl Transfers in Cross-Coupling Reactions

2.1. Grignard Cross-Coupling Reactions and Related Processes

Today, palladium- and nickel-catalyzed cross-coupling reactions are some of the most prominent C–C bond-forming reactions.[6] Numerous reagents, such as aryl stannanes, boranes, and boronates, to name just a few, have been developed for efficient aryl transfers of this type. Grignard reagents were among the first to be used in asymmetric aryl cross-coupling reactions[17] as developed by Consiglio and Botteghi,[15] and Kumada and co-workers.[16] For example, 2-phenylbutane (**3**) is formed in high yield when 2-butylmagnesium halide **1** is treated with halobenzene **2** and a nickel catalyst [Eq. (1)]. Asymmetric transformations have been

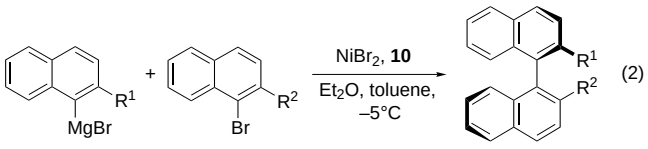


(1)



achieved with chiral diphosphanes such as diop (**4**; up to 17% *ee*), chiraphos (**5**; 43% *ee*), and prophos (**6**; up to 47% *ee*). Since **1** racemizes readily, the consumption of both enantiomers is possible, which allows for high conversion of this secondary alkyl Grignard reagent. The absolute configuration of **3** and the level of asymmetric induction both depend on the type of halide in **1** and **2**, with bromides being the substrates of choice.

A catalytic asymmetric synthesis of axial-chiral compounds—namely 1,1′-binaphthyl derivatives—became possible when aryl Grignard reagents were used. Early examples were hampered by low conversion and only very moderate enantioselectivity.[17] A major breakthrough was achieved when Hayashi, Ito and co-workers performed the nickel catalysis in the presence of (phosphanylferrocenyl)ethyl methyl ether (**10**).[18] Axial-chiral products **9** were obtained with high enantiomeric excesses (for example, for R^1, R^2 = Me: 95% *ee*) in moderate to good yields [Eq. (2)]. At low temperatures 1-chloronaphthalene could also be employed, and the product was formed in even higher enantiomeric excess relative to the corresponding bromide.



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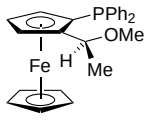
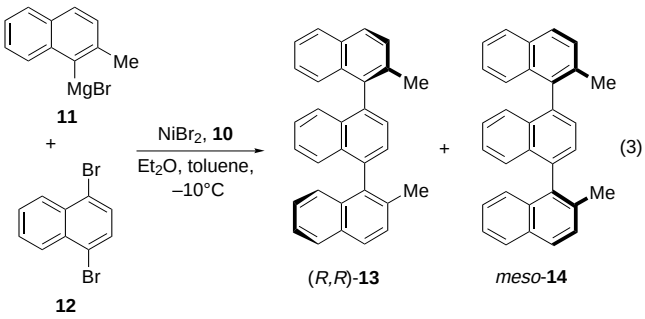


(*S*,*R*)-PPFOMe (**10**)

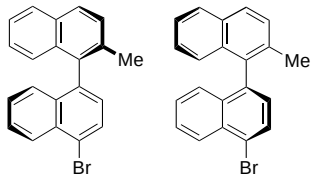
The ether moiety at the stereogenic center of **10** was crucial for the success of this asymmetric aryl transfer. Nickel complexes bearing structurally related bisphosphanes or P,N ligands displayed much lower activity. It is likely that the ether oxygen atom coordinates to the magnesium atom and guides the Grignard reagent into the appropriate position for transmetalation to the nickel center.

This type of cross-coupling could also be extended to the enantioselective synthesis of axial-chiral ternaphthalenes [Eq. (3)].[19] Thus, (*R*,*R*)-**13** was obtained with a very high *ee* value (up to 95%) from 1,4-dibromonaphthalene (**12**).[19b] However, its formation was accompanied by the production of achiral *meso*-ternaphthalene **14** (**13**:**14** = 86:14).



(3)

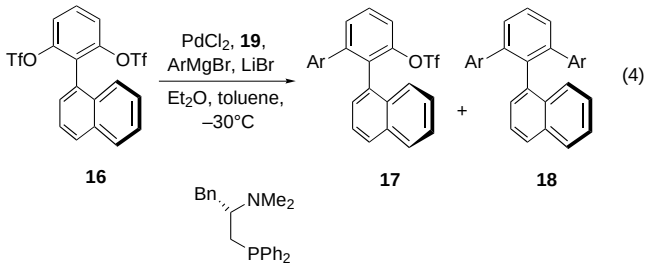
The stereochemistry and the product ratio of this catalysis were rationalized as follows: the asymmetric cross-coupling between **11** and **12** proceeds with similar enantioselectivity as observed for the corresponding monobromonaphthalenes in the synthesis of 1,1′-binaphthyls[18] to afford (*R*)- and (*S*)-**15** in a ratio of 90:10. Since the newly formed stereochemical



element (a chiral axis) in **15** has only a minor effect on the second coupling and the reaction path, with the *R* enantiomer dominating again, the major enantiomer of **15** gives almost exclusively (*R*,*R*)-**13** and the minor one mainly *meso*-**14**. As a

consequence, this two-step coupling sequence leads to an increase in the enantiomeric excess of the final product and allows the synthesis of ternaphthalene (*R*,*R*)-**13** with a very high *ee* value.

An interesting alternative to the "conventional" asymmetric cross-coupling between two aryl moieties is the selective substitution of an enantiotopic group at a prochiral substrate. In 1995 Hayashi et al. described an elegant desymmetrization of biaryls such as **16** that led to axial-chiral **17** in both high yield (87%) and enantioselectivity (93% *ee*).[20] The transformation was accomplished by selective low-temperature coupling of an arylmagnesium bromide with one of the enantiotopic triflate groups of **16**. A chiral palladium complex with (*S*)-phephos (**19**) served as the catalyst [Eq. (4)].[21] As in



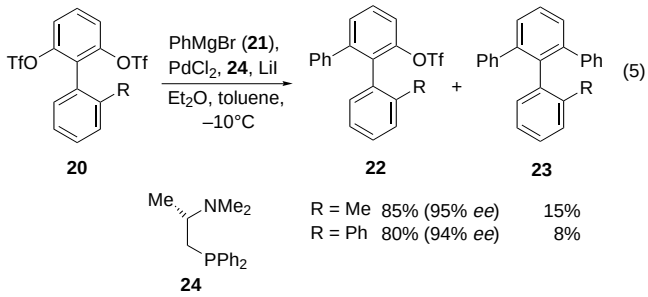
16 **17** **18** **19** (4)

many other cross-coupling reactions, additives had a pronounced effect:[22] lithium bromide was found to enhance both the yield and the asymmetric induction.[23] Lithium iodide was equally as effective in many reactions, while the corresponding chloride proved unsuitable. Interestingly, the amount of additive only influenced the reaction rate, not the enantioselectivity. While equimolar quantities led to high product yields, the contrary was observed when more or less lithium salt was present.

The catalysis also involves a kinetic resolution,[24] which results in an increase in the enantiomeric excess of the initially formed **17**.[25] Studies with racemic **17** showed that the minor enantiomer, (*R*)-**17**, formed in the first phenylation of **16**, with the palladium/(*S*)-phephos catalyst being consumed about five times faster than its enantiomer (*S*)-**17** to give achiral diarylated compound **18**.[26] As a result, the enantiomeric excess of **17** is increased, although at the expense of the product yield.

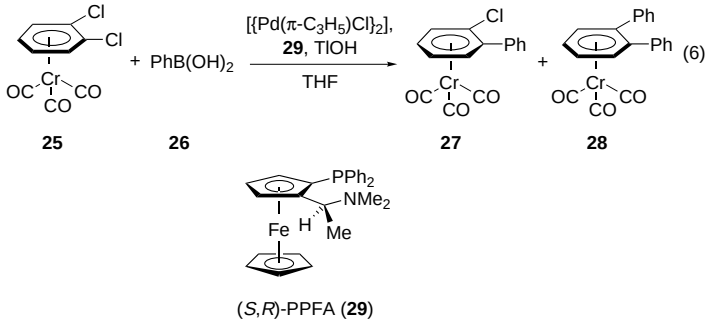
While catalyses with *m*-tolylmagnesium bromide also led to highly enantioenriched biaryls, other Grignard reagents such as *o*- and *p*-tolylmagnesium halide or *p*-chlorophenylmagnesium halide were unreactive. Later, the authors disclosed that prochiral bi- and terphenyls could also be employed as substrates.[27] In this case, P,N ligands derived from amino acids with smaller substituents at the stereogenic center were more effective, and a palladium catalyst containing (*S*)-alaphos (**24**) proved superior to other Pd^{II}/ligand combinations [Eq. (5)].

A range of other Grignard reagents including alkynylmagnesium halides[28] were also found to be applicable, thereby extending the scope of this asymmetric cross-coupling involving the discrimination of enantiotopic groups.



20 **22** **23** **24** (5)

Using the same principle, Uemura and Hayashi et al. studied the desymmetrization of planar-prochiral compounds such as **25**.[29] Thus, when a palladium catalyst with (*S*,*R*)-PPFA (**29**) was used as the ligand, planar-chiral **27** was obtained with 69% *ee* together with a small amount of the achiral bis-coupling product **28** [Eq. (6)]. It is noteworthy that



25 **26** **27** **28** (6)

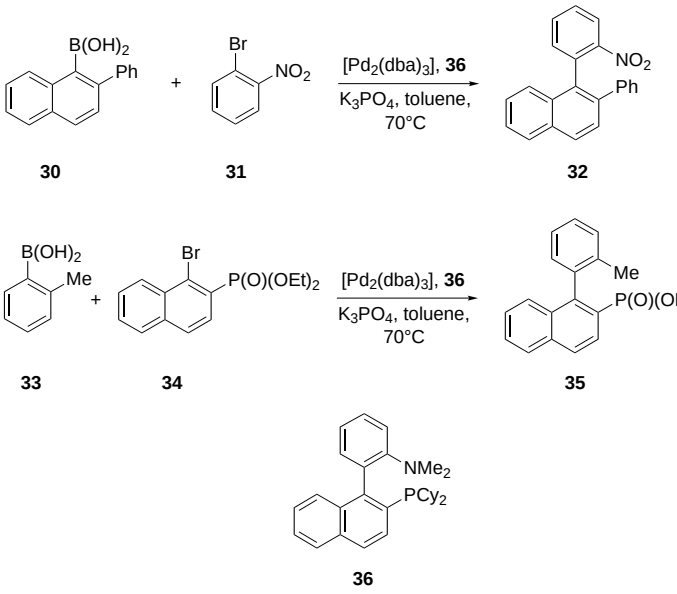
(*S*,*R*)-PPFA (**29**)

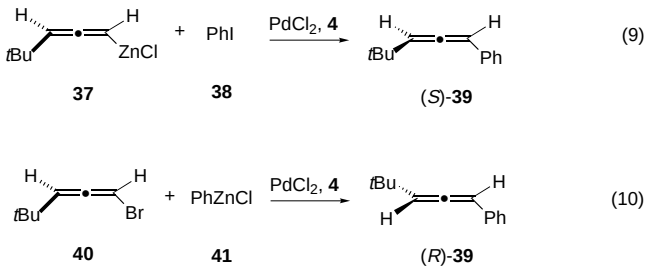
in this case the aryl transfer reagent was a boronic acid and that this reaction is therefore a rare example of an asymmetric Suzuki–Miyaura coupling.[30] The reaction is sensitive to electronic effects, and the use of the more electron-rich 4-methoxyphenyl boronic acid caused a decrease in enantioselectivity together with a dramatic reduction in the reaction rate.

Examples of asymmetric Suzuki couplings of aryl boronates to give axial-chiral biaryls were very recently described by Cammidge and Crépy.[31] The reactions closely resemble asymmetric Grignard cross-coupling reactions and rely on the same catalyst as reported by Hayashi, Uemura, et al. For example, use of $PdCl_2$/**29** in the coupling of the starting materials **7** and **8** ($R^1 = R^2 = Me$) afforded product **9** ($R^1 = R^2 = Me$) with up to 85% *ee*.

The first catalytic enantioselective synthesis of functionalized biaryls was reported by Yin and Buchwald almost simultaneously as the results of Cammidge and Crépy were published.[32] Here, axial-chiral versions of Buchwald's highly active cross-coupling catalysts[33] were employed to afford products **32** and **35** in up to 92% *ee* [Eqs. (7) and (8)]. Compound **36** proved the most effective in this transformation. The catalyst loading could be lowered to 0.2 mol% without deterioration of the *ee* value. The use of an aryl iodide and an aryl chloride gave almost identical results.

The catalytic synthesis of enantioenriched allenes was reported by van Koten, Elsevier, and co-workers [Eqs. (9) and (10)].[34] When racemic **37** was coupled with phenyl iodide





(**38**) in a Negishi-type reaction catalyzed by a palladium complex with diop (**4**) as a chiral ligand the *S* enantiomer of **39** was formed with 25% *ee*. The same product was obtained from the catalyzed coupling of bromoallene **40** and phenylzinc chloride (**41**). However, **39** now had the opposite configuration (and only up to 9% *ee*). Reactions with magnesium or copper derivatives of **37** afforded *S*-configurated **39**. Although in this early work the enantioselectivity was rather low, the use of other ligands might lead to further significant improvements.

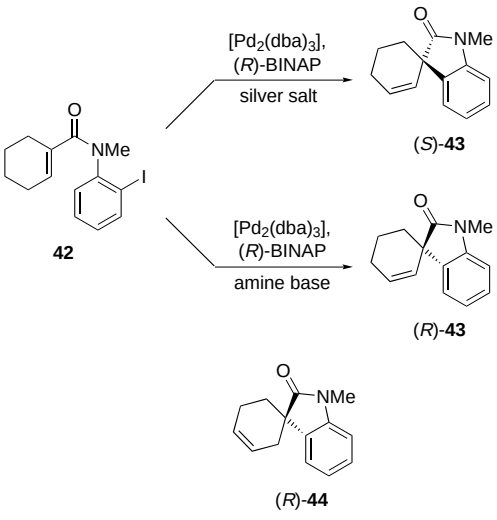
More than twenty-five years after Consiglio and Botteghi,[15] and Kumada and co-workers[16] demonstrated the concept, impressive enantioselectivities have been achieved in arylations involving palladium- and nickel-catalyzed cross-coupling reactions. In this context, the synthesis of biaryl derivatives using aryl halides and aromatic Grignard reagents are particularly noteworthy. However, even at this advanced stage, further progress is required. The development of more universal catalysts and truly general procedures that allow for the use of a broad range of aryl transfer reagents still remains a major challenge for future work. Moreover, the extension of the current cross-coupling concept of organomagnesium reagents to boronates, zinc reagents, or stannanes should provide the synthetic chemist with a useful portfolio of asymmetric cross-couplings. These should then allow for the transfer of an aryl group onto almost every substrate with excellent enantioselectivities.

2.2. Asymmetric Arylation by Heck Reactions

A very important aryl transfer reaction for both academic and industrial purposes is the palladium-catalyzed cross-coupling of aryl halides or sulfonates with olefinic double bonds which was independently discovered by Mizoroki et al.[35] and Heck and Nolley.[36] This transformation has emerged as one of the most useful tools for organic synthesis[37] and was employed in the groundbreaking total syntheses of taxol by Danishefsky et al.[38] and morphine by Overman and co-workers,[39] to name just two of the vast number of examples.[40] An important extension has been the development of asymmetric variants for both intra- as well as intermolecular couplings, which have again found numerous applications in natural product synthesis.[41]

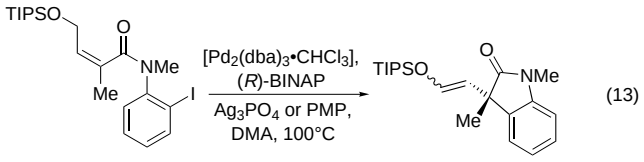
The first asymmetric Heck reaction was reported by Shibasaki and co-workers in 1989 when they described the synthesis of *cis*-decalins with moderate enantiomeric excesses (up to 46%) through an intramolecular Heck-type cyclization.[42] Almost simultaneously, Overman and co-workers published their results on asymmetric aryl/vinyl couplings.[43] In this case, a trienyl triflate underwent polycyclization when subjected to a catalyst system consisting of palladium acetate and diop (**4**) to afford spirocyclic dienones. The enantioselectivities were similar to those achieved in the decalin synthesis by Shibasaki et al. Interestingly, both procedures were intramolecular[44] and relied on an asymmetric delivery of an unsaturated moiety to the olefinic double bond to form a quarternary carbon center.[45]

Recent efforts have focussed on the synthesis of spirooxindols, which are important building blocks for the construction of complex natural products. The intramolecular asymmetric Heck reaction allows a convenient approach to such heterocycles containing a stereogenic all-carbon quarternary center. If the cyclization of **42** was carried out under "conventional" conditions, that is, with a (*R*)-BINAP-modified palladium catalyst in the presence of a silver salt, the (*S*)-configured product, (*S*)-**43**, was formed with good enantioselectivity (80% *ee*) in good yield (Eq. (11)].[46]

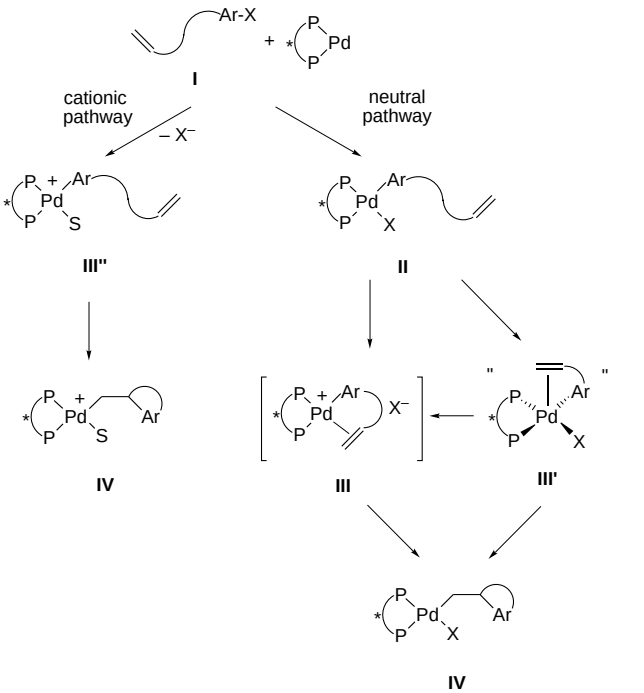


In the absence of an additive, the product has the opposite absolute configuration [Eq. (12)].[47] This reaction path that yields (*R*)-**43** with the same catalyst ((*R*)-BINAP/[$Pd_2(dba)_3$]) can be enhanced by the addition of 1,2,2,6,6-pentamethylpiperidine (PMP).[48] Additionally, a β-hydride elimination/readdition/β-hydride elimination sequence takes place resulting in a kinetic resolution of the initially formed enantioenriched spirooxindole **43** (for the analogous phenomenon in intermolecular Heck reactions, see Scheme 3). Thus, cyclization of **42** to (*R*)-**43** (45%, 89–95% *ee*) was accompanied by the formation of regioisomeric (*R*)-**44**. The latter product had an enantiomeric excess of only 31%, which indicates that the minor *S*-configured isomer of **43** had undergone a more rapid isomerization than its enantiomeric counterpart. As a consequence, this process leads to an enantiomeric enrichment of (*R*)-**43** at the expense of product yield.

As a result of an analogous kinetic resolution (*Z*)-α,β-unsaturated anilide **45** gave product **46** with high enantioselectivity (up to 92% *ee*) under both neutral and cationic conditions [Eq. (13)].[41b, 49]

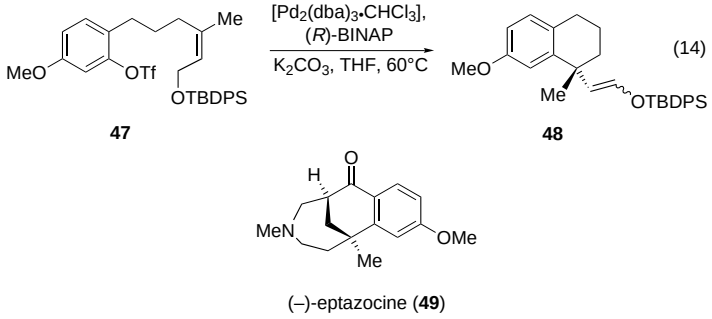


Scheme 2 summarizes the processes from a mechanistic point of view. In the cationic process the silver salt was suggested to serve as a halide scavenger as well as removing the halide from the palladium complex. The resulting cationic palladium intermediate **III″** is then characterized by its reduced tendency for ligand dissociation. As demonstrated by Hayashi et al. in related intermolecular Heck-type reactions (see below), the intermediacy of a four-coordinate species with a chelating BINAP ligand is essential for high enantioselectivity, and bidentate binding can only be ensured if the halide is efficiently removed. The basicity of the additive also has a pronounced effect on the yield and asymmetric induction of the reaction. Thus, weakly basic silver salts impede the cyclization, and the enantioselectivity is decreased significantly. While the cationic path apparently proceeds via **III″**, the enantiodiscriminating step of the neutral route was suggested to be either olefin coordination (**III**/**III′**) or insertion (**IV**), with halide displacement by the tethered alkene (**III**) being the most likely.



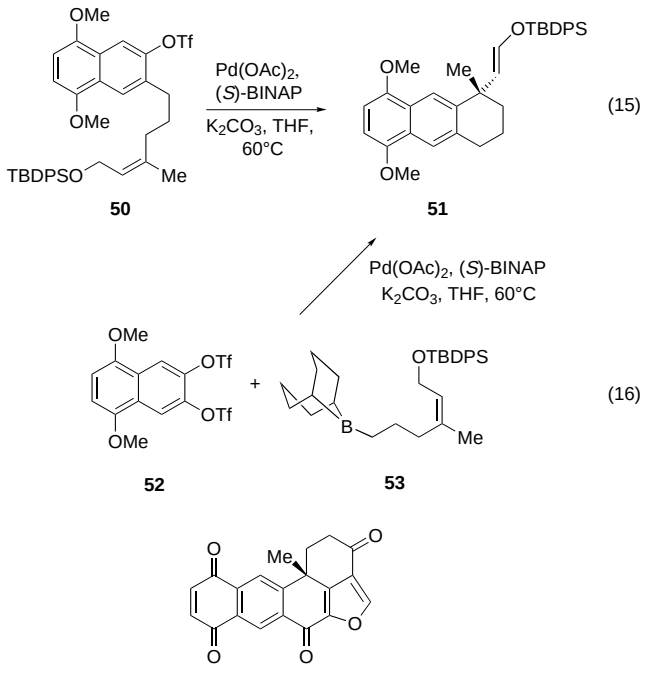
Scheme 2. The possible mechanistic pathways of intramolecular Heck reactions (S = solvent).

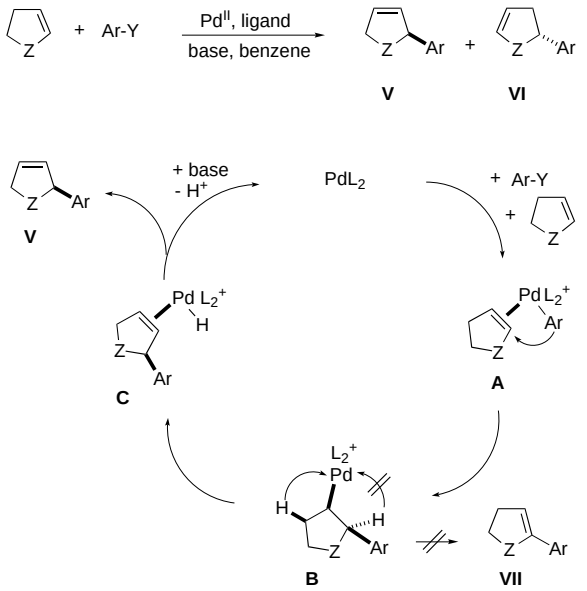
Asymmetric Heck processes can also be used in the synthesis of tetraline derivatives with quarternary stereogenic centers. For example, in the total synthesis of (–)-eptazocine (**49**) by Shibasaki and co-workers, tetraline core **48** was assembled in both high yield (90%) and excellent enantiomeric excess (90%) [Eq. (14)].[50] Furthermore, the depicted *Z* alkene **47** gave much higher enantioselectivities than the *E* isomer, and the two diastereomers afforded opposite enantiomers of **48** in the Heck-type cyclization.[44d]



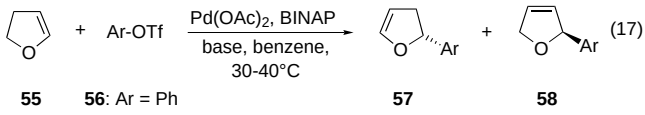
The tetralines can also be formed by other cyclizations, which occur with exceptionally high enantioselectivity. Thus, in the total synthesis of (+)-halenaquinone (**54**), catalysis of the ring-closure of **50** by a BINAP-modified palladium complex gave key intermediate **51** with 87% *ee* and 78% yield [Eq. (15)].[51] The same compound was obtained in almost identical enantiomeric excess (85%) in a "one-pot" tandem-type transformation by using **52** and **53** as starting materials in a Suzuki coupling/asymmetric Heck cyclization sequence [Eq. (16)].[52]

Intermolecular reactions between olefins and aryl sources have been devised mainly for cyclic substrates. The general idea is depicted in Scheme 3. Generation of a Pd^0 species from an appropriate Pd^{II} precursor is followed by its oxidative addition into the arene–heteroatom bond (Ar–Y). After displacement of substituent Y, coordination of the olefin furnishes cationic Pd–olefin complex **A**. Regioselective aryl transfer with *syn* addition gives a pallada species **B**, which releases the metal by reductive β-hydride elimination to give to **C**. Since such a process must occur in a *syn* fashion, the hydrogen atom at the stereogenic center can not be removed and formation of achiral product **VII** is excluded. Instead, β-hydride elimination occurs at the remaining neighboring





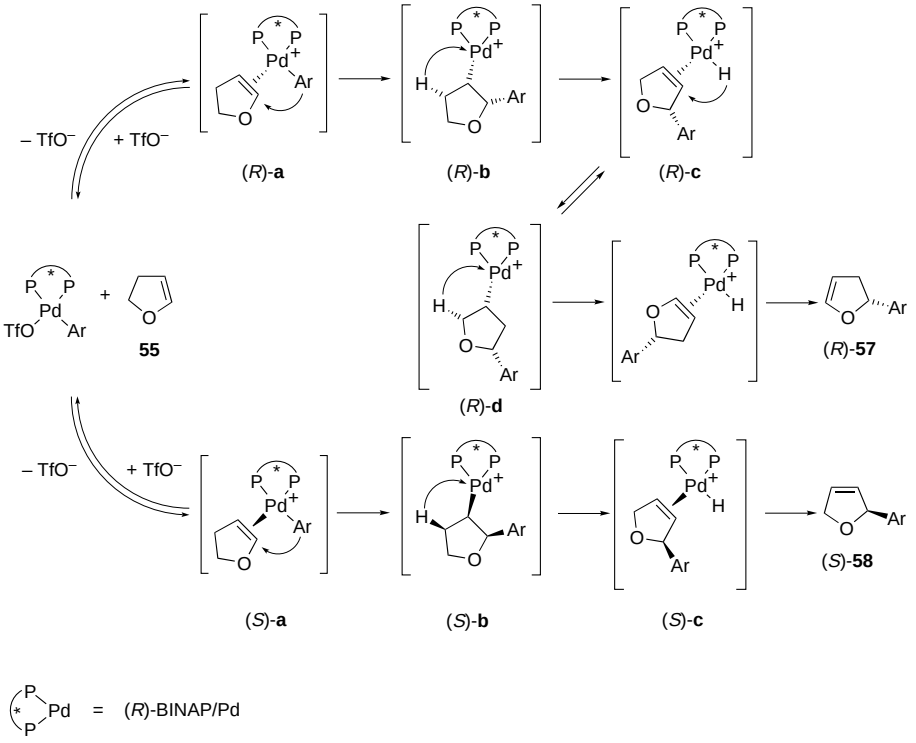
Scheme 3. Mechanistic pathways of intermolecular Heck reactions.



carbon atom giving rise to hydride–olefin complex **C**, which finally releases the desired chiral product **V**. The presence of base regenerates the Pd^0 catalyst. In many cases regioisomeric **VI** is the major product, and its formation will be discussed in detail later.

Enantioselective versions of such intermolecular Heck reactions were first reported by Hayashi and co-workers in 1991.[53] Aryl triflates afforded 2-aryl-2,3-dihydrofurans **57** with enantioselectivities of up to 93% *ee* when 2,3-dihydrofuran (**55**) was employed as the olefinic substrate[54] together with a catalyst derived from palladium acetate and using BINAP as a bidentate ligand [Eq. (17)].[55] In contrast, the use of aryl iodides gave only racemic material, and it was proposed that, in this case, partial dissociation of the ligands from the neutral [Pd{Ar-(BINAP)I}] intermediate took place during the reaction with the olefin, thus furnishing a reactive, albeit unselective, catalyst.

As well as **57**, regioisomeric 2-aryl-2,5-dihydrofurans **58** with opposite configuration at the stereogenic center were generated, and it was found that an enantiomeric enrichment of **57** occurred during the catalysis.[56] The rationalization of such reaction behavior follows the mechanistic path[57] depicted in Scheme 4 for the transfer of an aryl group onto 2,3-dihydrofuran (**55**). After oxidative insertion of an initially formed (*R*)-BINAP/palladium(0) intermediate into the aryl triflate bond, dissociation of the triflate anion generates a cationic palladium complex which is prone to olefin coordination. Coordination to either of the enantiotopic faces of the dihydrofuran results in the formation of two diastereomeric intermediates (*R*)-**a** and (*S*)-**a**.[58] Delivery of the aryl group by addition to the respective double bond gives

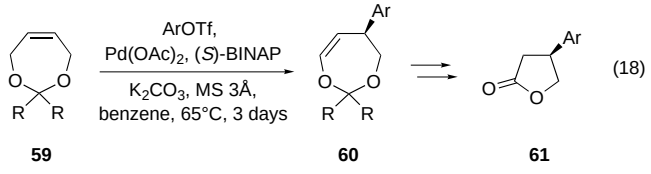


Scheme 4. Mechanistic pathway for the transfer of an aryl group onto **55**.

rise to (*R*)-**b** and (*S*)-**b** which both undergo β-hydrogen elimination to afford the diastereomeric coordination complexes (*R*)-**c** and (*S*)-**c**, respectively. The latter bears (*S*)-**58** as an olefinic ligand which can be directly released. In contrast, (*R*)-**c** undergoes selective hydropalladation to yield (*R*)-**d**. In an overall reversible process, β-hydrogen elimination of this intermediate finally leads to (*R*)-**57**. The different behavior of the diastereomeric complexes **c** is explained as follows: (*S*)-**c** suffers from severe steric interactions between the transferred aryl group and one of the phenyl groups on BINAP, which results in an enhanced rate for olefin decomplexation. Diastereomer (*R*)-**c** lacks this steric strain, and it can therefore more easily undergo addition to the coordinated olefinic double bond leading to (*R*)-**d** as the intermediate in the synthesis of (*R*)-**57**. Thus, the observed product distribution and the enantioselectivity of (*R*)-**57** are indicative of the stereochemical effectiveness of the chiral ligand BINAP.[55] A high enantioselectivity in the formation of the major product ((*R*)-**57**) may be achieved since the two diastereomeric intermediates **c** undergo different subsequent reactions (isomerization of the major intermediate (*R*)-**c** versus ligand dissociation of (*S*)-**c**). Consequently, the authors refer to this transformation as a kinetic resolution process.

Further studies revealed that the choice of the base had a pronounced effect on the regio- and enantioselectivity. Thus, **57** (Ar = Ph; resulting from phenyl transfer from phenyl triflate **56**) was the exclusive product when substituted pyridines were present as bases during the catalysis. Unfortunately, the enantiomeric excess was only moderate (67% *ee* for 2,6-dimethylpyridine), with the *R* enantiomer being formed predominantly. The use of 1,8-bis(dimethylamino)-naphthalene (a proton sponge) led to a sharp increase in the enantioselectivity (>96% *ee*), but now the two isomeric dihydrofurans (*R*)-**57** and (*S*)-**58** (Ar = Ph) were formed in an unsatisfying ratio of 71:29. Furthermore, the *ee* value of the latter product was only 17%.[56]

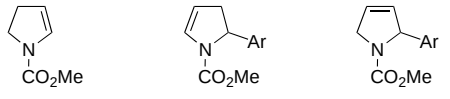
With the goal of obtaining products of the general type **60**, which could be regarded as masked chiral β-aryl-γ-butyrolactones **61**, 4,7-dihydro-1,3-dioxepins **59** have been employed as olefinic substrates in intermolecular Heck reactions [Eq. (18)].[59] Thus, the enantioselective cross-coupling of **59**



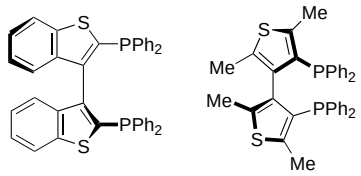
59 **60** **61** (18)

with aryl triflates catalyzed by a BINAP-modified palladium complex furnished the 5-aryl-substituted products **60** with moderate to good enantiomeric excesses (up to 75% *ee*). The presence of a combination of 3-Å molecular sieves (MS) and potassium carbonate as a base was found to be of major importance for achieving this enantioselectivity. The use of 4- or 5-Å MS resulted in the yields dropping while the enantiomeric excess remained about the same. Further improvements of this transformation were subsequently reported by Pfaltz and co-workers (see below).[60]

Arylations of dihydropyrroles by asymmetric Heck couplings were described by Ozawa and Hayashi,[61] Hallberg and co-workers,[62] and Tietze and Thede.[40c] Ozawa and Hayashi reported that when 1-methoxycarbonyl-2,3-dihydropyrrole (**62**) was subjected to conditions similar to those for Pd/BINAP-catalyzed couplings of aryl triflates with dihydrofurans the corresponding arylated products **63** were obtained in moderate to good yield with an *ee* value of up to 83% (Ar = *p*-chlorophenyl). Again, a kinetic resolution-type process



62 **63** **64**

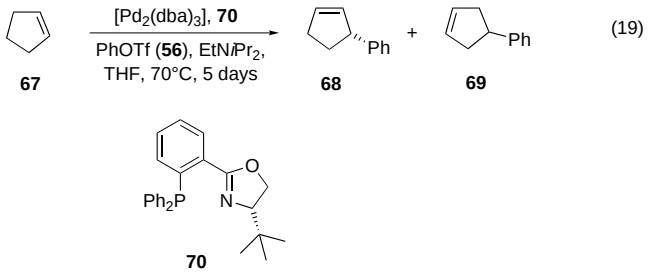


65 **66**

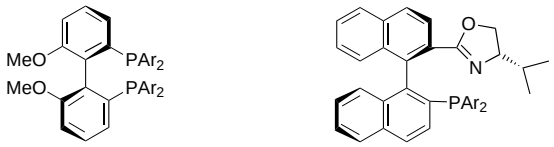
afforded regioisomeric **64** (with a low *ee* value) containing the double bond in the 3,4 position. Tietze and Thede were able to show that the ratio between **63** and **64** was significantly improved (up to 31:1) when BITIANP (**65**) was used as a ligand, and that the enantioselectivity was raised to 93–95% *ee*.[40c] Contrary to expectations, palladium catalysis with TMBTP (**66**) as the chiral ligand gave **64** as the predominant isomer (**63**:**64** = 1:4), although as a racemate.

The new axial-chiral ligands **65** and **66** were also applied in the intermolecular phenylation of 2,3-dihydrofuran (**55**).[40c, 63, 64] Tietze, Sannicolò, and co-workers found that ligand **65** was highly regio- and enantioselective, and afforded exclusively 2,5-dihydrofuran **58** (Ar = Ph) with 91% *ee*. Also, **65** proved suitable in transformations employing a number of aryl triflates (up to 96% *ee*) as well as cyclohexenyl triflate (86% *ee*). It is noteworthy that **66** was superior to **65** in intramolecular Heck reactions terminated by a silane group.[64]

Substantial improvements in the intermolecular asymmetric Heck reactions were achieved early on by Pfaltz and co-workers, who employed C_1-symmetric P,N ligands containing oxazoline moieties such as **70**.[60, 65] These ligands together with a Pd^0 source showed remarkably enhanced levels of both enantioselectivity and the ratio of regioisomeric products.[60] Aryl and vinyl triflates could be used together with cyclic olefins, dihydrofurans, and dioxepins. For example, the phenylation of 2,3-dihydrofuran (**55**) afforded 2-phenyl-2,5-dihydrofuran (**58**, Ar = Ph) with an excellent *ee* value (97%) and in 87% yield. The formation of regioisomer **57** (Ar = Ph) was not observed. The related vinylation with cyclohexenyl triflate took place with complete enantioselection under a variety of reaction conditions. Since these catalysts displayed decreased reactivity relative to Pd/BINAP complexes, they allowed the use of substrates such as cyclopentene (**67**), which afforded **68** with high enantiomeric excess (up to 91% *ee*) [Eq. (19)]. Furthermore, the regioselectivity was excellent,



67 68 69 70 (19)



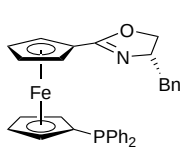
74, 75

76, 77

74, **76**: Ar = phenyl
75, **77**: Ar = 3,5-di-*tert*-butylphenyl

and achiral **69** was only obtained in traces (**68**:**69** = 99:1 in THF).

An interesting extension of Pfaltz's work was recently disclosed by Hou and co-workers,[66] who employed catalysts bearing ferrocenyloxazolines **71**–**73**. These ligands differ in



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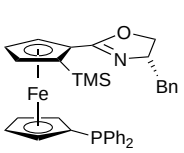

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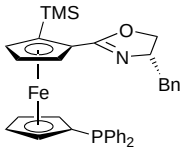


73

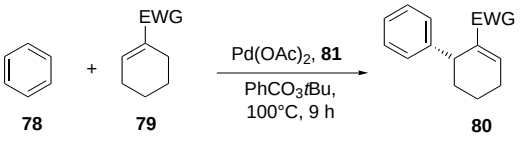
their substitution patterns at the upper cyclopentadienyl fragment and in their relative configurations of the chirality elements. Initial studies with compound **71** having a stereogenic center resulted in the exclusive formation of a 2,5-dihydrofuran (*R*)-**58** (Ar = Ph) with 77% *ee* after a relatively short reaction time of eight hours (at 60 °C). The introduction of planar chirality by adding substituents *ortho* to the oxazoline moiety improved the enantioselectivity. Thus, *ee* values of 84 and 92% were obtained with **72** and **73**, respectively. Interestingly, both products now differed in their absolute configuration, with a dominance of the *S* enantiomer in the former and the *R* isomer in the latter reaction. The authors attributed this result to the presence of the plane of chirality directing the behavior of the ligand during the catalysis.[67, 68]

Pregosin and co-workers studied the Pd-catalyzed enantioselective intermolecular Heck reaction using ligands **74** and **75**.[69] The enantioselection of **75** with bis(3,5-*tert*-butylphenyl) substituents at the phosphorus atom proved superior to **74**, which has a diphenylphosphanyl group. For example, the transfer of a phenyl group to 2,3-dihydrofuran (**55**) to give **57** (with Ar = Ph) occurred regioselectively with **75**, and afforded the product with excellent enantiomeric excess (> 98%) and in 65% yield. On the other hand, the enantioselectivity was only 84% *ee* (71% yield) when **74** was employed. However, presumably because of steric reasons, **75** displayed lower reactivity, and arylation at 40 °C was slow.

The same trend was observed by Pregosin, Albinati, and co-workers with ligands **76** and **77**; they found that the latter with the bis(3,5-*tert*-butylphenyl) substituents was superior and led to enhanced enantioselection (by 10–12% *ee*).[70] The catalyses with ligands **76** and **77** proceeded at similar rates.

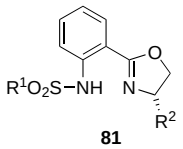
The superiority of the ligands with the sterically demanding *tert*-butyl group at the 3 and 5 position was attributed to an increased rigiditiy of the chiral cleft around the palladium center. The authors also disclosed that the use of $[Pd_2(dba)_3]$ in these catalyses led to a sharp decrease in the reaction rate. This result was attributed to the dba ligand reducing the nucleophilicity of the palladium catalyst by lowering the electron density at the metal through π back-bonding. Thus, this palladium(0) catalyst is almost unreactive towards oxidative addition to phenyl triflate (**56**) under the standard reaction conditions.[71]

A mechanistically related aryl–olefin coupling, which involves the activation of an arene C–H bond, is the Fujiwara–Moritani reaction.[12, 13a] Recently, Mikami et al. described the first example of an asymmetric version of this transformation.[14] A catalyst derived from palladium acetate and sulfonamide **81** promoted this reaction in an enantioselective manner. Benzene (**78**) was chosen as the substrate for the C–H activation, and cyclic olefins were employed to ensure that achiral products were not formed (compare with **VII** in Scheme 3). With *tert*-butyl perbenzoate as the reoxidant, electron-deficient olefins **79** reacted at 100 °C to give arylated products **80** with up to 49% *ee* and yields of 6 to 33% yields [Eq. (20)]. Further improvements in the reaction might result from the use of other ligands. This asymmetric catalysis involves a C–H activation of an otherwise unreactive substrate,[13] and hence it deserves particular attention.



78 **79** **80** (20)

EWG = CO_2CH_3, NO_2, CN



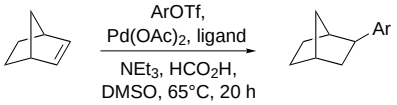
81

Intramolecular enantioselective Heck reactions appear to be much more mature than their intermolecular counterparts, which might—at least in part—be a consequence of the importance of such processes for the synthesis of natural products incorporating all-carbon quarternary stereocenters. Major progress has undoubtedly also been made in the intermolecular versions, but developments in that field still deserve particular attention. Often the availability of catalysts that provide sufficient reactivity, enantio-, and regioselectivity—especially for substrates other than dihydrofurans—is rather limited. Thus, future investigations will have to be

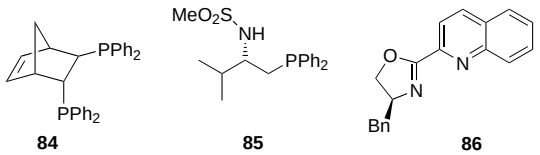
devoted to the identification of catalysts for intermolecular Heck reactions with broader applicability to different substrate classes and increased activity as well as enantioselectivity.

2.3. Hydroarylation of Bicyclo[2.2.1]hept-2-enes

An interesting example of a reductive cross-coupling was first reported by Brunner and Kramler in 1991.[72] Norbornene (**82**) was treated with aryl iodides in the presence of a catalyst composed of palladium acetate and NORPHOS (**84**) to give *exo*-2-arylnorbornanes **83** [Eq. (21)]. At this early stage, the



82 **83** (21)



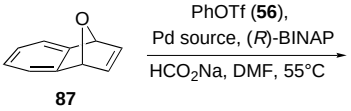
84 **85** **86**

enantiomeric excesses were only moderate, with a maximum value of 41%. Later, Achiwa and co-workers substantially improved the enantioselectivity to 74% *ee* (**83** with Ar = Ph) by using phenyl triflate (**56**) and aminophosphane **85** as the ligand.[73] Recently, Namyslo and Kaufmann[74] reported a comprehensive study of this transformation and confirmed the superiority of **85** relative to bisphosphanes as well as other chelating P,N ligands. The use of phenyl nonaflate (nonaflate = nonafluorobutane sulfonate) gave the product in 47% yield and with an enantiomeric excess of 86%. More conventional leaving groups afforded the enantioenriched arylnorbornane with lower selectivity. Replacement of triethylamine by piperidine or a proton sponge did not result in any change in the enantioselectivity.

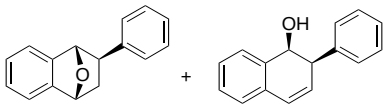
Although several aromatic and heteroaromatic arenes can be used in the asymmetric hydroarylation, the yields generally suffer from side reactions which lead to relatively large amounts of hydrodehalogenated aryl halides or reduced aryl sulfonates. The hydride source, usually formic acid, is responsible for the formation of an intermediate aryl–palladium hydride, which after reductive coupling gives rise to the reduced aromatic compounds.

In another recent report Zhou and co-workers[75] described the use of $[Pd_2(dba)_3]$ and the chiral ligand quinolinyl oxazoline **86**. The results achieved with this catalyst were comparable to those obtained by Achiwa with phenyl iodide (**38**) as an aryl source. Contrary to other reports in this field, the enantioselectivity was temperature dependent, and the best results were achieved at room temperature.[76]

Moinet and Fiaud studied the hydrophenylation of 7-oxybenzonorbornene (**87**) catalyzed by chiral palladium complexes.[77] BINAP proved to be the most suitable ligand. Again phenyl triflate (**56**) was superior to phenyl iodide (**38**) when used as the aryl source and afforded the hydroarylated product **88** with 64% *ee* [Eq. (22)]. Moreover, 15% of the corresponding ring-opened alcohol **89** (83% combined yield of **88** and **89**) was formed with a remarkable 96% *ee*.



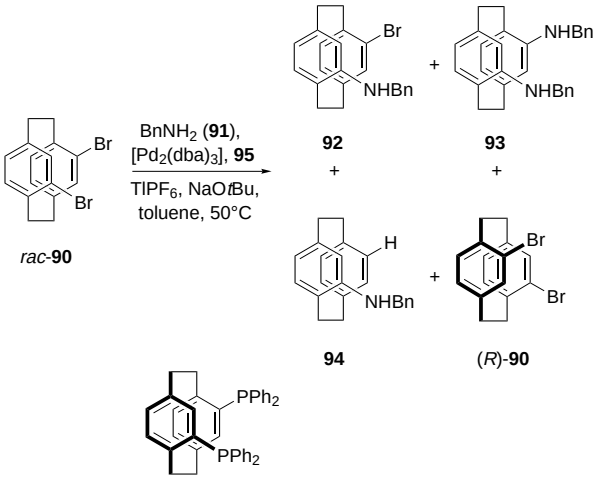
87



88 **89** (22)

2.4. Asymmetric Arylations of Amines

Another interesting aryl transfer reaction in which a primary amine serves as the aryl acceptor was recently disclosed by Rossen, Pye, et al.[78] An enantioselective variant of the Hartwig/Buchwald coupling[79] was developed for the kinetic resolution of racemic 4,12-dibromo-[2.2]paracyclophane (**90**). Thus, when *rac*-**90** was treated with benzylamine (**91**) in the presence of 2 mol% of a palladium catalyst containing (*S*)-[2.2]PHANEPHOS (**95**)[80] as the chiral ligand a product mixture consisting of monoaminated paracyclophane **92**, a small amount of diamine **93**, a dehalogenated derivative **94**, and recovered starting material **90** was obtained [Eq. (23)]. The determination of the enantiomeric excess of **90** revealed that a kinetic resolution had taken place. Thus, at 50 °C the rate of reaction for the amination of (*S*)-**90** was three to four times higher than for (*R*)-**90**. The use of a palladium complex derived from BINAP gave lower overall rates.



rac-**90** (23)

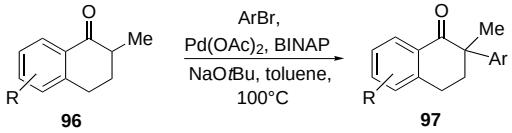
(*S*)-[2.2]PHANEPHOS **95**

The addition of thallium hexafluorophosphate resulted in a significant rate enhancement, and by allowing the conversion to reach 79%, an *ee* value of 93% was obtained for the remaining (*R*)-**90**. An *ee* value of 99.9% could be achieved at about 90% conversion. The mechanism of the Hartwig/Buchwald amination reaction is proposed to proceed via insertion of palladium into the arene–halogen bond, followed

by coordination of the amine to the resulting complex, and, finally, reductive release of an aryl amine from the metal complex. This sequence of events is analogous to the proceedings in other coupling reactions, and hence the described kinetic resolution may be regarded as an asymmetric transfer of a paracyclophane onto an amine catalyzed by a chiral palladium complex. However, unlike in the other cases described in this review, the chirality-inducing step does not consist of a mere stereodiscriminating transfer reaction, but rather of a prior enantiodiscriminating aryl activation.

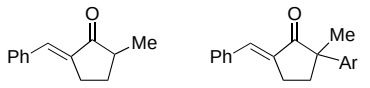
2.5. Asymmetric α-Arylations of Carbonyl Compounds

Palladium-catalyzed α-arylations of ketone enolates were first reported by Kuwajima and Urabe[81] in 1982 and then by Migita and co-workers[82] in 1984. They used silylenol ethers and enol acetates in their studies. About a decade later Palucki and Buchwald[83] and Harmann and Hartwig[84] independently reinvestigated this useful transformation and developed protocols for the catalytic introduction of aryl moieties into the α-position of ketones. These methods rely on the use of palladium/bisphosphane complexes which have proven to be excellent catalysts for related amination reactions. After having first employed racemic BINAP in the α-arylation, Buchwald and co-workers introduced an asymmetric version using the same catalyst (10–20 mol%) with enantiopure BINAP [Eq. (24)].[85] Enantiomerically



(24)

96 **97**

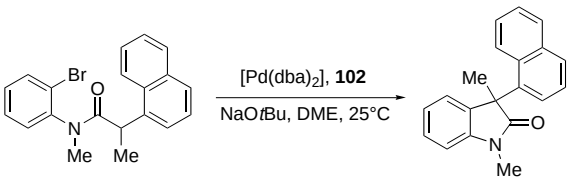


98 **99**

enriched products **97** with all-carbon quarternary centers were obtained from α-monomethyl-substituted tetralones **96** and a twofold excess of aryl bromides. Unfortunately, the asymmetric induction remained only moderate to good (61–88% *ee*).

A suprising fact was revealed when α'-blocked α-methylcycloalkanones such as **98** were employed. In this case, the enantioselectivity was highly dependent on the ring size of the substrate, and cyclopentanones were α-arylated with significantly higher enantioselectivities than their six-membered counterparts. Aryl bromides with *meta* and *para* substituents could be used to furnish α,α-disubstituted ketones **99** with high enantioselectivities (up to 98% *ee*) and excellent yields. For reasons still to be revealed, a number of other aryl and vinyl bromides led to racemic products.[85]

Recently, Lee and Hartwig reported on asymmetric syntheses of oxindoles by intramolecular α-arylation of amides.[86] Optically active heterocyclic carbenes served as the ligands in the palladium catalysts which gave α,α-disubstituted oxindoles with substantial enantioselectivity. For example, **101** was obtained from **100** in 93% yield with 67% *ee* by using [Pd(dba)$_2$] and **102** as the chiral ligand (5 mol% each) and with sodium *tert*-butoxide as the base [Eq. (25)]. The enan-



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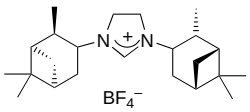
100 **101**

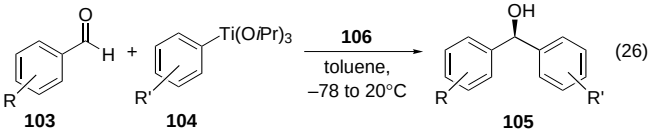


102

tioselectivity could be increased to 76% *ee* by lowering the reaction temperature (from 25 to 10 °C) and increasing the catalyst amount to 10 mol%. Optically active phosphane ligands were also tested, but the respective palladium catalysts gave only products with lower *ee* values.[87]

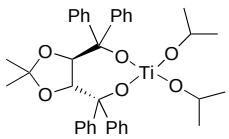
3. Asymmetric Aryl Addition to Carbonyl and Heterocarbonyl Groups

Whereas a stoichiometric enantioselective aryl transfer onto aldehydes was reported by Seebach et al. as early as 1985,[88] it took until 1994 before a catalyzed version of this reaction, which employed titanium–TADDOLate complex **106** as the chiral catalyst, was described by the same group [Eq. (26)].[89] The aryltitanium reagents **104**, which were used



(26)

103 **104** **105**

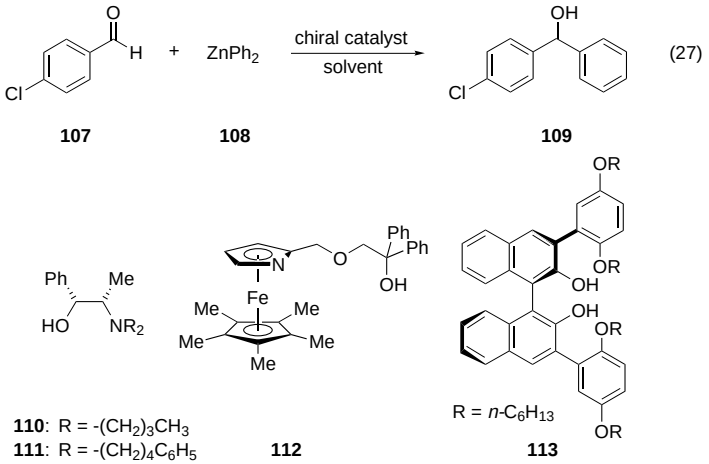


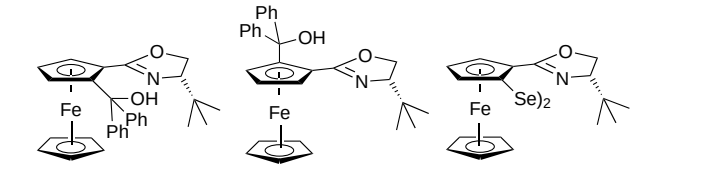
106

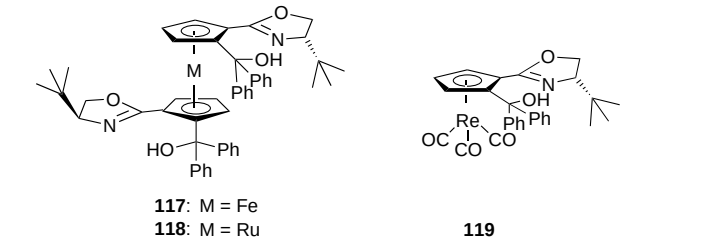
as the aryl sources, were prepared by treatment of the appropriate aryl Grignard or aryllithium reagents with chlorotriisopropoxytitanium. Since the inorganic magnesium/lithium salts had a detrimental effect on the catalysis, they had to be removed by centrifugation followed by filtration.[90] The resulting soluble titanium reagents were then applied to the catalyzed aldehyde additions. However, the major disadvantages of this reaction were the relatively high catalyst loading of 20 mol% and the fact that substituted aromatic titanium reagents (**104** with R′ ≠ H) afforded products with very low enantioselectivities or even as racemic mixtures. The method also proved effective for aliphatic aldehydes, and even acetaldehyde gave the corresponding product with

97% *ee*. Both electron-poor and electron-rich aromatic substrates showed remarkable levels of enantioselection (up to 96% *ee*) with phenyl derivative **104** (R′ = H).

An alternative asymmetric transfer of an aryl group to an aldehyde was described by Soai et al., who reported on the use of a zinc species generated in situ from zinc dichloride and phenylmagnesium bromide.[91] Excess of stoichiometric amounts of *N*,*N*-dibutylnorephedrine (**110**) served as the chiral modifier giving enantiomerically enriched products with up to 82% *ee*.[92] Surprisingly, the face selectivity of the process was altered with respect to that of the closely related dialkylzinc additions. It is important to note, that isolated diphenylzinc reacted very sluggish in the aryl transfer. Its use in asymmetric aldehyde additions was first decribed by Fu and co-workers [Eq. (27)].[93] In an asymmetric catalysis using 3 mol% of chiral azaferrocene **112** the reaction of 4-chlorobenzaldehyde (**107**) with diphenylzinc (**108**) afforded the corresponding diarylmethanol **109** with 57% *ee* in nearly quantitative yield at room temperature.







The report by Fu and co-workers initiated intense research in this area and shortly thereafter two other catalytic asymmetric arylation of aldehydes were described which relied on structurally very different ligands. Huang and Pu reported successful applications of catalysts formed in situ from diorganozincs and chiral binaphthols (BINOLs), such as **113**, which gave enantiomerically enriched alcohols with up to 94% *ee* in the phenylation of aldehydes.[94] By comparing the absolute configurations of these products with those from related diethylzinc additions[95] it was found that the stereochemical course of both transformations was identical. Furthermore, the authors reported a dependence of the enantioselectivity on the substrate concentration. Hence, the products had higher enantiomeric excesses in more dilute solutions. This behavior was explained by the fact that under these conditions the uncatalyzed transfer of the phenyl group to give racemic alcohols was less efficient. The reaction conditions were optimized for individual substrates, and significant differences were found. For example, several product alcohols could be obtained in a satisfying manner at room temperature in toluene with a relatively low catalyst loading (5 mol%), while reactions with other substrates required a solvent change or even the presence of methanol. In some cases an initial addition of diethylzinc to the binaphthol ligand generated a more active catalyst.

The chiral BINOLs were also incorporated into chiral polymers, which catalyzed the asymmetric phenylation of aldehydes to afford products with up to 92% *ee*.[96] These results were comparable to those achieved with the low molecular weight BINOL-derived catalysts.

Since diphenylzinc itself is capable of adding to aldehydes, the final *ee* value of the product is usually lowered by a relatively strong uncatalyzed background reaction. With the goal to further activate the catalyst by ligand modification, Huang and Pu refined the BINOL structure and introduced electron-withdrawing substitutents such as fluorine. As a result, more active catalysts were obtained, and as hoped for, the rate enhancement of the catalyzed pathway became more dominant and led to higher enantioselectivities (up to 95% *ee* for 4-chlorobenzaldehyde).[97]

At the same time, Bolm and Muñiz described a catalyst system based on the chiral ferrocene **114**.[98] The use of 5 to 10 mol% of the catalyst in toluene at 0 °C led to a smooth addition of (isolated) diphenylzinc to various aldehydes to give secondary alcohols with good enantioselectivities. Aromatic substrates afforded synthetically interesting diarylmethanol compounds with up to 88% *ee*.[98b] In addition, a range of aliphatic aldehydes were converted into the corresponding enantiomerically enriched benzyl alcohols with enantioselectivities of up to 75% *ee*. Asymmetric amplification studies illustrated that the actual catalytic species was monomeric. It is again important to note that the absolute stereochemistry of the product suggested an analogous reaction path as in the related diethylzinc addition with **114**, which had been investigated by the same authors earlier.[99]

Ferrocene **114** is *S* configured at the stereogenic center and has an R_p configuration at the plane of chirality (subscript p).[100] Comparative studies with its *S*,S_p-configured diastereomer **115** revealed how well-balanced the stereogenic elements of the ligand had to be in order to achieve high enantioselectivity.[68] Thus, the addition of $ZnPh_2$ (**108**) to aldehyde **107** in the presence of the ferrocene **115** gave diarylmethanol **109** with only 9% *ee*.[101] This result was again attributed to the significant uncatalyzed background reaction between $ZnPh_2$ and the aldehyde giving a racemic product. As

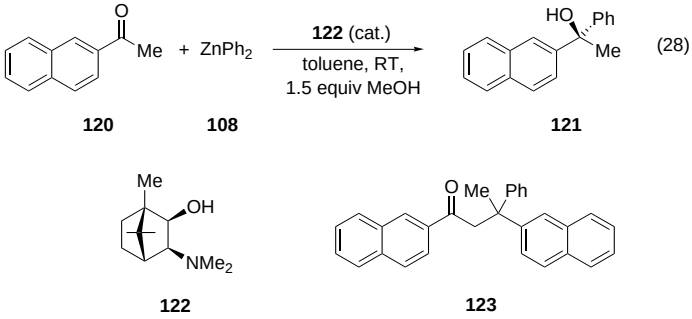
had previously been shown in alkylation reactions,[102] the relative rate enhancements by the two diastereomers **114** and **115** are distinctively different and thus, the competitive unselective background reaction becomes more important in the catalysis with the less active catalyst **115** and leads to a reduction in the enantiomeric excess of the final product.

Efforts to overcome the problem of the parallel unselective addition of $ZnPh_2$ led to the development of an improved protocol, which relied on a modified phenyl transfer reagent. Thus, when isolated $ZnPh_2$ was replaced by a zinc reagent formed in situ by combining $ZnPh_2$ with $ZnEt_2$ in a ratio of 1:2, the enantioselectivity of the aryl transfer catalyzed by **114** was significantly improved to 90–98% *ee* for a wide spectrum of substrates.[103, 104] Three more aspects are particularly noteworthy: Firstly, the reaction temperature could be raised from 0 to 10 °C without loss of enantioselectivity. Secondly, *ortho* substituents were better tolerated in aromatic aldehydes. For example, compounds such as 2-bromobenzaldehyde gave greatly improved enantioselectivities (91 versus 73% *ee*). Thirdly, the amount of the relatively expensive diarylzinc reagent $ZnPh_2$ was reduced to 0.65 equivalents (versus 1.5 equiv), which indicates that both phenyl groups could now be activated and then transferred to the aldehydes, while the product alcohols were still obtained in almost quantitative yields.

Under these improved conditions the less-active S,S_p-configured ferrocene **115** directed the addition of the modified phenylzinc reagent to 4-chlorobenzaldehyde (**107**) and yielded (*S*)-**109** with 68% *ee* rather than 9% *ee* as before. Using a 1:1 mixture of the diastereomeric ferrocenes **114** and **115** gave (*R*)-**109** with 91% *ee*.[105]

Early attempts to improve the activity and enantioselectivity of the catalysts led to the development of other metallocenes such as ferrocenes and ruthenocenes **116**–**118**.[106–108] Although in several reactions a good asymmetric induction in the aryl transfer was achieved (for example, the use of 5 mol% of **116** and **117** gave **109** with 84 and 94% *ee*, respectively), the overall catalyst performance was at best equal to that of ferrocene **114**. Other metal catalysts were prepared and tested,[109] and, finally, a major breakthrough was achieved by the introduction of cyrhetrene **119**.[110] The enantioselectivities in the phenyl transfer to aldehydes were further improved and *ee* values of up to 99% were reached in the formation of diarylmethanols by application of 2–10 mol% of this chiral Re complex. Furthermore, the use of **119** enabled the reaction to be carried out with a decreased catalyst loading; the enantiomeric excesses remained remarkably high even with less than 5 mol% of **119**. For example, use of only 2 mol% of **119** gave **109** with 96% *ee*, as compared to the previously obtained 97% *ee* with 10 mol% of **114**.[103] Clearly, cyrhetrene **119** is an outstanding catalyst for the transfer of a phenyl group to an aldeyde.[111]

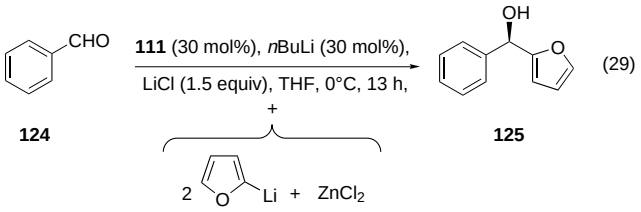
In the aryl transfers discussed previously the aldehydes have served as reaction partners. Attempts to use other carbonyl compounds as aryl acceptors have only been described to a limited extent. An early example was reported by Dosa and Fu, who developed an asymmetric 1,2-addition of diphenylzinc (**108**) to ketones catalyzed by Noyori's DAIB (**122**). The corresponding tertiary alcohols were obtained with good to high enantioselectivities [Eq. (28)].[112] Since the use of isolated diphenylzinc (**108**) and **120** afforded relatively



(28)

large quantities of **123** (60%), derived from an aldol condensation reaction followed by 1,4-addition, the desired product **121** was only obtained in low yield (26%; 64% *ee*). It was found that the reaction yielding **123** could be efficiently suppressed by the addition of methanol (1.5 equiv relative to the ketone). Both the chemical yield and enantioselectivity of **121** were improved (58% yield, 72% *ee*). Presumably, a less reactive zinc alkoxide was formed, which underwent 1,2-addition more selectively.[22, 113]

Heteroaromatic groups can also be transfered to aldehydes. Thus, N,N-disubstituted norephedrine derivative **111** proved to be the best auxillary for an enantioselective furylation of benzaldehyde (**124**), as described by Soai and Kawase [Eq. (29)].[114] A complex reaction protocol had to be

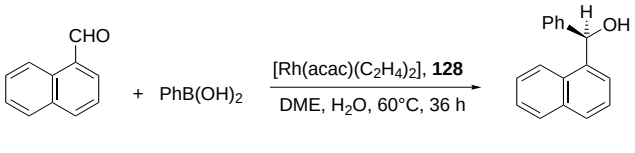


(29)

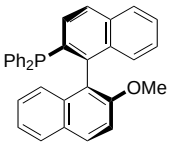
developed to obtain reasonable results: this included the supposed in situ formation of di(2-furyl)zinc from 2-furyllithium and zinc dichloride, as well as a pretreatment of **111** with one equivalent of *n*-butyllithium and five equivalents of LiCl. Thus, alcohol **125** was obtained with 30% *ee* by using 30 mol% of **111** and using benzaldehyde (**124**) as the substrate. Stoichiometric quantities of **111** were required to improve the enantioselectivity to 72% *ee*.

Miyaura and co-workers described an asymmetric 1,2-addition of phenylboronic acid (**26**) to 1-naphthaldehyde (**126**) using (*S*)-MeO-MOP (**128**) as a chiral ligand [Eq. (30)]. Contrary to the analogous 1,4-additions (see Section 4), only a moderate enantioselectivity was achieved to give **127** with 41% *ee* (78% yield).[115]

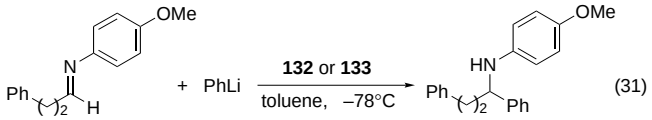
Heterocarbonyl compounds can also be applied as aryl acceptors. An asymmetric addition of phenyllithium (**130**) to imine **129** in the presence of substoichiometric quantities of sparteine (**132**) [Eq. (31)] was reported by Denmark et al.[116–118] When reactions of organolithium reagents with imines were studied it was found that both sparteine (**132**) as



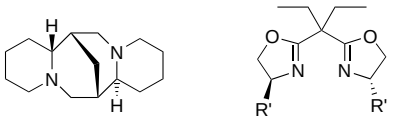
126 26 127



128



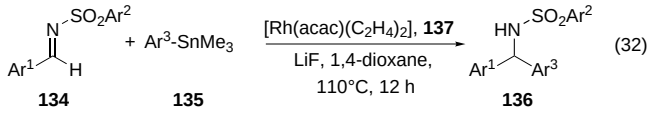
129 130 131



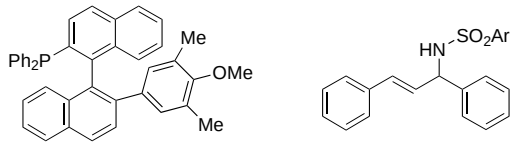
132 133

well as bisoxazolines **133** were suitable chiral ligands for the synthesis of optically active amines. The former gave significantly higher enantioselectivities in the transfer of a phenyl group from **130** onto **129**. Unfortunately, a major decrease in enantioselectivity was observed when substoichiometric quantities of the chiral ligand were used. Thus, the addition of **130** to imine **129** in the presence of one equivalent of **132** yielded **131** with 82% *ee* (99% yield). When 0.2 equivalents of **132** were used, the same product had only 39% *ee* (97% yield).[119]

The first catalytic asymmetric addition of aryl stannanes to imines was described by Hayashi and Ishigedani [Eq. (32)].[120] This transformation is rhodium-catalyzed in a



134 135 136

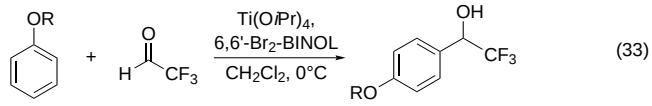


137

138 (Ar = 4-NO_2-C_6H_4)

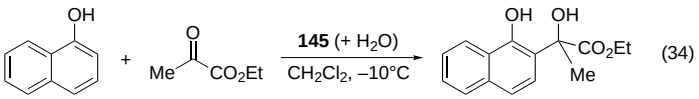
similar way to related reactions, such as conjugate additions and aldehyde arylations, however, here organostannanes are utilized as aryl sources instead of arylboronic acids. Rhodium catalysts with monophosphane (MOP) ligands such as **137** (3 mol% of Rh and 6 mol% of ligand) were superior to complexes bearing chelating bisphosphanes such as BINAP or diop (**4**).[121] The imines were used in the form of *N*-alkylidenesulfonamides **134**, which yielded the corresponding products **136** with enantioselectivities that depended on the substituents Ar^2 at the sulfonamide group. Compounds bearing a *p*-nitrobenzene sulfonyl (nosyl) group were among the best in terms of both enantioselectivity (up to 96% *ee*) and yield. Furthermore, the resulting sulfonamides could easily be deprotected to give the corresponding optically active diarylmethylamines. Chiral allylamines could also be obtained by this method. Thus, when the sulfonamide derived from cinnamyl aldehyde was used, the phenylation occured smoothly to give allylic amine **138** with 93% *ee* and in 77% yield. In this study only aryl and α,β-unsaturated imines were used. It remains to be established whether the protocol is also applicable to simple aliphatic imines.[122]

The aryl transfer reactions discussed so far in this section have involved the formation of organometallic intermediates with aryl–metal bonds. Conceptionally different are Friedel–Crafts-type additions of electron-rich arenes onto catalyst-activated carbonyl or heterocarbonyl compounds. An early result employing stoichiometric amounts of a chirally modified aluminum reagent in the enantioselective *ortho*-hydroxyalkylation of phenol with trichloroacetaldehyde (up to 80% *ee*) was reported by Casiraghi and co-workers.[123, 124] Recently, a modification of this approach was used by Mikami and co-workers in asymmetric Friedel–Crafts reactions of phenol ethers **139** and fluoral (**140**). The use of 10 mol% of a titanium catalyst bearing 6,6′-Br_2-BINOL as the ligand afforded 1-aryl-2,2,2-trifluoroethanols **141** with up to 90% *ee* [Eq. (33)].[125, 126] Even the use of only 1 mol% of the catalyst led to relatively high enantioselectivities. Asymmetric activation[127] allowed the efficiency of the catalyst to further increase.

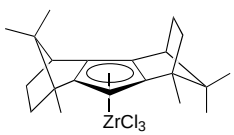


139 140 141

Erker and van der Zeijden reported in 1990 that 1-naphthol (**142**) reacted with ethyl pyruvate (**143**) under catalysis with camphor-derived zirconium complex **145** to give product **144** in an asymmetric manner [Eq. (34)].[128] With only 1 mol% of



142 143 144

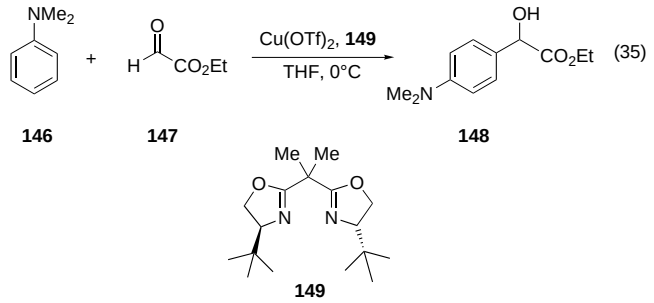


145

the catalyst, 70% of **144** having 27% *ee* was obtained after 2 h at room temperature. The enantioselectivity was conversion dependent, and hence decreased during the reaction. When the temperature was lowered to $-10\,^{\circ}C$ and, most remark-

ably, when a well-defined amount of water was added, the *ee* value of **144** acutely increased. Thus, the *ee* value of the product reached 89% at 70% conversion using a ratio of **142**:**143**:**145**:H_2O of 100:500:5:27. At 90% conversion **144** had 84% *ee*.

This Friedel–Crafts chemistry was recently extended by Jørgensen and co-workers who found that bisoxazoline–copper(II) complexes catalyzed the enantioselective Friedel–Crafts reaction between *N*,*N*-dimethylaniline (**146**) and ethyl glyoxylate (**147**) [Eq. (35)].[129] Exclusive *para*-substitution took place on ligand **149** to give **148** with up to 94% *ee*. Substituted *N*,*N*-dimethylanilines, furans, and other related compounds also worked well and afforded the corresponding products with moderate to good enantioselectivities.

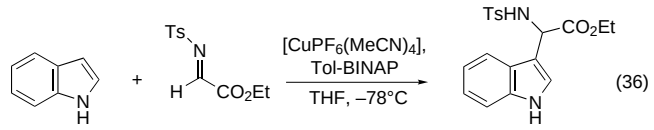


(35)

146 **147** **148**

149

The catalyzed asymmetric addition of heteroaromatic nucleophiles onto the *N*-tosylimine **151** derived from ethyl glyoxylate was developed by Johannsen.[130] The catalyst system $[CuPF_6(MeCN)_4]$/Tol-BINAP[131] is very efficient, and the novel *N*-tosylamino acid esters were obtained with high enantioselectivity and good yield with a catalyst loading of only 1 mol%. For example, catalyzing the reaction of indole (**150**) with imine **151** afforded product **152** with 96% *ee* and 89% yield [Eq. (36)]. Whereas indoles reacted selectively

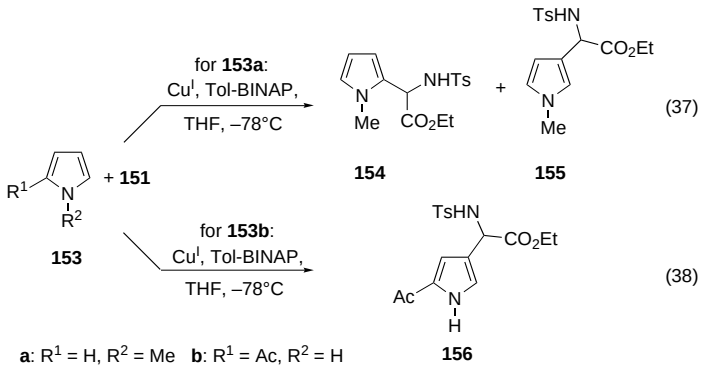


(36)

150 **151** **152**

at the 3 position, pyrroles **153** showed less regioselectivity. Thus, in the reaction with *N*-methylpyrrole (**153a**), an approximately 1:1 mixture of the 2- and 3-substituted products **154** and **155** (having 84 and 56% *ee*, respectively) was formed in a total yield of 89% [Eq. (37)].[132] The regioselectivity problem can be delineated by introduction of a deactivating acetyl group in the 2 position of the pyrrole ring. Thus, the addition of **151** to **153b** took place with high selectivity to give 3-substituted pyrrole **156** with 94% *ee* and 76% yield [Eq. (38)].

Jørgensen and co-workers used the Cu^I/Tol-BINAP catalyst system for the asymmetric addition of electron-rich aromatic compounds to α-imino esters.[133] Optimization of the reaction protocol (5 mol% of catalyst in THF at $-78\,^{\circ}C$) allowed the synthesis of **159a** with 96% *ee* and in 75% yield from *N*,*N*-dimethylaniline (**157**) and imine **158a** [Eq. (39)]. The *N*-ethoxycarbonyl group of **159a** could then be cleaved to

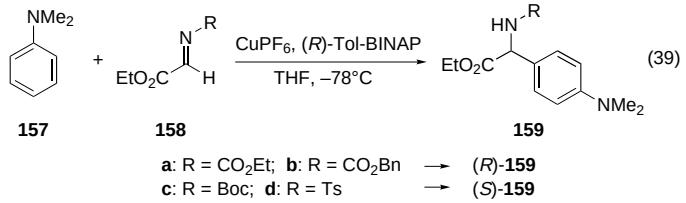


(37)

154 **155**

(38)

156



(39)

157 **158** **159**

liberate the corresponding N-unprotected amino acid ester. The imine protecting group had a pronounced effect on the absolute configuration of the product: when (*R*)-Tol-BINAP was used as a ligand, *N*-alkoxy- and *N*-benzyloxycarbonyl-protected imines of **158** gave the *R* enantiomer of the corresponding addition products **159**, which is in contrast to more bulky N-protecting groups such as Boc or tosyl (Ts), which led to the formation of the *S* enantiomer of **159**. On the basis of an observed drastic temperature dependence of the enantioselectivity it was proposed that two competitive coordination modes were responsible for the switch of mechanistic pathways leading to opposite asymmetric induction.

The examples of catalyzed asymmetric aryl transfer reactions onto carbonyl compounds summarized in this review illustrate that significant progress has been achieved in recent years. However, several factors still need improvement. For example, in the case of arylzinc reagents the catalysis is still hampered by the fact that phenyl transfers from diphenylzinc have been predominantely studied. The applicability of other arylzinc reagents still needs to be demonstrated. Thus, at this stage it may be concluded that the rhodium-catalyzed 1,2-additions employing aryl boronic acids and stannanes have a wider scope despite the problems related to cost and potential toxicity of reagents. However, in many cases, the aryl transfer reagent has to be employed in large excess, and therefore further developments are desirable for the improvement of the catalyst efficiency. Since this process is closely related to rhodium-catalyzed conjugate additions (see Section 4), it should follow that progress will be achieved for both transformations almost simultaneously.

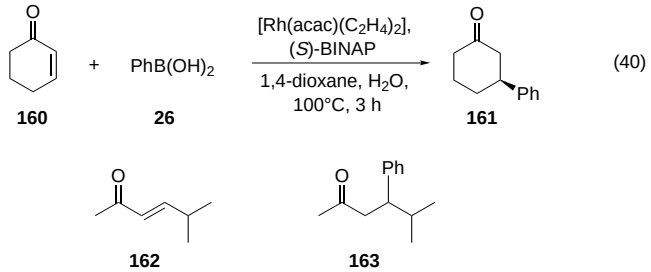
Very impressive results have recently been reported in the area of Friedel–Crafts-type aryl transfers. The catalysts used in these reactions for the activation of the carbonyl or heterocarbonyl compounds are simple and lead to high enantioselectivities. Improvements are still required regarding the regioselectivity, because often potentially highly useful

products are obtained as regioisomeric mixtures. Here, also, new catalyst systems can be expected to offer solutions to overcome the currently existing limitations.

4. Conjugate Addition Reactions and Allylic Substitutions

Achieving high enantioselectivities in catalyzed asymmetric 1,4-additions of nucleophiles to α,β-unsaturated carbonyl compounds has been a longstanding goal.[134] Most significant progress has been made with respect to nickel- and copper-catalyzed conjugate additions to enones using dialkylzincs and, in certain cases, with organomagnesium reagents. Only recently, a novel rhodium-catalyzed process has been developed, which appears to be of high generality with respect to reagents, substrates, and selectivity.

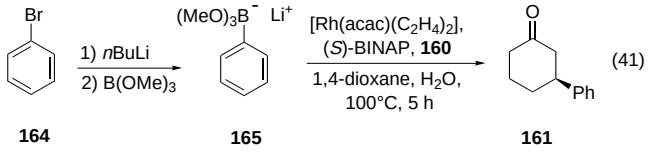
Hayashi, Miyaura and co-workers described the highly enantioselective 1,4-addition of alkenyl- and arylboronic acids to enones catalyzed by a rhodium(I)/BINAP catalyst.[135] For example, phenylboronic acid (**26**) and cyclohexenone (**160**) reacted smoothly to give ketone **161** with 97% *ee* and in >99% yield [Eq. (40)]. Linear *trans* enones such as **162** also



(40)

added **26** with excellent enantioselectivity to give **163** with 97% *ee* and 82% yield. No 1,4-addition was observed in the absence of the rhodium catalyst. Since boronic acids undergo decomposition under the standard reaction conditions (dioxane/H_2O, 100 °C), they had to be employed in a relatively large excess (often fivefold) to obtain high product yields. The mechanism of this process was proposed to involve an aryl–rhodium intermediate, which after insertion into the enone double bond rearranges to a rhodium–enolate. Hydrolysis and transmetalation releases the product and regenerates the catalytically active aryl–rhodium species.

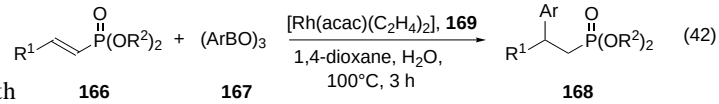
Given the fact that arylboronic acids are readily generated from the corresponding aryl halides, it appeared desirable to directly employ the latter. This is indeed possible by an in situ sequence including lithiation of an aryl bromide (for example, phenyl bromide (**164**)), subsequent formation of the corresponding arylborate **165** with trimethylborate, and 1,4-addition catalyzed by the chiral rhodium/BINAP complex [Eq. (41)].[136, 137] Moreover, the excess of arylating reagent



(41)

could be significantly lowered from 5 to 2.5 equivalents with this new method. Interestingly, while *p*-methoxyphenyl boronic acid did not react under the original conditions because of the competing decomposition, the use of 4-bromoanisole in accordance with the new protocol gave both high yields and excellent asymmetric induction in the addition to cyclic enones. The catalysis also displayed a pronounced dependence on the amount of water present. Thus 0.5 equivalents were sufficient to keep it at an acceptable rate whereas almost no addition (4%)[138] was observed under anhydrous conditions. With 10 equivalents of water (relative to the aryl bromide) the enantioselectivity remained at a very high level (98% *ee*), but the yield was significantly lowered (19%).[138] It should also be noted that in this in situ process, substrate to catalyst ratios of up to 1000:1 still afford almost complete enantioselection (99% *ee*). The species responsible for transmetalation to rhodium is suggested to be either Li[ArB(OMe)$_2$OH] or ArB(OMe)(OLi) as determined in control experiments using phenyl dimethoxyboronate and lithium hydroxide. Both protocols can also be applied in the conjugate addition to α,β-unsaturated esters.[139] Again, as described for enones, the one-pot method proved superior and prevented the hydrolysis of the boronic acid from occurring—the process responsible for the low product yields. Surprisingly, when lactones were employed, the in situ method largely failed, whereas the use of arylboronic acids led to smooth catalysis.

Unsaturated phosphonates **166** can also be employed as substrates in 1,4-additions. When used together with arylboroxines **167** and a rhodium complex containing **169** they afford the corresponding β-arylated phosphonates **168** in good to high yield with excellent enantioselectivities [Eq. (42)].[140]



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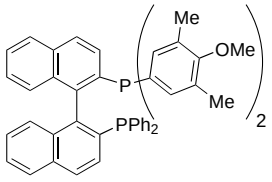
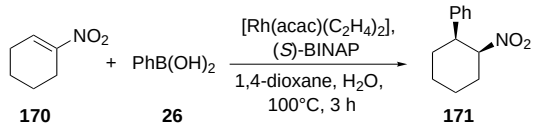


169

Attempted use of arylboronic acids under the previously described conditions proved less efficient. This occurs as a consequence of a reduced catalyst activity in the presence of relatively large quantities of water, which served as the cosolvent. On the other hand, utilizing arylboroxines **167** and a strictly limited amount of water (only one equivalent of water with respect to the boron compound) led to an improvement in both the yield and enantiomeric excess.

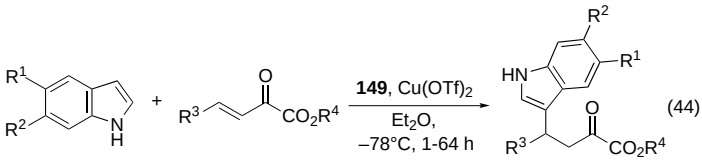
Recently, Hayashi et al. demonstrated that arylboronic acids could also be added enantioselectively to α-substituted 1-nitroalkenes using rhodium catalysis.[141] For example, the reaction between **26** (5 equiv) and 1-nitrocyclohexene (**170**) in the presence of 3 mol% of [Rh(acac)(C$_2$H$_4$)$_2$]/BINAP at 100 °C in dioxane/water led to the formation of **171** with up to 99% *ee* [Eq. (43)]. The diastereoselectivity was also high,



170 **26** **171** (43)

with the thermodynamically less-stable *cis* isomer being prefered (*cis*:*trans* = 87:13). Base treatment of the *cis*-rich mixture resulted in equilibration and afforded a *trans*:*cis* ratio of 97:3 without changing the *ee* value.

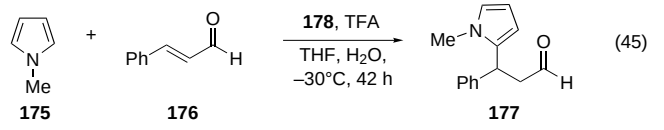
Metal-catalyzed Friedel–Crafts-type additions of electron-rich arenes onto unsaturated carbonyl compounds are mechanistically very different. Jørgensen and co-workers described such a process using a combination of the bisoxazoline ligand **149** and copper(II) triflate as the catalyst (2–10 mol%) [Eq. (44)].[142] The addition occured with excellent enantio-



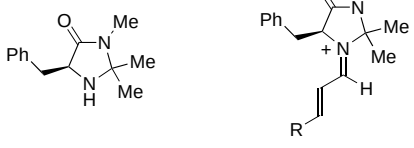
172 **173** **174** (44)

selectivities (up to >99.5% *ee*) with indols **172** and β,γ-unsaturated α-ketoesters **173** as substrates, and afforded products **174** in high yields. Other heteroaromatic compounds, such as furans and anisoles, also gave the corresponding Friedel–Crafts products, but the *ee* values remained below 90%.

In this context the organocatalytic addition of pyrroles to α,β-unsaturated aldehydes developed by Paras and MacMillan is also of interest.[143] A smooth reaction between N-substituted pyrroles such as **175** and enals occured in the presence of 20 mol% of imidazolidinone **178** and TFA as cocatalyst to afford the 1,4-addition products with up to 97% *ee* [Eq. (45)]. The utility of the protocol was demon-



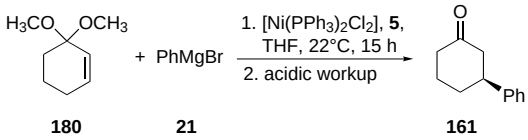
175 **176** **177** (45)



178 **179**

strated in the reaction of cinnamaldehyde (**176**) and **175** on a 25-mmol scale, where **177** was obtained with 93% *ee* and in 87% yield. The sence of asymmetric induction was readily explained by the directing effect of the proposed intermediate iminium ion **179**.

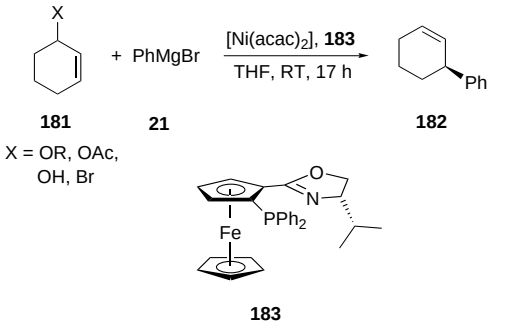
Enantiomerically enriched 3-phenylcyclohexanone (**161**) can also be obtained from phenylmagnesium bromide (**21**) and cyclohexenone ketal **180** [Eq. (46)].[144] For this allylic substitution type reaction, Hoveyda et al. developed a protocol which makes use of a nickel complex containing chiraphos (**5**) as the chiral ligand. The product was obtained (after



180 **21** **161** (46)

hydrolysis of the intermediate enol ether) with good enantioselectivity (83% *ee*) and satisfying yield (67%) under optimized reaction conditions. The enantiomeric excess was strongly dependent on the reagent and additive. Thus, the enantioselectivity was significantly lower (**161** with 66% *ee*) in the catalysis when phenylmagnesium chloride was used as the aryl transfer reagent. The presence of an additional 10 mol% of triphenylphosphane was essential for obtaining high asymmetric induction in several other reactions. Lower enantioselectivities were observed with 5 and 20 mol% of this additive. At present, the precise role of the triphenylphosphane is unclear and hence general trends concerning benefical effects of Lewis basicity or the structure of other phosphane additives can not be deduced.

Asymmetric allylic arylations starting from 3-substituted cyclcohexenes **181** and phenylmagnesium bromide (**21**) have recently been described by Uemura and co-workers [Eq. (47)].[145] By using a combination of $[Ni(acac)_2]$ and



181 **21** **182** (47)

183

ferrocene **183** as the chiral catalyst 3-phenylcyclohexene (**182**) was obtained with an *ee* value of up to 88% (for **181** with X = Br). Other aryl Grignard reagents could also be applied, and afforded products with a maximum *ee* value of 95% (from the reaction of **181** (X = OPh) and 2-naphthylmagnesium bromide).

Uemura and co-workers also demonstrated that arylboronic acids could be used in a nickel catalysis to afford the allylic substitution products with moderate enantiomeric excesses (**182** with 53% *ee*) in good yields.[146] In this case the catalytic system required the addition of DIBAL and KOH to be active. It was proposed that the initial mechanistic step involves a transfer of an aryl group from a boron to a nickel atom. All attempts to employ palladium-derived catalysts failed and gave **182** in very low yield.

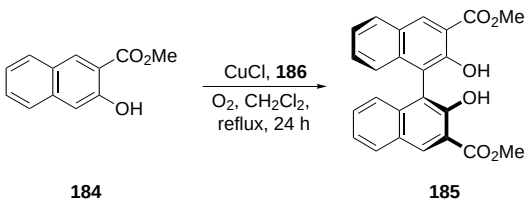
As noted before, the development of efficient catalytic processes to achieve enantioselective conjugate additions and allylic substitutions has been a long-standing goal in asym-

metric catalysis. For alkylations, the achievements in copper-catalyzed conjugate additions of diorganozinc reagents and palladium-catalyzed alkylations marked the first major steps towards a general solution of these problems. On the basis of these successful reactions, improvements of other asymmetric addition reactions including the transfer of aryl groups can now be expected. The emergence of the rhodium-catalyzed 1,4-addition of aryl moities to α,β-unsaturated carbonyl compounds, which allows the transfer of various sp^2-hybridized groups in a highly enantioselective fashion, already represents an important breakthrough in this area. This transformation is characterized by low catalyst loading as well as the utilization of readily available ligands and substrates. Simple compounds such as boronic acids serve as convenient aryl transfer reagents, of which many are either commercially available or easily prepared from inexpensive starting materials. At present, the only drawback of this method is that often relatively large quantities of the aryl source have to be employed. With the development of more active catalysts and new reaction protocols these negative aspects can also be expected to be eliminated in the very near future.

5. Enantioselective Oxidative Coupling of Naphthols

The oxidative coupling of naphthols is a widely used method for the synthesis of binaphthols. Since the latter and their derivatives belong to the most successful chiral ligands in asymmetric catalysis,[55, 96] an enantioselective catalytic version of this coupling reaction appeared most desirable. Early achievements have been described by Smrcina et al.,[147] and further developments along the same lines have recently been reported by Nakajima et al.[148] Both research groups used copper complexes containing chiral amino ligands. For example, when substituted naphthol **184** was oxidatively coupled the corresponding biaryl **185** was formed in good yield [Eq. (48)]. The enantioenriched product had an *ee* value of 78% when a combination of copper(I) chloride and proline-based diamine **186** was used, while significantly lower enantioselectivities resulted when (−)-sparteine (**132**) was used as a ligand.[149]

The ester substituent on the naphthol was essential to achieve a good asymmetric induction in the coupling sequence. This behavior was explained by a necessary coordination of the copper catalyst in a chelate fashion to the substrate. The enantiodiscrimination is then believed to



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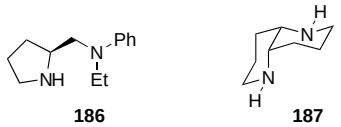
184 **185**

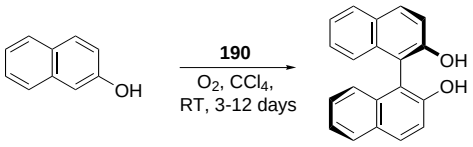


186 **187**

proceed by keto–enol tautomerism after oxidative carbon–carbon bond formation between the two naphthol units.

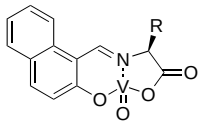
Recently, copper-catalyzed oxidative biaryl coupling reactions have also been investigated by Yang and Kozlowski, who used 1,5-diazadecalin (**187**) as a ligand.[150] Enantioselectivities of up to 93% *ee* were achieved in the coupling of **184** when 10 mol% of a 1:1 mixture of a copper(I) or copper(II) source and **187** were employed. Again, the ester substituent in the 3 position proved essential, and other substrates lacking this moiety gave lower enantioselectivities.

Chen and co-workers found that oxovanadium(IV) complexes **190** could be used as catalysts for the enantioselective oxidative coupling of 2-naphthols.[151] For example, the dimerization of 2-naphthol (**188**) in the presence of 10 mol% of **190** (with R = *i*Pr) gave **189** with 62% *ee* in 94% yield [Eq. (49)]. Other substrates afforded substituted coupling products with enantioselectivities in the range of 10–68% *ee*.



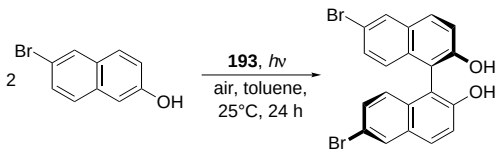
(49)

188 **189**



190

Another approach towards the asymmetric oxidative coupling of 2-naphthol derivatives was recently reported by Katsuki and co-workers.[152] A photopromoted aerobic coupling occured when salen–ruthenium complex **193** was used as the catalyst, and gave 2,2′-binaphthols with moderate to good enantioselectivties.[153] In contrast to various other systems, substituents at the 3 position of the 2-naphthols were not required. The best results were achieved with compounds bearing electron-withdrawing groups at C6. For example, the asymmetric coupling of 6-bromo-2-naphthol (**191**) in the presence of 5 mol% of **193** afforded **192** in 30% yield with 71% *ee* [Eq. (50)]. With 2-naphthol (**188**) itself, the corre-



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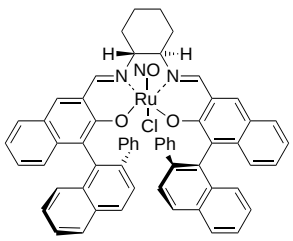
191 **192**



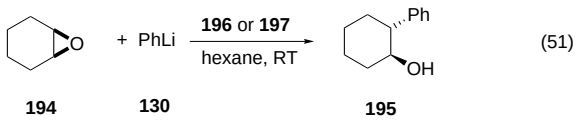
193

sponding product **189** was obtained with 65% yield and 57% *ee*.

It is noteworthy that these coupling reactions do not involve one of the species outlined in Scheme 1. Instead, aryl radicals are involved at the stage prior to dimerization which generate the binaphthylene upon formal combination.

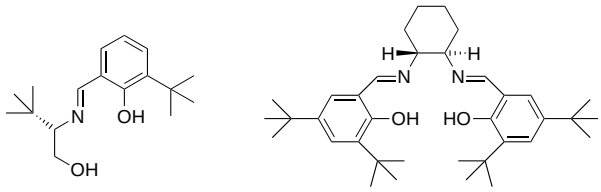
6. Asymmetric Ring Opening of Epoxides and Aziridines

A desymmetrization[154] of *meso*-epoxides such as **194** by means of enantioselective ring opening using phenyllithium (**130**) was developed by Oguni et al. [Eq. (51)].[155] The



(51)

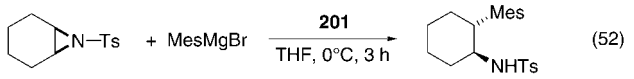
194 **130** **195**



196 **197**

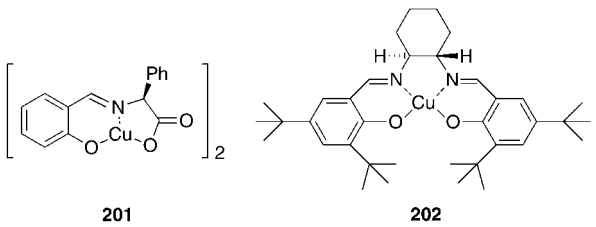
catalysts used in this study were either the tridentate Schiff base **196**, or salen ligand **197**, which afforded the corresponding alcohol **195** with enantioselectivities of up to 90% *ee*. Surprisingly, the reaction of the same substrate with alkyllithium reagents resulted in both low yields and enantioselectivities. It was suggested that the catalytically active species in the arylation was either a lithium alkoxide or a lithium amide which was initially formed by attack of phenyllithium on the imine moieties of the ligands.

Recently, Müller and Nury described a related transformation that utilized *meso*-aziridines as starting materials [Eq. (52)].[156] Aryl Grignard reagents were found to add to



(52)

198 **199** **200**



201 **202**

N-sulfonylaziridine **198** under copper catalysis to afford the corresponding products with moderate enantiomeric excesses. Whereas the transfer of the phenyl group from PhMgBr (**21**) occured with low enantioselectivities (best result: 29% *ee*), the catalyzed addition of mesitylmagnesium bromide (**199**) by 10 mol% of **201** gave **200** with 72% *ee*. Surprisingly, the absolute configuration of the phenyl addition product with **202** as the catalyst proved opposite to the one expected from the related alkyl Grignard addition.

Particularly noteworthy is the fact that these transformations described by Oguni et al.[155] and Müller and Nury[156] represent rare examples of asymmetric openings of epoxides and aziridines with carbon nucleophiles.[154, 157, 158]

7. Conclusion and Outlook

Although the great potential of catalytic asymmetric arylations is apparent, transformations of such type have only recently started to emerge as useful tools in organic synthesis. Many limitations still have to be overcome before these catalyses reach the same remarkable level of maturity as their corresponding counterparts in alkylation chemistry. Until now, general catalysts have only been found for a small number of reactions, and hence it is of no surprise that these rely on readily available ligands such as BINAP or related compounds. A major obstacle in the development of efficient asymmetric arylation reactions is the lack of practical aryl transfer reagents. Further studies can be expected to be devoted towards their improvement in order to broaden the scope of this reaction. Since many reactions are asymmetric variants of well-established viable cross-coupling reactions (or at least utilize substrates commonly used in those transformations), it is foreseeable that achiral cross-coupling variants will most likely have a major impact on the development of novel asymmetric aryl transfer reactions.

Appendix: Abbreviations

acac	= acetylacetonate
alaphos	= (2-dimethylaminopropyl)diphenylphosphane
BINAP	= 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl
BINOL	= 1,1′binaphthalene-2,2′-diol
BITIANP	= 2,2′-bis(diphenylphosphanyl)-3,3′-dibenzo[*b*]-thiophene
Boc	= *tert*-butoxycarbonyl
chiraphos	= 2,3-bis(diphenylphosphanyl)butane
Cy	= cyclohexyl
DAIB	= 3-*exo*-dimethylaminoisoborneol
dba	= dibenzylidene acetone
DIBAL	= diisobutylaluminum hydride
diop	= 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenyl-phosphanyl)butane
DMA	= *N*,*N*-dimethylacetamide
DME	= 1,2-dimethoxyethane
DMSO	= dimethylsulfoxide
EWG	= electron-withdrawing group
MeO-MOP	= 2-diphenylphosphanyl-2′-methoxy-1,1′-binaphthyl
Mes	= mesityl = 2,4,6-trimethylphenyl
NORPHOS	= 5,6-bis(diphenylphosphanyl)-2-norbornene

[2.2]PHANEPHOS = 4,12-bis(diphenyphosphanyl)-[2.2]paracyclophane
phephos = 2-dimethylamino-1-diphenylphosphanyl-3-phenylpropane
PMP = 12,2,6,6-pentamethylpiperidine
PPFA = 1-(2-diphenylphosphanylferrocenyl)ethyldimethylamine
PPFOMe = 1-(2-diphenylphosphanylferrocenyl)ethyl methyl ether
prophos = 1,2-bis(diphenylphosphanyl)propane
TADDOL = $\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-1,3-dioxolane-4,5-dimethanol
TBDPS = *tert*-butyldiphenylsilyl
Tf = triflate = trifluoromethanesulfonyl
TFA = trifluoroacetic acid
TIPS = triisopropylsilyl
TMBTP = 4,4′-bis(diphenylphosphanyl)-2,2′,5,5′-tetramethyl-3,3′-bithiophene
TMS = trimethylsilyl
TolBINAP = 2,2′-bis-(di-*p*-tolylphosphanyl)-1,1′-binaphthyl
Ts = tosyl = toluenesulfonyl

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