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Review

Synthesis and application of chiral monodentate phosphines in asymmetric hydrogenation

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Contents

Abstract

Chiral monodentate phosphines ligands were the first ligands to be investigated in the field of asymmetric hydrogenation. After years of neglect, these ligands have recently experienced a new renaissance. This review discusses the structural design of the most successful monodentate phosphines and, following a historical line, reports on their application in the asymmetric hydrogenation of C=C and C=O bonds.

Keywords: Asymmetric hydrogenation; Monodentate chiral ligands

1. Introduction

In the last decades the selective preparation of enantiopure compounds has become one of the major challenges for organic synthesis and it is very likely that this will remain in the focus of chemistry in the foreseeable future. Among all of the techniques considered thus far, asymmetric catalysis offers one of the most efficient and economical ways to achieve this goal [1]. In particular, homogeneous asymmetric hydrogenation mediated by transition metal catalysts modified by chiral phosphorus ligands is one of the first and most successful examples of practical asymmetric catalysis.

Based on the pioneering work on asymmetric hydrogenation by Knowles, Kagan and others in the late 1960s of the last century, extensive efforts were undertaken to further improve such reactions. In the early stages of the investigations, phosphorus ligands have proven to be beneficial due to their high affinity to late transition metals and their ability of enforcing catalyst activity. A large number of successful ligand concepts have been developed since the 1970s leading to Rh, Ir or Ru complexes able to effectively catalyze a number of C=C, C=O and C=N bond hydrogenations [2]. However, even if several industrial applications on a small to medium scale were established, the final breakthrough has so far not been reached, due to the low transferability of this technique whenever requirements change. Specifically tailored catalysts designed to serve in specified tasks are important tools for achieving high activity and enantioselectivity, but the real quest is to find ligand concepts which support catalyst activity and transfer the chiral information to a wide range of substrates [3]. In this context, the discovery of innovative and effective ligands is a key challenge for industrial and academic research. Besides a reasonable activity and enantioselectivity, novel catalysts for industrial applications need, however, to meet several additional requirements. The synthetic

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approach must be readily adoptable on large-scale processes and the key structure of the ligand needs to allow straightforward structural variations (ligand library). Furthermore, the application may not be restricted by potential violations of protected intellectual property [4].

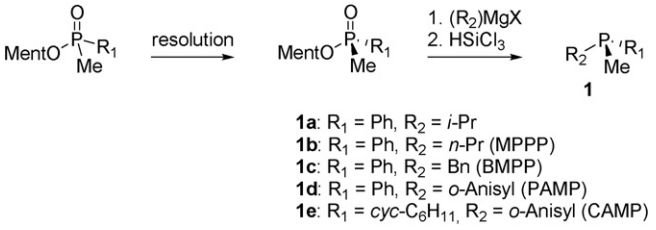
The development of new phosphine ligands for asymmetric hydrogenation has focused on the synthesis of bidentate ligands for nearly 30 years. Bidentate ligands claimed their privileged position due to their inherent characteristics of conformational rigidity and strong coordination to the metal center which appeared to be extremely important for the reaction outcome. However, at the end of the 20th century the predominant role of bidentates was challenged by the development of effective monodentate ligands, which subsequently received more and more attention [5,6].

Monodentate phosphorus ligands have the advantage of easier syntheses and tuning as compared with their bidentate counterparts. The applicability of monodentate ligands was successfully demonstrated in several reactions [7], so that nowadays monodentate ligands are fully accepted as an additional tool in asymmetric hydrogenation and are supposed to hold a vast potential for future applications. This review will first discuss the structural design of the most successful monodentate phosphines and then report on their application in the asymmetric hydrogenation of C=C and C=O bonds.

2. Design and synthesis of chiral monophosphines

Monophosphine ligands are among the earliest ligands studied for asymmetric catalysis and the number of candidates investigated in the literature is vast. In the following, the discussion is therefore restricted to those monophosphines which achieved the best results in asymmetric hydrogenation.

An important class in this context are phosphines whose chirality stems solely from a chiral phosphorus center [8]. The general method to accomplish the resolution of phosphine oxides or quaternary phosphinates is to use a chiral acid from the chiral pool (i.e. tartaric acid) [9]. As early as 1967 Mislow et al. [10] reported the synthesis of P-chiral ligands via resolution of diastereomeric phosphinates by the aid of a chiral auxiliary (i.e. menthyl group). Addition of Grignard reagents and reduction of the phosphine oxide with trichlorosilane yielded the chiral phosphine (Scheme 1). The nucleophilic displacement from chiral phosphinates is a convenient and efficient way to form chiral phosphines [10b].

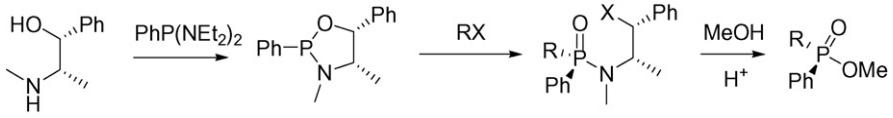


Scheme 1. Synthetic approach to P-chiral monodentate phosphines.

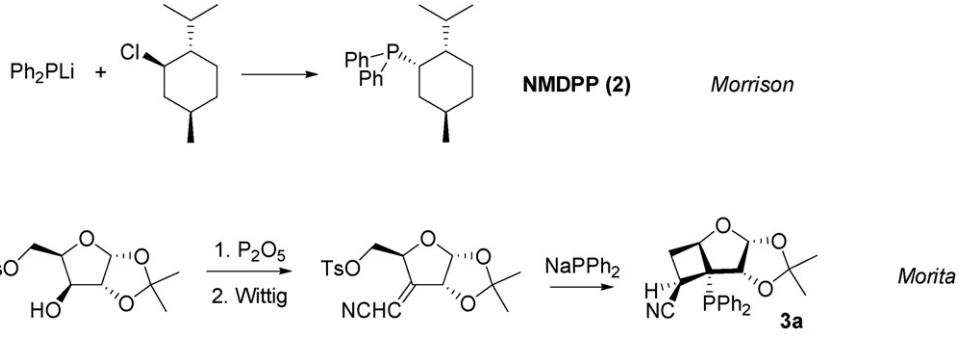
About 20 years later, Jugé and Genêt [11] and Corey et al. [12] described new methodologies for the preparation of enantiopure phosphinates avoiding chiral resolution. The stereodifferentiation was achieved by the thermodynamically controlled formation of chiral oxazaphospholidines (Scheme 2) or oxathiaphospholidines and the subsequent diastereoselective displacement by alkyl/aryl halides.

Tertiary phosphines with a stereogenic carbon in the side chain can be readily prepared, for instance by reaction of a chiral alkyl halide or tosylate with lithiumdiphenylphosphine. Representative examples are neomenthyldiphenylphosphine **2** (NMDPP) that can be prepared from inexpensive and easily available natural chiral precursors such as (−)-menthol [45] or ligand **3a** which was obtained from readily available D-glucose [58] (Scheme 3).

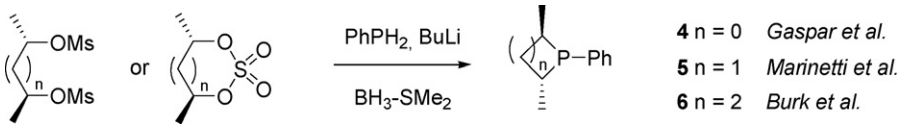
Monophosphines with phosphorus embedded in a cycle, can, in part, require a more tedious preparation, also depending on whether the phosphorus is actually a stereogenic center or not. General synthetic approaches for preparing phospholanes



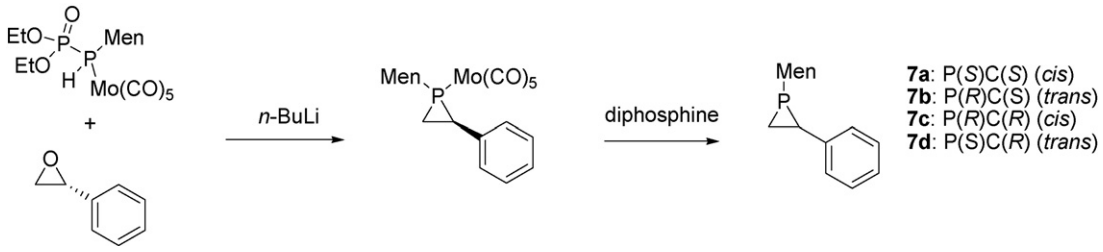
Scheme 2. Synthesis of P-chiral phosphines according to Genêt et al.



Scheme 3. Synthesis of NMDPP and chiral carbohydrate-based ligands.



Scheme 4. General synthetic approach to chiral phosphanes with phosphorus embedded in a ring.



Scheme 5. Synthesis of phosphiranes **7** via Mo complexes according to Marinetti et al.

[13] and phosphetanes [14] are typically based on the reaction of lithium phosphides and bis-mesylates or cyclic sulfates of optically active 1,4- or 1,3-diols (Scheme 4, $n = 1$ and 2, respectively).

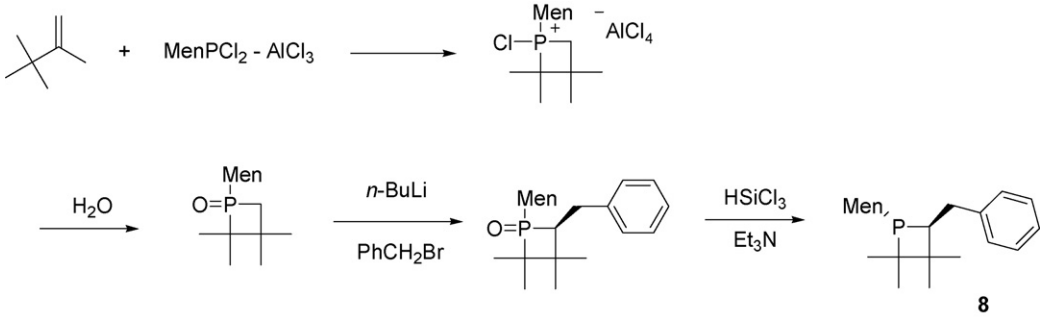
A similar general method has been successfully applied by Gaspar et al. to the synthesis of chiral phosphiranes ($n = 0$, Scheme 4) [15], which were previously reported by Marinetti et al. [16] via insertion of optical active phosphorus compounds into enantiopure styrene oxide (Scheme 5). Ligands **7** were stabilized as molybdenum phosphirane complexes and subsequent transmetallation with rhodium complexes yielded suitable precursors for asymmetric hydrogenation. The synthesis of chiral phosphiranes, which are interesting ligands because of the high s-character of the phosphorus lone pair, is unfortunately accompanied by high cyclic strain, which causes easy ring opening.

The same group reported the first synthesis of chiral phosphetanes of type **8** (Scheme 6), carried out according to the McBride approach, by reaction of branched olefins with chlorophosphine-$AlCl_3$ complexes [17]. The stereochemistry was regulated by chiral induction of L-menthyl as auxiliary. The acidic protons adjacent to the phosphorus atom enable further functionalization, for instance deprotonation with *n*-butyl lithium and subsequent quenching with benzyl bromide yields ligand **8**.

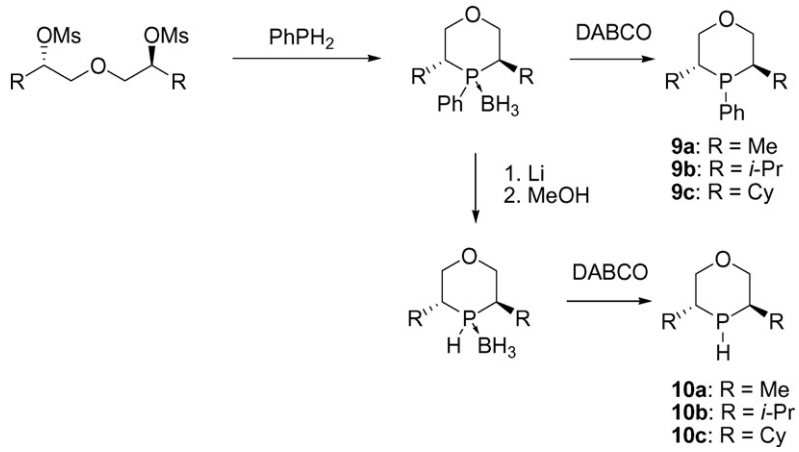
The first example of phosphanes with a larger ring ($n > 2$) was reported much later, in 2002, when Helmchen et al. [18] described the preparation of analogous phosphinanes where additional oxygen was incorporated into the ring to allow wider modularity (Scheme 7). The ligands were synthesized by mesylation of enantiopure diol ethers and subsequent reaction with dilithiophenylphosphine. Due to the high oxygen sensitivity, stabilization with BH_3 is required. The oxaphosphinanes boranes were deprotected with DABCO (1,4-diazabicyclo[2.2.2]octane) before pre-catalyst formation was carried out. The same group reported also the synthesis of a secondary oxaphosphinane **10** which represented the first example of secondary phosphine in asymmetric hydrogenation.

The general method previously described by Burk et al. for the synthesis of the phospholane (Scheme 4) suffered from major drawbacks, as it merely allowed a variation on the alkyl group due to the limited availability of precursors and the inevitable side reaction of elimination, which yields the diene after treatment with BuLi. The promising performance of this type of ligand in asymmetric hydrogenation, especially in the bidentate form (see DuPhos and BPE, Fig. 2), nevertheless encouraged other research groups to invest further synthetic effort in order to enlarge the ligand library of this class.

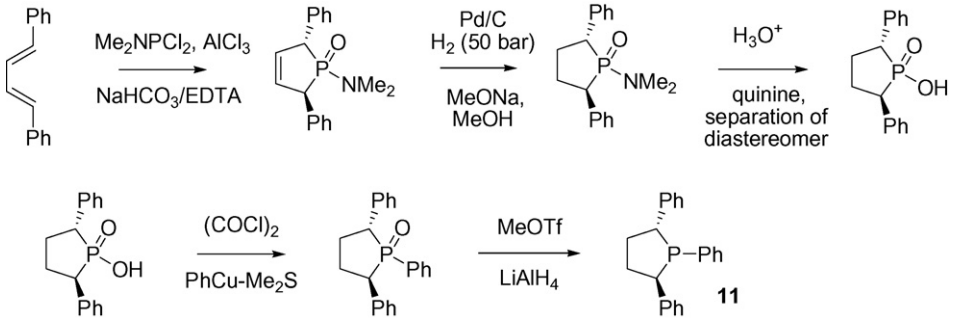
In 1999 Fiaud and Guillen reported an improved synthesis of enantiomerically pure *trans*-(2,5)-diphenylphospholane **11** via formation of the corresponding acid (Scheme 8) [19,20]. McCormack reaction of diphenylbuta-1,3-diene with Cl_2PNEt_2 followed by hydrogenation and isomerization yielded the *trans*-phospholane amide, which could in turn be hydrolyzed and resolved by crystallization of the diastereomeric salts. The



Scheme 6. Synthesis of phosphetane **8** according to Marinetti et al.



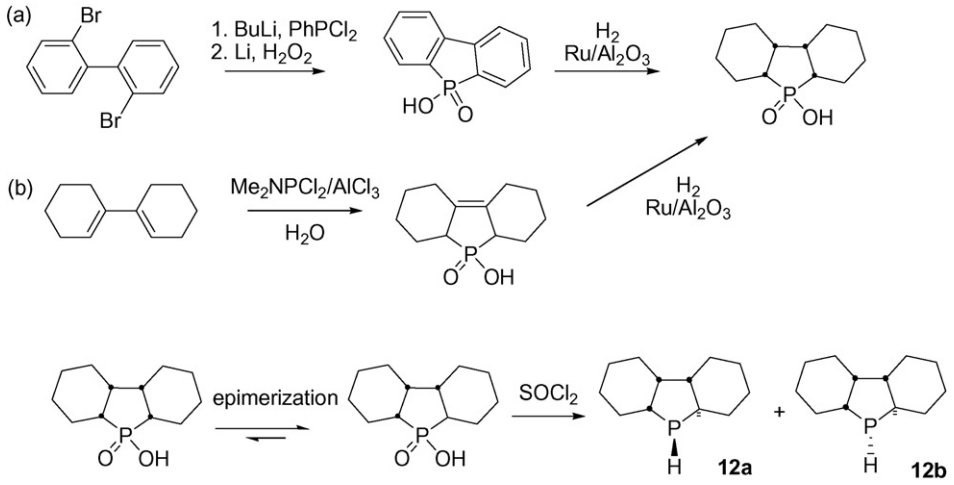
Scheme 7. Synthesis of oxaphosphinanes **9** and **10** according to Helmchen et al.



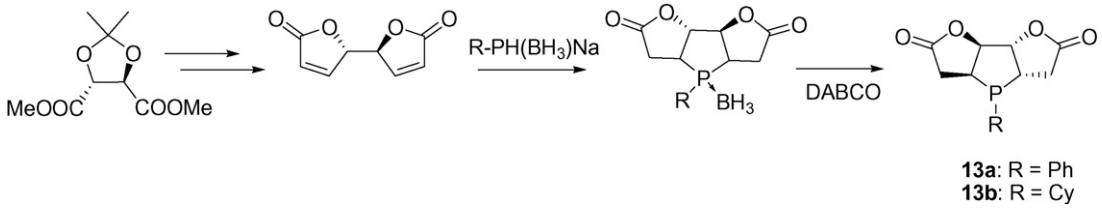
Scheme 8. Synthesis of chiral *trans*-diphenylphosphinophospholane **11** according to Fiaud et al.

phospholane **11** was obtained from the acid via two different synthetic procedures: (1) by reaction of the corresponding chloride with a lithium cuprate reagent which introduces the phenyl group or (2) by reduction with DIBAL-H and subsequent Pd-catalyzed coupling with iodobenzene. The resulting phosphine oxide is reduced with lithiumaluminum hydride and protected as a borane adduct.

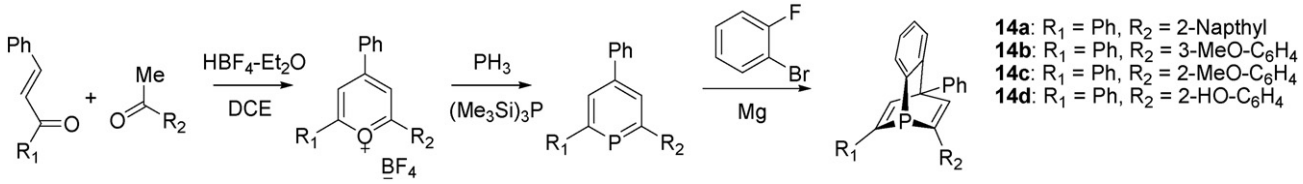
The Börner group reported the synthesis and catalytic application of monodentate chiral phospholanes **12** (Scheme 9) [21]. Two general synthetic sequences were envisaged. The key step of the first approach was the heterogeneous arene hydrogenation of dibenzophosphole acid, but unfortunately only one of the, in total, five possible diastereomers could be isolated. The X-ray structure analysis indicated a *cis*-selective hydrogenation. The second approach included an improved McCormack reaction to build up the basic ligand structure, so that follow up chemistry could yield ligand **12**. In order to broaden the access to other diastereomers, an extensive study on epimerization was



Scheme 9. Synthesis of phospholane **12** according to Börner et al.



Scheme 10. Synthesis of phospholane **13**.



Scheme 11. Synthesis of phosphabarrelenes ligands **14**.

conducted. As had been predicted by prior calculations, the stereocenter adjacent to the phosphorus atom allowed epimerization in the presence of base and subsequent acidification. Transformation of obtained acids to the corresponding secondary phosphines yielded two diastereomers, which were separated via the borane adduct. Unfortunately, deprotection of the single diastereomers led to epimerization of the stereogenic phosphorus atom.

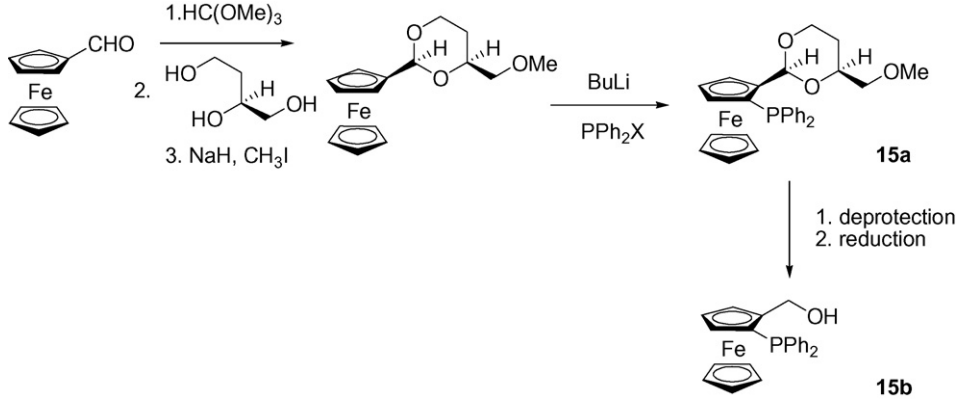
More recently, Börner et al. reported a second type of monodentate phosphole, based on tartaric acid, which allowed easy integration of chiral information [22]. The key step was a double hydrophosphination (Scheme 10).

A more exotic arrangement of the phosphorus in a six-membered ring was reported by Breit et al. in the synthesis of chiral phosphabarrelenes **14**, which contained highly pyramidalized phosphorus atoms [23]. The ligands were accessible by Diels–Alder reaction of substituted phosphabenzene and benzyne and subsequent separation of isomers (Scheme 11). These ligands possessed unique geometric characteristics, such as a remarkably strong constraint of the phosphorus in a pyramidal conformation, as well as an unusual chirality in case of different substituents R_1 and R_2.

At the end of the 20th century the synthesis of monodentate ligands with C_2 or C_1 symmetry found increasing interest. The group of Kagan, for instance, reported efforts on the synthesis of ferrocene-based ligands with planar chirality (Scheme 12) [24]. As part of the three-step synthesis starting from ferrocenecarboxaldehyde, a chiral acetal was used as auxiliary in order to control the stereochemistry of *ortho*-lithiation before quenching with Ph_2PCl.

In the first years of the new millennium, several independent research groups followed this trend by proving extraordinary transfers of chirality when applying monodentate phosphorus ligands based on binaphthol in different oxidation states [25–28]. The main advantages of this type of monodentate phosphorus ligands were their easier synthesis and high tunability compared to bidentate phosphines, as designated targets could typically be reached in a one- or two-step synthesis from inexpensive chiral binaphthol (see examples in Fig. 1).

Other than the binaphthyl backbone, those ligands shared several common elements, such as the phosphorus in a seven-membered ring. The closest related phosphine ligand is 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine **21** which has been known since the early 1990s when Gladiali and coworkers reported the first successful synthesis of this ligand class (Scheme 13) [25]. As initial step 2,2′-dimethylbinaphthyl **20** was synthesized via nickel-catalyzed Kumada coupling reaction of 1-bromo-2-methylnaphthalene its Grignard reagent [26].



Scheme 12. Synthesis of the (diphenylphosphino)ferrocenyl ligand **15**.

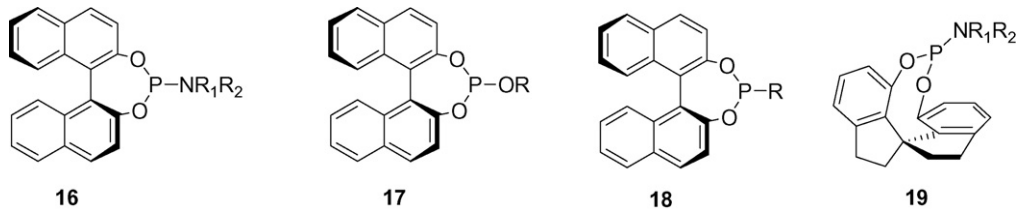


Fig. 1. Selection of chiral monodentate biaryl phosphites, phosphonites and phosphoramidites for asymmetric hydrogenations.

The racemic 2,2′-dimethylbinaphthyl **20** was selectively double-lithiated on the methyl groups and subsequently quenched with dichlorophosphines to yield the racemic 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines **21a**. Resolution of the enantiomers was carried out by forming diastereomeric complexes of a racemic mixture with (+)-di-μ-chloro-bis[(*S*)-*N*,*N*-dimethyl-α-phenylethylamine-2C-*N*]-dipalladium **22** [27]and subsequent separation via crystallization. Finally, the enantiopure monodentate phosphine **21a** (Ph-BINEPINE) was liberated by reacting the single diastereomeric complex with bidentate phosphines (e.g. dppe).

Some years later the group of Stelzer reported the synthesis of secondary phosphine based on phosphepine scaffold **21** (R = H) in good yields [28].

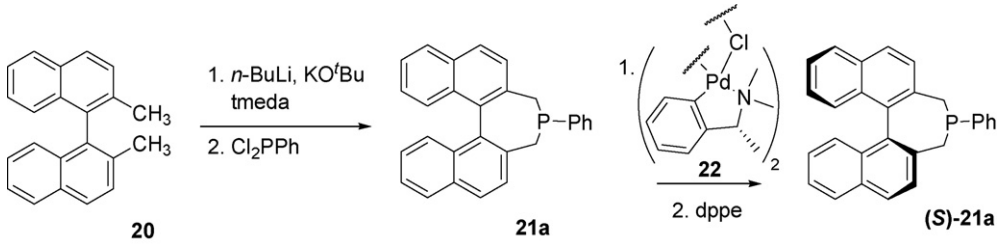
However, from a practical point of view the approaches developed by Gladiali et al. and Stelzer et al. caused some difficulties with respect to up-scaling and other industrial requirements due to the expensive auxiliaries and low overall yields.

A more convenient two-step pathway starting from enantiomeric pure 2,2′-binaphthol (>98% ee) was only recently established as nowadays enantiopure 2,2′-binaphthol is commercially available on a large scale [29,30]. The improved synthesis of binaphthophosphepines starts with a diesterification of enantiomerically pure 2,2′-binaphthol **23** with trifluoromethanesulfonic acid anhydride in the presence of pyridine (Scheme 14) [31]. The corresponding diester was obtained in quantitative yield and subsequent nickel-catalyzed Kumada coupling with methyl magnesium bromide led to 2,2′-dimethylbinaphthyl **20** in 95% yield [32]. Two different synthetic strategies were established to obtain 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine ligands **21**. In the first procedure double metallation of 2,2′-dimethylbinaphthyl **20** with *n*-butyl lithium in the presence of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) followed by quenching with commercially available dichlorophosphines gave ligands **21a** (P-phenyl) and **21b** (P-*t*-butyl) in 60–83% yield, which were both synthesized on >10g scale.

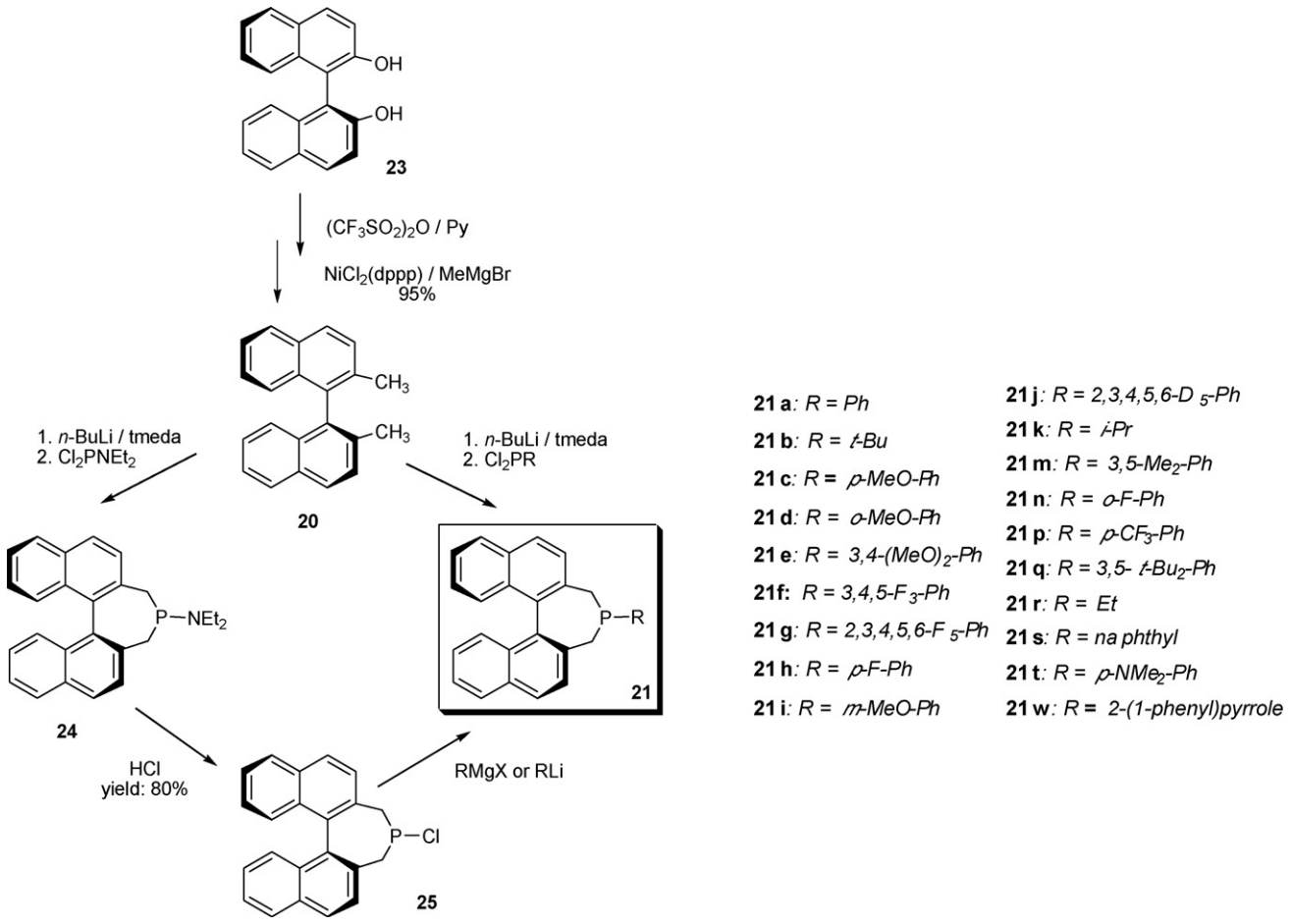
In the second procedure the dilithiated 2,2′-dimethylbinaphthyl **20** was quenched with diethylaminodichlorophosphine to produce the amino phosphepine **24** [33] which, upon treatment with gaseous HCl was converted into 4-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine **25** in 80% yield. This enantiomerically pure chlorophosphine was readily coupled with various Grignard or lithium reagents to render a broad selection of ligands **21**. The limited number of commercially available dichlorophosphines and the large diversity of Grignard compounds make the access through 4-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine **25** the route of choice for a library of ligands **21** (Scheme 14) [30].

In parallel to the work of Beller et al., the group of Zhang described a similar synthetic approach, however, the monodentate system was merely used as an intermediate since their research was dedicated to bidentate ligands and only preliminary unpromising results for ligand **21b** were obtained (hydrogenation of methyl 2-acetamidoacrylate aMe, 6% ee) [34]. In contrast to that extraordinary enantioselectivity was scored by bidentate ligands containing the phosphepine moiety (Scheme 15, **26**–**28**) [35].

While the group of Beller mainly focused on a variation of the substituent at the phosphorus in 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines, Widhalm et al. reported efforts on the α-substitution to the phosphorus atom (Scheme 16) [36]. The rise of new stereocenters closer to the metal promised a better transfer of chiral information. Starting from **21a**, synthesized according to literature procedures, the corresponding sulfide **29** was prepared. In addition to that, a deprotonation protocol was established which offered a huge variety of mono- and disubstituted ligands after simple quenching with electrophiles. The substitution was highly stereoselective, because only single diastereomers were obtained. The synthesis of compound **33b**



Scheme 13. First synthesis of phosphepines **21** according to Gladiali et al.

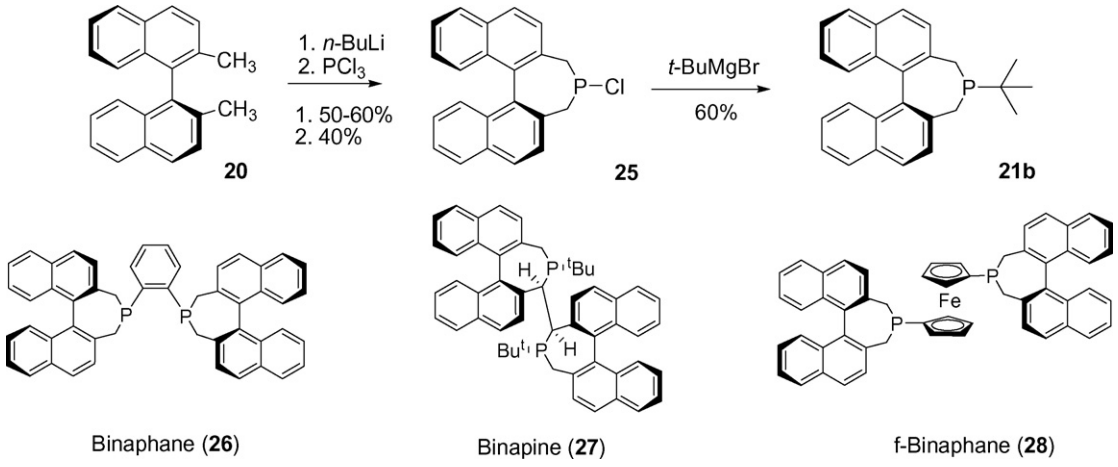


Scheme 14. Synthetic approach to 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines developed by Beller et al.

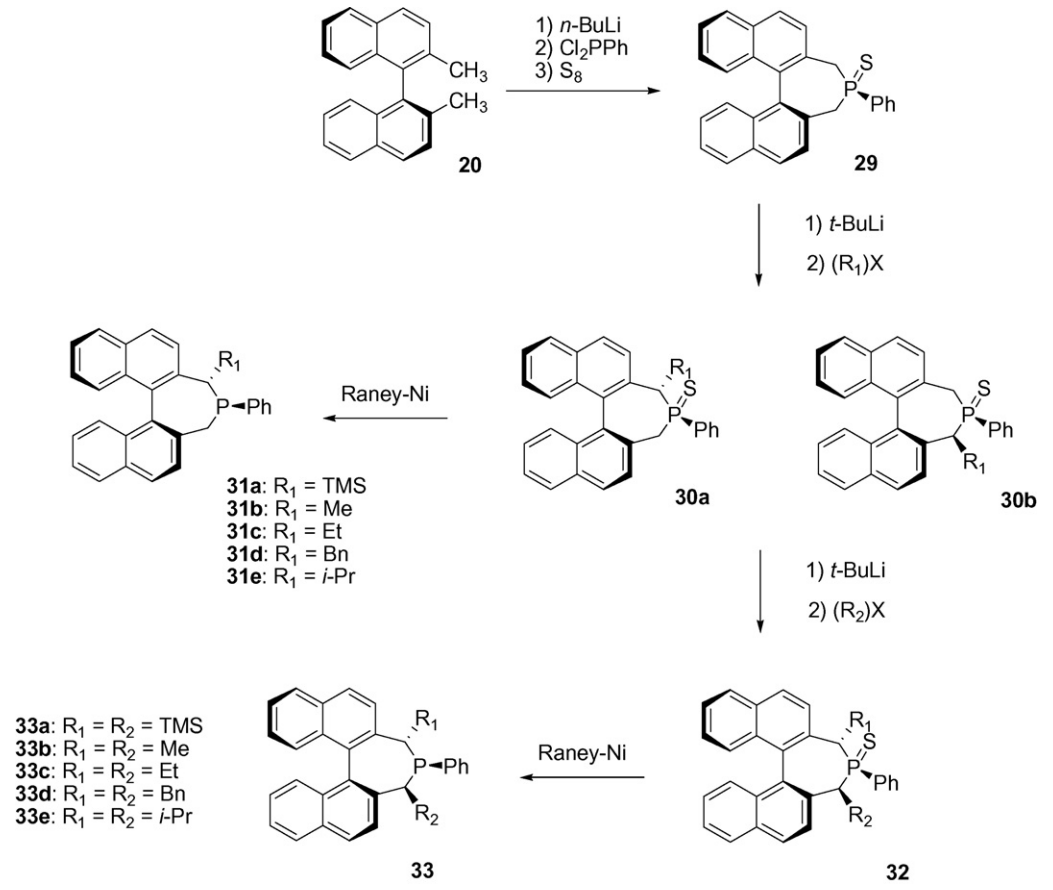
was also reported by us via the phosphine oxide and similar deprotonation/alkylation protocol [37]. The observed stereochemistry was identical and again only one diastereomer is formed.

Another atropisomeric ligand with additional chirality was described very recently by Jahjah et al. [38]. A derivative of HMOP, **34** was prepared by Ni-catalyzed coupling of 1,1′-binaphthyl-2,2′-diyl-bis(trifluoromethanesulfonate) with a racemic *o*-anisyl-phosphine borane complex, followed by oxidation with H_2O_2. The diastereomeric mixture was separated by column chromatography and the resulting enantiopure oxide was reduced with $HSiCl_3$ without epimerization (Scheme 17).

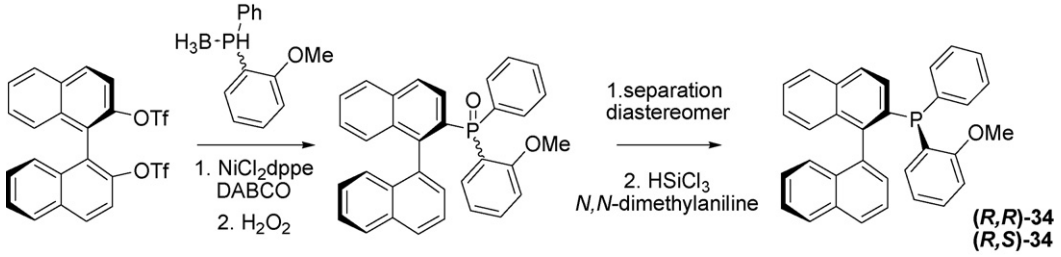
In addition to the ligands shown many more chiral monodentate phosphines have been reported in the literature. However, they have not been applied successfully in asymmetric hydrogenation and thus are excluded from this review.



Scheme 15. Synthesis of 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines by a protocol established by Zhang et al.



Scheme 16. Synthesis of α- and α,α′-substituted 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines.



Scheme 17. Synthesis of (*R*)-(2-methoxyphenyl)(1-(naphthalen-8-yl)naphthalen-2-yl)phenylphosphine **34**.

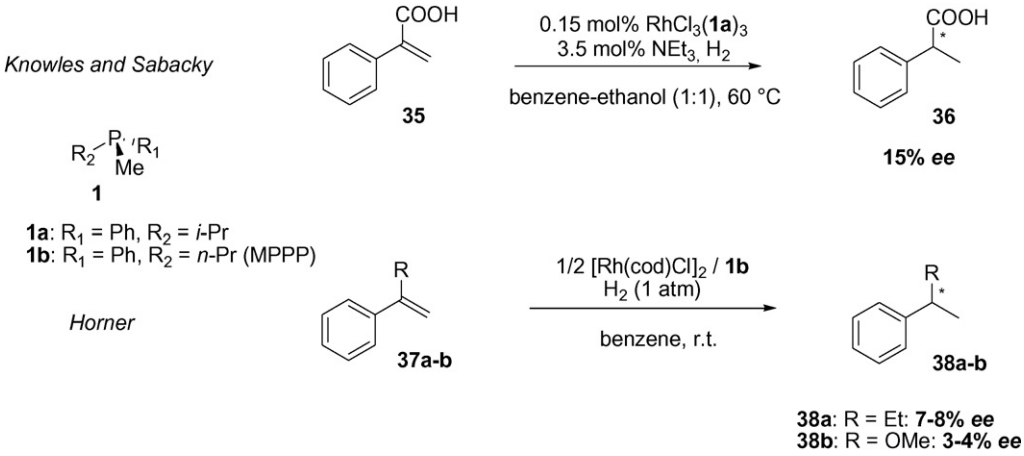
3. Catalytic asymmetric homogeneous hydrogenation

3.1. Reduction of C=C double bonds

Hydrogenation of C=C double bonds is of major importance in the field of asymmetric catalysis, as it allows, in fact, access to a variety of chiral compounds of different substitution. It is nevertheless true that a carbonyl group in α- or β-position to the double bonds is advisable in order to improve the transfer of chirality, so that unsaturated prochiral acid or amino acids, as well as enamides are favorite substrates for this reaction.

The beginning of homogeneous hydrogenation dates back to 1965 when the group of Wilkinson reported the first successful application of a well-defined complex $[RhCl(PPh_3)_3]$ (Wilkinson's catalyst) [39] in homogeneous hydrogenation of simple olefins with molecular hydrogen. Shortly after, Vaska and Rhodes obtained similar results with $Ir(CO)(PPh_3)_3$ as a catalyst (Vaska's complex) [40]. Monodentate phosphines were found to be active also in other metal-catalyzed reactions, while bidentate phosphines such as bis(diphenylphosphanyl)ethane depressed the hydrogenation. In subsequent mechanistic studies this relationship was further clarified, as the dissociation of a phosphane from Wilkinson's catalyst was found to be essential for the initiation of the catalytic cycle [41].

Based on this seminal work, the first chiral version was independently presented by the groups of Knowles and Sabacky [42] as well as Horner et al. [43] in 1968 right after Korpiun and Mislow [10] and Horner et al. [9] established a stereoselective approach to P-stereogenic derivatives (Scheme 18).



Scheme 18. First examples of asymmetric hydrogenation carried out with homogeneous catalysts.

In the reduction of α-phenylacrylic acid **35** a promising enantiomeric excess of 15% was obtained when using rhodium complexes with ligands of type **1**. Thereupon, various attempts focused on modifications of the ligand structure in order to improve the enantioselectivity, but unfortunately no significant improvement was reached [44]. Parallel to this work Horner et al. applied an *in situ* catalyst composed of $[Rh(cod)Cl]_2$ and 4 equiv. of optical active methylphenyl-*n*-propylphosphine **1b** in the asymmetric hydrogenation of α-ethylstyrene **37a** and α-methoxystyrene **37b**, only low enantioselectivities (<8% ee) were observed [43]. These partially disappointing results did obviously not stimulate a rapid adoption of the new method. Besides, P-stereogenic phosphanes were difficult to synthesize at that time and often suffered racemization. An important milestone was achieved when Morrison reported in 1971 improved enantioselectivities, up to 61% ee, applying neomenthyldiphenylphosphine (NMDPP) **2** in the hydrogenation of (*E*)-β-methylcinnamic acid [45].

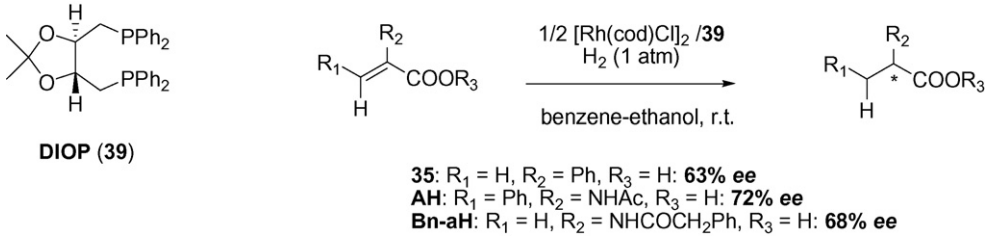
The real breakthrough in homogeneous asymmetric hydrogenation was reached in the early 1970s when Kagan and Dang bridged two monodentate phosphines to synthesize the first chiral chelating bidentate phosphine. Extraordinary enantioselectivities up to 72% ee were obtained in the presence of a rhodium-DIOP complex (Scheme 19) [46,47].

The improvement of this ligand concept was accompanied by two additional positive strategies. The Kagan group used tartaric acid as a carrier for the chiral information, which is accessible from the chiral pool, so that the complicated separation of ligand enantiomers was avoided. Additionally the chiral information was moved from the phosphorus atom to the backbone of the ligand as previously discussed by Morrison et al. [45], delivering at the same time two chemically equivalent phosphorus atoms (C_2 symmetry).

The great advantages presented by DIOP and the impressive enantioselectivities achieved in a number of substrates have surely played an important role in the general change of research focus from mono- to diphosphines, which came as a result. In the following period the concept of bidentate ligands was refined to further improve the enantioselectivity in asymmetric hydrogenation. Also chiral ruthenium [49] and iridium [50] complexes of those ligands were successfully employed in hydrogenation and the mechanism of the reaction was elucidated [51]. In Fig. 2 a selection of privileged bidentate ligand systems is presented. Enantioselectivities greater than 99% for a tremendous number of substrates were reported.

In the early stage of bidentate ligands, in 1972, Knowles et al. achieved enantioselectivities up to 90% ee in the hydrogenation of phenylalanine derivatives with the monodentate CAMP ligand **1e** by increasing the optical purity of the ligand to 95% and thanks to the introduction of *o*-anisyl group, which probably affords a hemilabile second coordination over the methoxy group (Scheme 20) [53,44,54].

Although an excellent enantioselectivity was achieved, the replacement of monodentate ligands by bidentate systems could not be impeded and led to a resting state in the research for monodentate ligands of approximately 30 years (Fig. 3). Also the pioneers of this research area directed their efforts to bidentate ligands, e.g. Knowles et al. synthesized a dimeric



Scheme 19. First asymmetric hydrogenation catalyzed by rhodium-diphosphine complexes [48].

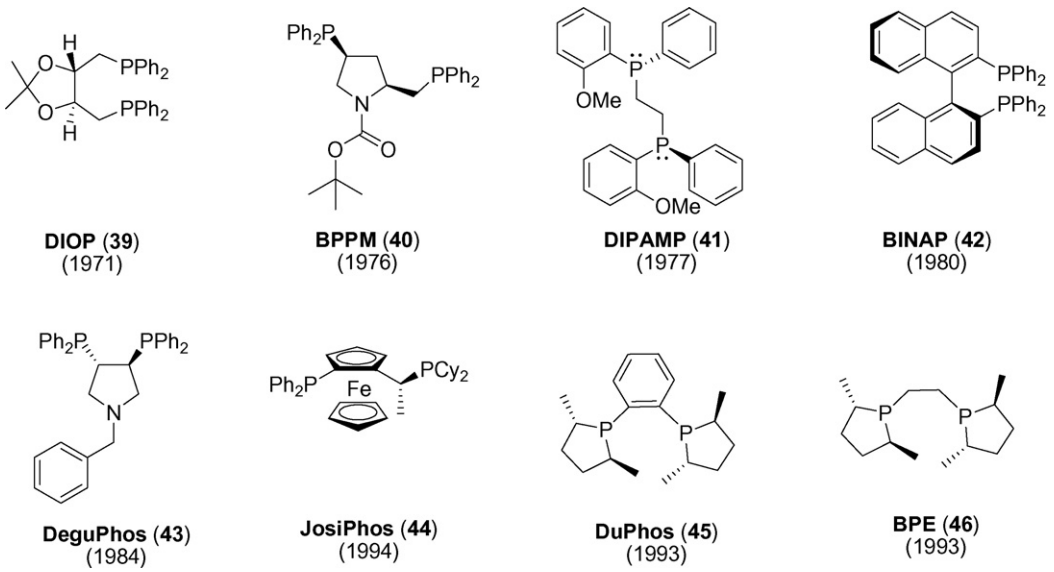


Fig. 2. Selection of privileged bidentate phosphine ligands [46,52].

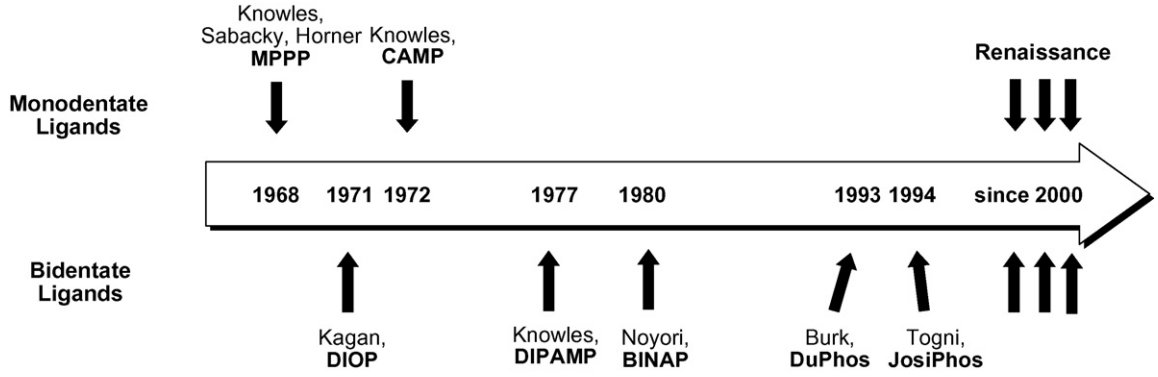
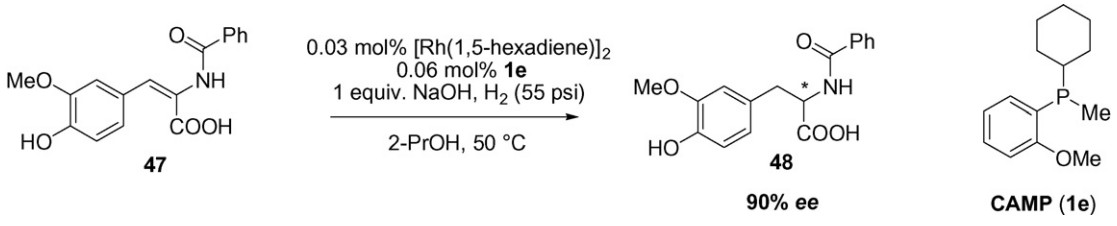


Fig. 3. Historical classification of chiral phosphine synthesis.

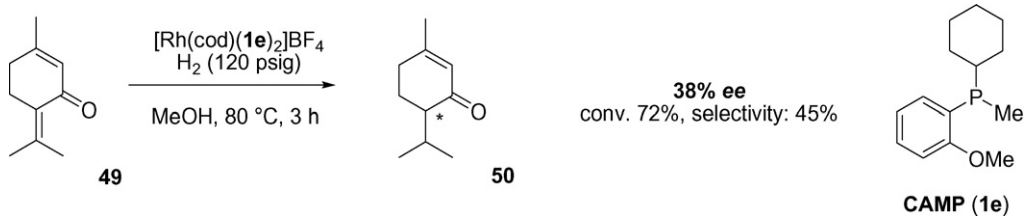
version of the PAMP ligand (Scheme 1, **1d**), so called DIPAMP **41** (Fig. 2) and achieved enantioselectivities up to 96% ee [55].

Although from time to time attempts were undertaken to refocus on monodentate systems the situation did not change significantly. For instance at the end of the 1970s the ligand concept presented in Scheme 1 was taken up again by Solodar for the asymmetric hydrogenation of challenging piperitenone **49**, thereby monodentate ligands induced higher enantioselectivity than bidentate systems, although the enantiomeric excesses obtained were rather low (up to 38% ee) (Scheme 21) [56]. The influence of reaction conditions on enantioselectivity and chemoselectivity were studied in detail but no considerable improvements were obtained.

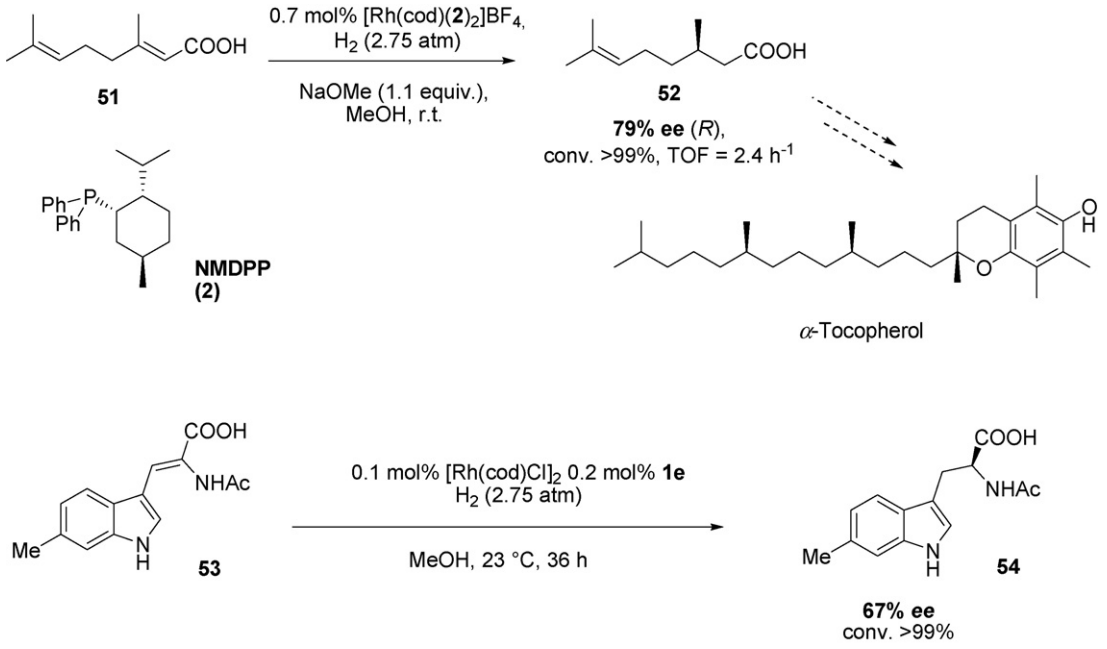
Valentine et al. modified the Morrison's NMDPP ligand and introduced a new stereogenic P-centre by substituting a P-phenyl group with a methyl. The new ligands were used for the reduction of **51** (Scheme 22), which resembled a precursor of α-tocopherol (vitamin E) or phylloquinone (vitamin K_1) [57]. The best enantioselectivities as high as 79% ee were obtained, however, with the rhodium catalyst of the unmodified ligand **2** $[Rh(cod)(NMDPP)_2]BF_4$. A study on the influence of matched and mismatched chirality (for the ligand with chiral phosphorus) on the outcome of the reaction did not bring any improvement.



Scheme 20. Asymmetric hydrogenation of α-dehydroamino acid derivate to yield an L-DOPA precursor.



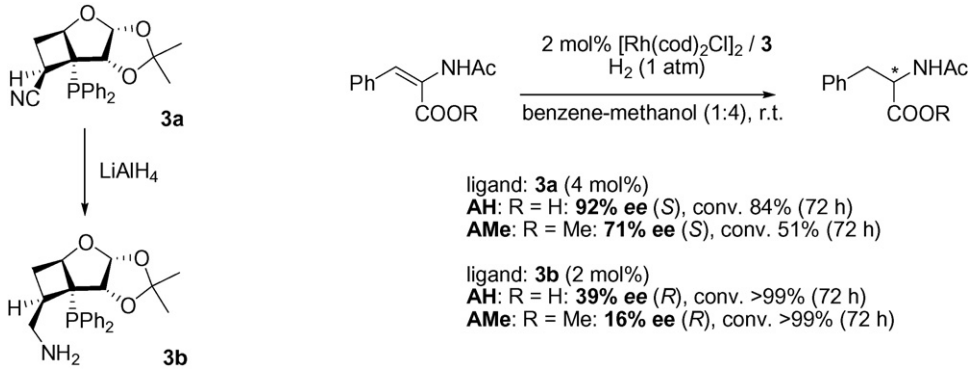
Scheme 21. Synthesis of piperitone **50** via asymmetric hydrogenation.



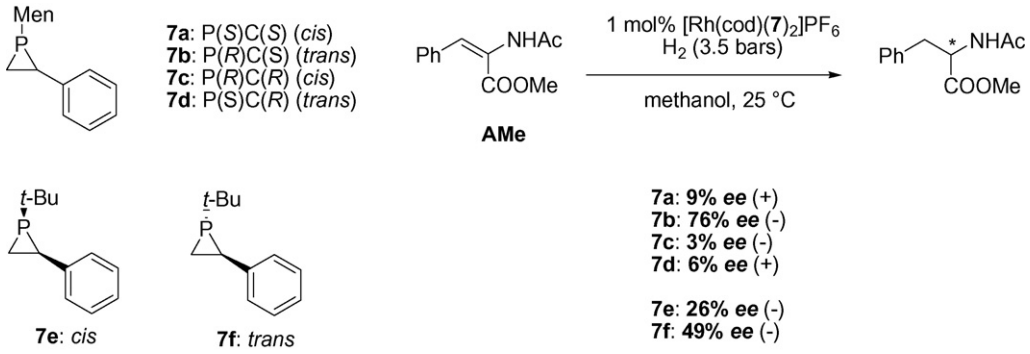
Scheme 22. Asymmetric hydrogenations carried out by Valentine et al.

The same group hydrogenated α-dehydroamino acids precursors in the presence of monodentate ligands, e.g. CAMP **1e**, in a comparative study with DIOP **39**. The results obtained led to a marginally higher enantioselectivity for DIOP (72% ee) as compared to CAMP (67% ee, Scheme 22).

In the mid-1980s Morita et al. developed an approach to sugar-based monodentate phosphines [58]. The catalytic potential was tested in the rhodium-catalyzed asymmetric hydrogenation of *N*-acetyl dehydrophenylalanine and the corresponding methyl ester (Scheme 23). Excellent enantioselectivity of 92% ee was obtained, albeit long reaction times were necessary. A competitive experiment performed with DIOP as ligand led to somewhat lower enantioselectivity (75% ee) and demonstrated the uncommon properties of the monodentate ligand **3a** under the conditions described. The drawback of the long reaction time was overcome by increasing the initial hydrogen pressure, but unfortunately this resulted in a deterioration of the enantioselectivity. At a metal–ligand ratio of 1:1 the enantioselectivity dropped to 31% ee and 1 week was necessary to reach full conversion. This result was in keeping with previous



Scheme 23. Asymmetric hydrogenation applying sugar-based monodentate ligands by Morita et al.



Scheme 24. Phosphiranes as ligands in asymmetric hydrogenation.

observations by Knowles et al. which suggested 2 equiv. ligands with respect to the metal to be necessary for a monodentate ligand to provide an efficient catalyst [59]. However, ligand **3b**, synthesized by reduction of **3a**, displayed a converse performance, since a slight increase of enantioselectivity and a reasonable conversion were obtained utilizing a metal–ligand ratio of 1:1. Due to the presence of the NH_2-group, the authors assumed that ligand **3b** could adopt a bidentate coordination in a six-membered chelate ring. Ligands **3a** and **3b** were tested also in the hydrogenation of itaconic acid derivatives where ligand **3a** exhibited once more an extraordinary enantioselectivity up to 90% ee.

Marinetti et al. carried out a matched and mismatched study of all diastereomeric combinations of ligand **7** in the hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester (AMe, Scheme 24). The best performance was shown by ligand **7b** with an enantioselectivity of 76% ee, while all other combinations yielded almost racemic mixtures [16]. Marinetti et al. assumed a better transfer of chirality, due to the *cis*-position of the phenyl group with respect to the metal, which caused steric hindrance and in consequence a formation of a more stereospecific pocket. This assumption was confirmed by changing from L-menthyl to *tert*-butyl group (**7e** and **7f**) as also in this case the *trans*-system led to higher enantioselectivity.

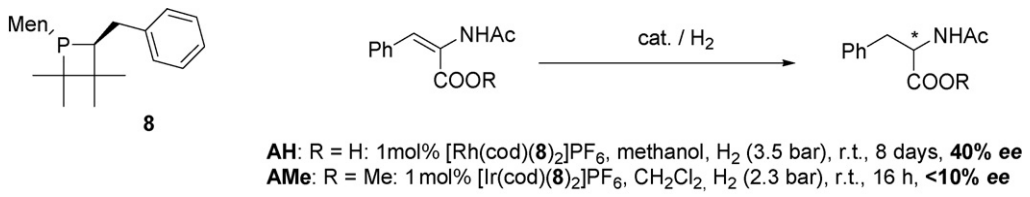
Later the same group described the expansion of the ring size of the ligand (Scheme 25) [17]. Ligand **8** was subjected to hydrogenation benchmark tests, but unfortunately the standard protocol, e.g. hydrogenation of *N*-acetyl dehydrophenylalanine with rhodium catalyst obtained only low catalytic activity (8 days reaction time) and moderate enantiomeric excess of 40% ee. After switching to iridium as metal source, improved activity after 16 h was observed, but accompanied by lower enantioselectivity (<10% ee).

In 1997 the ferrocene ligand **15a** obtained by Kagan et al. was investigated in the reduction of *N*-acetyl dehydrophenylalanine with cationic rhodium complexes under standard conditions [24]. Good enantioselectivity of 87% ee and yield (87%) were achieved. Furthermore, Kagan et al. presented an access to hydroxy ligand **15b** by removal of the chiral auxiliary of ligand **15a** and subsequent reduction with sodium borohydride. Obviously the free hydroxyl functionality had a disordered effect on enantioselectivity (30% ee), while full conversion was reached in the applied time frame (Scheme 26).

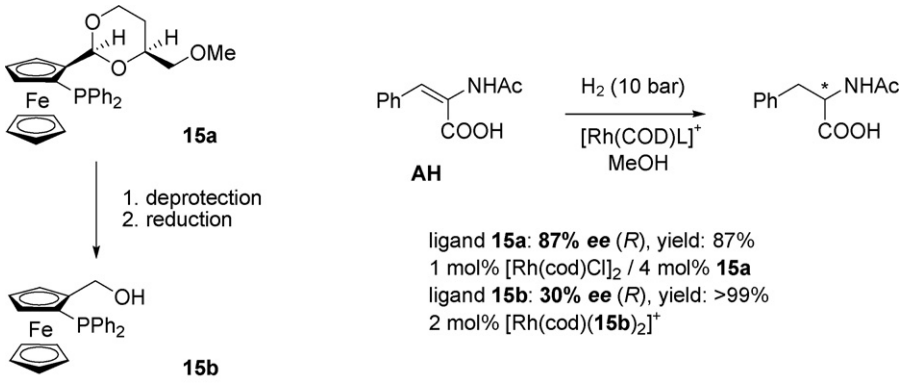
At the end of the 20th century the predominant role of bidentate ligands changed and monodentate ligands received more attention.

Pioneering work in the second age of monodentate ligands was presented in the late 1990s by Guillen and Fiaud [19] applying a monodentate phospholane ligand (*R*,*R*)-**11** (Scheme 27), which resembles the structural motif of DuPhos **45**. Albeit the group of Burk demonstrated in one of their early articles the potential of ligand (*R*,*R*)-**5** substituted with methyl groups in the hydrogenation of AMe (60% ee (*R*)) and dimethyl itaconate ($ItMe_2$, 65% ee (*R*)) with catalyst activities up to 500 h^{-1} (TOF), their research interest focused on the development of new chiral bisphosphines and **5** was mainly used as an intermediate or building block [13]. However, Fiaud obtained an enantioselectivity of 82% ee in the rhodium-catalyzed hydrogenation of AMe using an *in situ* catalyst composed of 1 mol% $[RhCl(cod)]_2$ and 2.1 equiv. of ligand **11** per rhodium.

Later on, the same group reported efforts on improving the enantioselectivity by switching from $[Rh(cod)Cl]_2$ as metal source to $[Rh(cod)_2]BF_4$ which resulted in a significant increase of enantiomeric excess to 93% ee [20]. The scope and limitation of ligand **11** was investigated on various substrates. Thus, dimethyl itaconate was hydrogenated in 55% optical yield, while for the corresponding acid a selectivity of 73% ee was obtained. Additionally *N*-acetyl enamides, for instance (*Z*)-*N*-(1-phenylprop-1-enyl)acetamide, were hydrogenated with good



Scheme 25. Monodentate phosphetane ligands for asymmetric hydrogenation.



Scheme 26. Asymmetric hydrogenation to *N*-acyl phenylalanine applying ferrocene-based monodentate ligands.

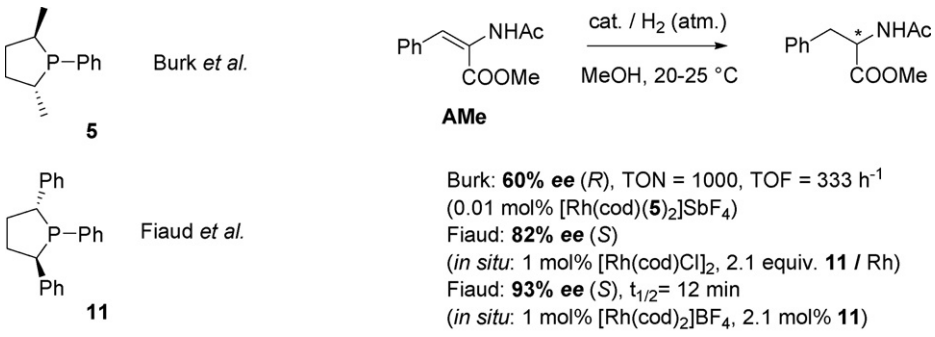
enantioselectivities up to 73% ee. During their research they also investigated the possibility of stabilizing the air-sensitive phosphine through formation of its respective phosphonium tetrafluoroborate salt and liberate the phosphine directly during the formation of the catalyst precursor. This air stable salt provided a slight decrease of enantioselectivity (86% ee (*R*)), accompanied by higher catalyst activities, in the hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester with comparable reaction conditions as previously reported by them [60].

The renaissance of monodentate ligands was furthermore driven by conceptual review articles of Kagan [5] and Börner [6], who predicted a better transfer of the chiral information due to the catalyst structure. As pointed out by Börner et al. it was ironic that Kagan, who had initiated the rapid development of chelating diphosphanes with DIOP in the first place, anticipated the incoming upsurge of monophosphines with the statement that: "Since in the early time of asymmetric hydrogenation there were no major improvements in enantioselectivities using rhodium/monophosphine complexes [. . .] However [. . .] This [recent results] leaves good hope that a suitable tuning of the structure of phospholane will lead to excellent ligands for asymmetric hydrogenation." (Lagasse and Kagan, 2000) [5].

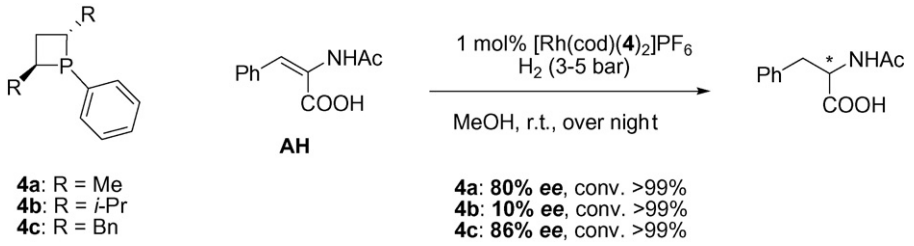
As a matter of fact, nowadays various monodentate systems based on the basic structure motif of Fig. 1 (**16–18**) have proven to be highly active in diverse classes of asymmetric hydrogenations with enantioselectivities >99% ee and a few representatives have been commercialized. Important contributions in this area came independently from Feringa and de Vries et al. [61] (phosphoramidites **16**), Reetz et al. [62] (phosphites **17**), and Pringle and Claver et al. [63] (phosphonites **18**). Furthermore, excellent enantioselectivity was shown by Zhou and co-workers applying monodentate spiro phosphoramidites (SIPHOS, **19**) [64] and many others [65].

However, during this time some progress on the use of monodentate phosphines was also reported. Marinetti et al. adopted the synthetic strategy of DuPhos–ligands, via formation of cyclic sulfates, for the synthesis of monodentate phosphetanes **4** (Scheme 28) [66]. Three ligands out of the huge number of the ones potentially accessible were chosen for testing their abilities in asymmetric hydrogenation of *N*-acetyl dehydrophenylalanine. In comparison to former achievements with phosphetanes an improved enantioselectivity up to 86% ee was achieved, albeit the *iso*-propyl derivative gave only low selectivity.

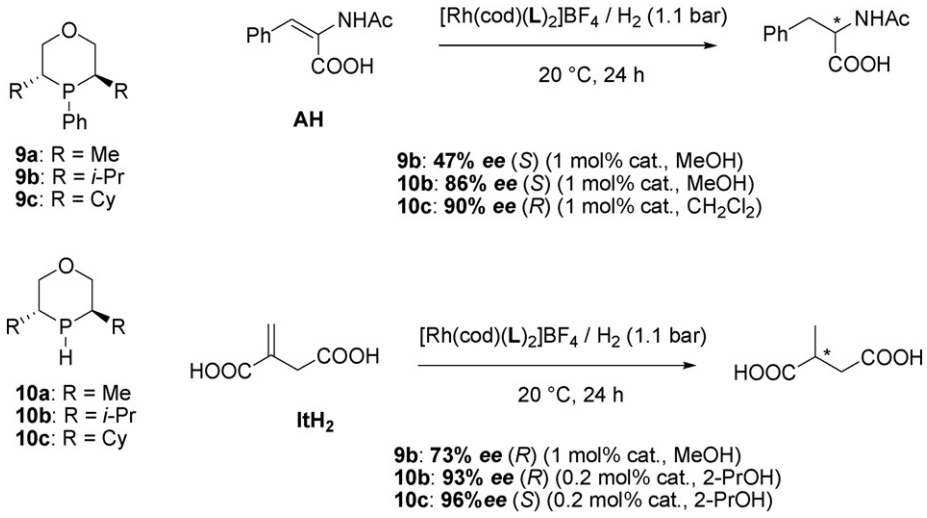
Afterwards Helmchen et al. portrayed the extraordinary catalytic behavior of oxaphosphinanes in asymmetric hydrogenation reactions (Scheme 29) [18]. Preliminary experiments with ligand **9b** revealed just a moderate enantioselectivity of 47% ee for the hydrogenation of *N*-acetyl dehydrophenylalanine. The authors suspected that the P-phenyl substituent exerted an unfavorable sterical shielding of the rhodium and consequently replaced the phenyl group with a proton. Indeed, significant higher enantioselectivity (86% ee) and reaction rates were observed with the secondary phosphine **10b**. This conceptual approach was further confirmed in the hydrogenation of itaconic acid, where 73% ee for **9b** and 93% ee for **10b** were respectively achieved. Even better enantioselectivity, up to 96% ee, was induced by structural modifications at the α-position adjacent to the phosphorus atom.



Scheme 27. Asymmetric hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester (AMe) with monodentate phospholanes.



Scheme 28. Asymmetric hydrogenation to *N*-acyl phenylalanine applying phosphetane ligands established by Marinetti et al.



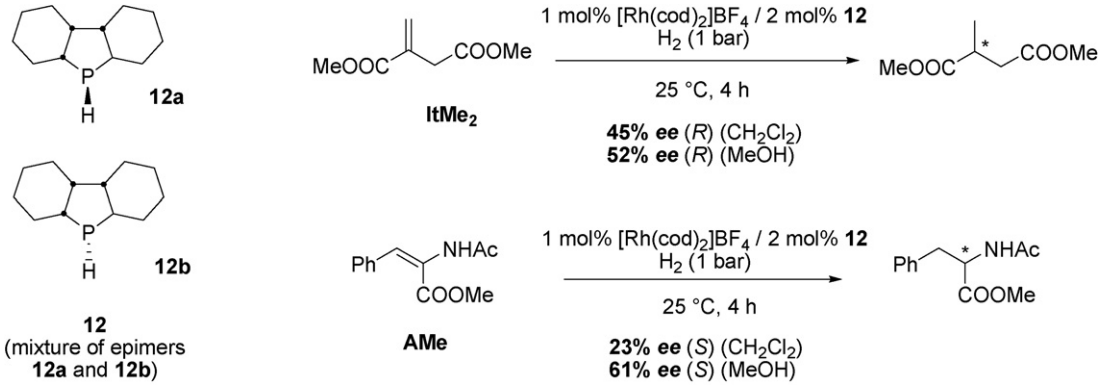
Scheme 29. Asymmetric hydrogenation in the presence of oxaphosphinanes by Helmchen et al.

Very recently in 2006, the Börner group reported the synthesis and catalytic application of monodentate chiral phospholanes **12** (Scheme 30) [21]. However, only a mixture of diastereomers could be tested in the hydrogenation of dimethyl itaconate and *N*-acetyl dehydrophenylalanine methyl ester, so that moderate enantioselectivities were obtained.

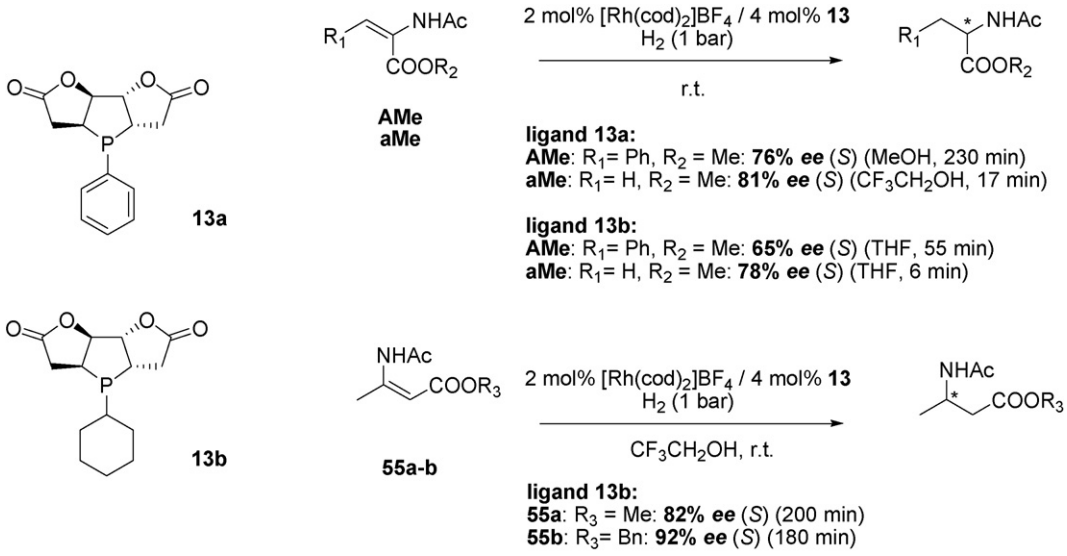
Immediately after, Börner et al. reported a second type of monodentate phospholes, based on tartaric acid [22]. The obtained ligands were tested in the asymmetric hydrogenation of α- and β-dehydroamino acid derivates. Here, an excellent enantioselectivity of 92% ee was observed for the hydrogenation of β-dehydroamino acid derivatives (Scheme 31).

In the same year Breit et al. reported the synthesis of a completely new class of chiral ligands: the chiral phosphabarrelenes **14**, which contain a highly pyramidalized phosphorus atom [23]. Unfortunately, testing these monodentate ligands in asymmetric hydrogenation protocols yielded only moderate enantioselectivities in the hydrogenation of itaconic acid dimethyl ester. However, a sharp improvement of enantioselectivity up to 90% ee was obtained when the phosphabarrelene **14d** was assembled in a bidentate ligand system in combination with the chiral phosphonite **18** (Fig. 1, R = Cl) (Scheme 32).

Driven by the success of monodentate phosphorus ligands based on the binaphthyl backbone of Fig. 1, a thorough



Scheme 30. Secondary phosphine based on phospholane in asymmetric hydrogenation.



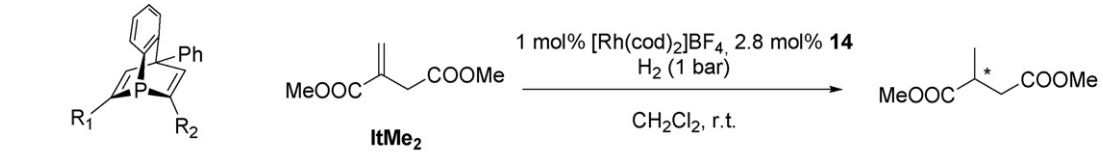
Scheme 31. Application of monodentate phospholane ligands based on tartaric acid.

investigation on the activity of phosphines based on the 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine scaffold **21** in asymmetric hydrogenation was conducted in our group. We applied the ligand tool box **21** in various asymmetric catalytic reactions. A first set of catalytic experiments was dedicated to the rhodium-catalyzed asymmetric hydrogenation of α-amino acid precursors [30c]. Here, methyl (*Z*)-α-acetamidocinnamate AMe and methyl α-acetamidoacrylate aMe were chosen as model systems. Best enantioselectivities up to 95% ee were achieved in toluene with high catalyst activities (TOF 1000–6000 h^{-1}), even though toluene is actually an unusual solvent for hydrogenation due to catalyst inhibition [67]. In some cases a slight improvement of enantioselectivity and reactivity was found when catalytic amounts of tenside sodium dodecylsulfonate (SDS) were added in the reaction. An in-depth analysis indicated a crucial influence of the substitution pattern at the phosphorus atom. Best enantioselectivities were obtained with aryl systems, while alkyl derivatives led to low enantiomeric excesses. In the case of asymmetric hydrogenation of AMe a detailed study of various ligands with substituted-aryl groups at the phosphorus demonstrated no significant change in enantioselectivity, when electron-donating or electron-withdrawing functionalities were situated in the *para*-position. Analogous substitution in *ortho*-position decreased the enantioselectivity. For the reduction of aMe a converse behavior was observed since substitution on the aromatic unit improved the enantioselectivity (Scheme 33).

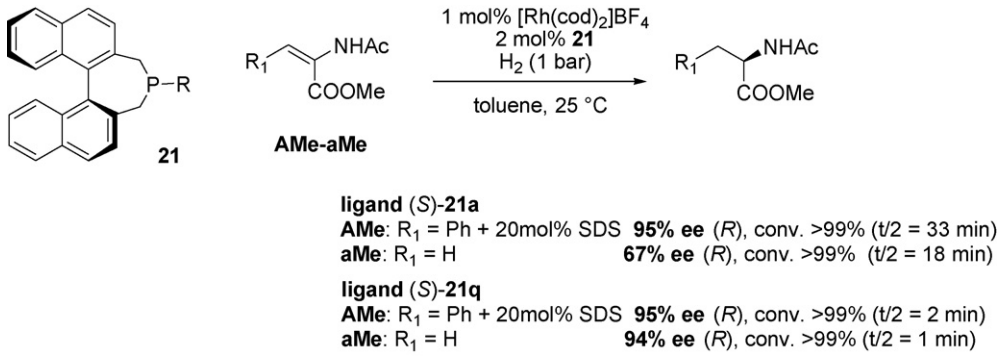
Subsequently, the potential of the ligand library **21** was tested in the asymmetric hydrogenation of dimethyl itaconate $ItMe_2$ (Scheme 34). Here, the best results (enantioselectivities up to 88% ee) were obtained in dichloromethane as solvent.

A more convincing approach to obtain enantiopure itaconic acid was recently reported by one of us (Scheme 35) [68]. Excellent enantioselectivities up to 97% ee were obtained when subjecting itaconic acid to a rhodium-catalyzed transfer hydrogenation under mild reaction conditions in the presence of well-defined cationic $[Rh(nbd)(\mathbf{21a})_2]^+$ complexes. As hydrogen source, formic acid was chosen which gives carbon dioxide as the only side product. Notably, by utilizing the corresponding dimethyl ester or the two possible monomethyl esters under the same conditions a decrease of enantioselectivity was noticed, accompanied by a switch of the product configuration. A comparative study was carried out by testing several monodentate ligands. The obtained results emphasized the potential of ligands **21**, since such a level of enantioselection had been observed previously only in two cases with bidentate diphosphines such as BINAP.

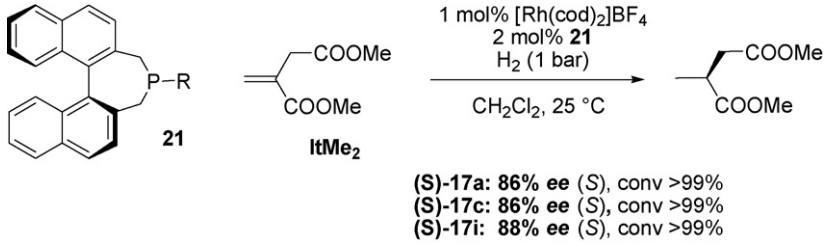
The ability of ligand class **21** to effectively induce chiral transformation has also been studied in the hydrogenation of *N*-acyl enamide **57** by the group of Reetz (Scheme 36) [62f]. The



Scheme 32. Chiral phosphabarrelenes by Breit et al. in asymmetric hydrogenation.



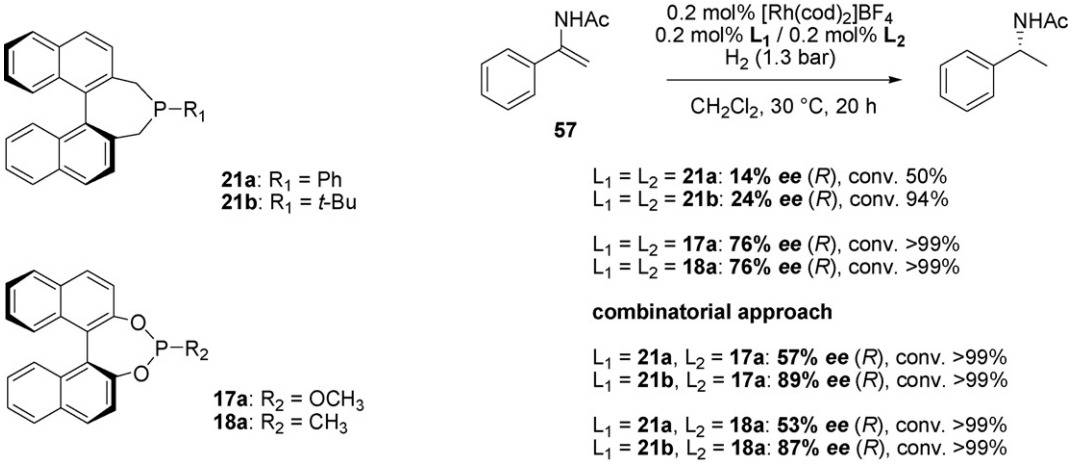
Scheme 33. Asymmetric hydrogenation of AMe and aMe in the presence of ligands **21**.



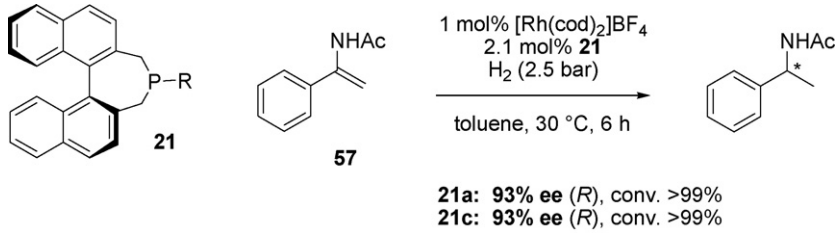
Scheme 34. Asymmetric hydrogenation of dimethyl itaconate $ItMe_2$.

Scheme 35. Transfer hydrogenation of itaconic acid derivatives.

obtained enantioselectivities are comparably low, but surprisingly the *tert*-butyl-substituted ligand **21b** (conversion: 94%; enantiomeric excess: 24% (*R*)) showed better selectivity and conversion than the phenyl-substituted ligand **21a** (conversion: 50%; enantiomeric excess: 14% (*R*)), while in most other hydrogenation benchmark tests the opposite behavior is observed. However, in combination with BINOL-derived phosphites or phosphonites a significant enhancement of enantioselectivity up to 89% ee was found. This combinatorial approach impressively demonstrates one major advantage of monodentate phosphorus



Scheme 36. Asymmetric hydrogenation of *N*-acyl enamides [62f].



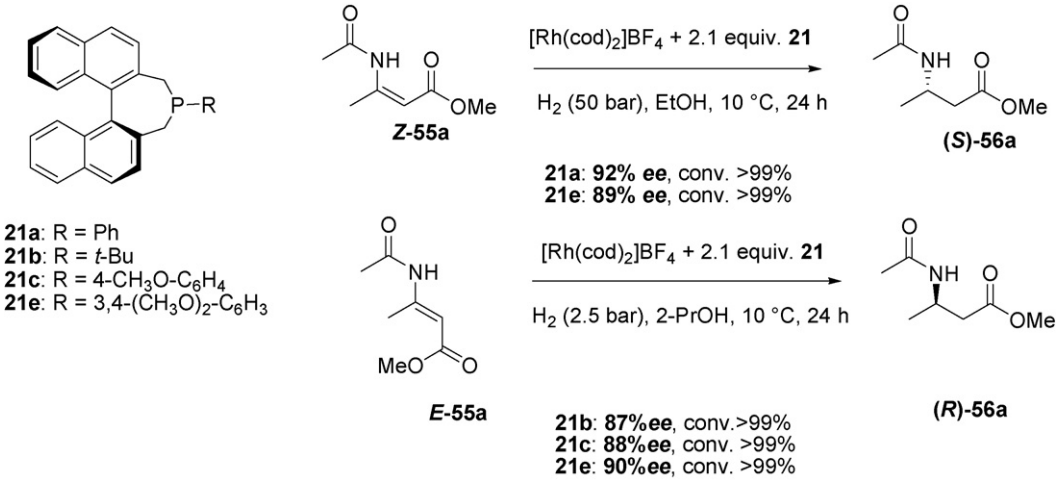
Scheme 37. Asymmetric hydrogenation of *N*-acyl enamides.

ligands, as the reaction outcome can easily be tuned by different combination of ligands [62f,69].

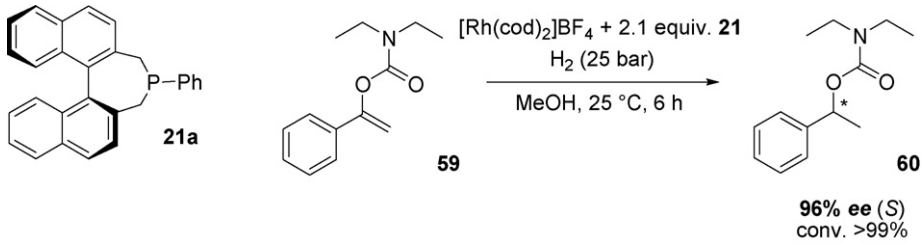
Following the original work of Reetz et al., our group investigated the reaction in presence of chiral monodentate 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine **21** in more detail (Scheme 37) [30d]. After optimization of different reaction parameters enantioselectivities up to 93% ee were achieved with a rhodium catalyst containing 2 equiv. of ligand **21a**. The enantioselectivity was largely dependent on the nature of the substituent at the phosphorus atom. Substrates featuring electron-donating substituents on the phenyl led to the highest ee, up to 95%. This is the best enantiomeric excess obtained up to now with monodentate phosphine ligands in this reaction. Substrates containing electron-withdrawing groups were hydrogenated with somewhat lower enantioselectivities.

In the last decade the hydrogenation of β-aminoacid precursors has found increasing interest, because the resulting products are useful building blocks for various novel biologically active compounds [70]. Hence, we reported on the successful application of ligand class **21** in the rhodium-catalyzed asymmetric hydrogenation of β-dehydroamino acids derivatives to give optical active β-amino acids derivatives [71]. First experiments highlighted the necessity of different reaction conditions for the *E*- and *Z*-isomer (Scheme 38). Good enantioselectivity (90% ee (*R*)) for the *E*-isomer was obtained by using 2-propanol at 2.5 bar hydrogen pressure, while higher pressure (50 bar) in ethanol turned out to be beneficial for the *Z*-isomer (92% ee (*S*)). Noteworthy, a switch of product configuration was observed depending on the nature of the double bond, which had been rarely reported before [72]. Furthermore, a higher reaction rate was monitored for the *Z*-isomer, in spite of the converse behavior reported for most other catalysts [73]. Surprisingly, in the case of hydrogenation of *E*-**55a** a good enantioselectivity was achieved with the *t*-butyl-substituted derivative **21b**, while P-alkyl ligands **21** usually provide poor to moderate enantioselectivities in all the other catalytic hydrogenation reactions (*vide supra*). However, in the hydrogenation of the corresponding *Z*-isomer the catalyst containing ligand **21b** was completely inactive. Here, the best enantiomeric excess was reached by ligand **21a**. The scope of the ligand system was confirmed on the hydrogenation of several β-dehydroamino acids derivatives. An improved enantioselectivity of 94% ee was obtained when the methyl ester was replaced by the ethyl ester. Some mechanistic investigations indicated the necessity of 2 equiv. of ligand per metal, which was in agreement with previous observations by Knowles et al. [59]. This circumstance offered the possibility for a combinatorial ligand approach. We adopted this concept and combined ligand **17a** with achiral phosphorus ligands. Unfortunately, no significant positive effect was observed.

More recently, we carried out an enantioselective reduction of enol carbamates, which is an alternative approach to chiral benzylic alcohols [37]. Pioneering work in the field of asymmetric hydrogenation of enol carbamates was reported by Feringa, de Vries, Minnaard and co-workers who obtained enantioselectivities up to 98% ee with rhodium-catalysts containing monodentate phosphoramidites (MonoPhos family) [61l,74]. Utilizing compound **59** as model substrate, we investigated in detail various reaction parameters achieving enantioselectivities



Scheme 38. Hydrogenation of *E*-**55a** and *Z*-**55a** with different 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines **21**.



Scheme 39. Hydrogenation of enol carbamate **59** in the presence of different 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines **21**.

up to 96% ee with an *in situ* catalyst composed of $[Rh(cod)_2]BF_4$ and ligand **21a**. Noteworthy, the catalyst gave similar enantioselectivity (94–96% ee) over the entire temperature range 10–90 °C (Scheme 39).

The influence of α- and α,α′-substitution in the ligand was also explored in a comparative study. Ligand **33b** induced the best enantioselectivity for some enol carbamates and caused in most cases a switch of configuration compared to the parent ligand [37].

In the rhodium-catalyzed hydrogenation of AH and AMe, with the α,α′-dimethyl substituted ligand **33b**, Widhalm et al. reported enantioselectivities comparable to the unsubstituted system, while monosubstituted and other disubstituted derivatives led to moderate selectivity. Interestingly, enantioselectivity and activity were unchanged even when using only 1 equiv. of ligand with respect to rhodium. Once more, substitution led to a switch of product configuration (Scheme 40).

So far, monodentate phosphines have been most frequently used in the asymmetric hydrogenation of C=C bond featuring different substitution patterns. However, their application has not yet matched the vast and reliable use of bidentate systems. The number of examples reported is still limited and more difficult substrates, such as unfunctionalized olefins, have not been explored by this tool.

3.2. Application in C=X bonds hydrogenation

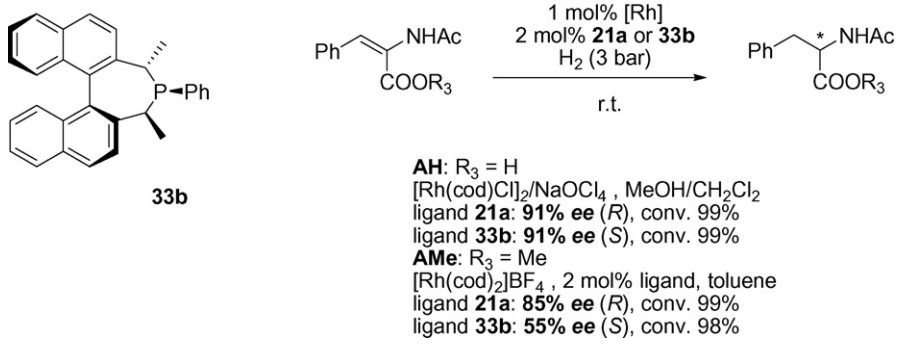
The asymmetric hydrogenation of carbonyl and imino groups provides a straightforward route to chiral alcohols and amines. In the case of hydrogenation of ketones many Ru or Rh complexes modified with bidentate phosphine have been successfully employed. In contrast to that, much less is known on the use of monodentate ligands in this kind of reaction. Even poorer results can be retrieved from scanning the literature on hydrogenation of C=N bonds; in spite of the synthetic importance of this reaction in industry, so far comparatively little research has been conducted on this topic.

Some P-stereogenic phosphines were initially tested in the hydrogenation of acetophenone and butan-2-one; the enantioselectivities were very poor, albeit comparable to those achieved in the reduction of olefins at that time. Rh complex of **1c** reacted very slowly at room temperature under 1 atm hydrogen pressure with acetophenone (8% ee) and butan-2-one (2% ee) [75]. Negligible ee's (<1%) were scored using ligand **1f** in the same hydrogenation [76]. A major improvement was realized in 1975 at Monsanto when CAMP **1e** was examined as ligand for the hydrogenation of methyl acetylacetate into methyl β-hydroxybutyrate (71% ee) [77].

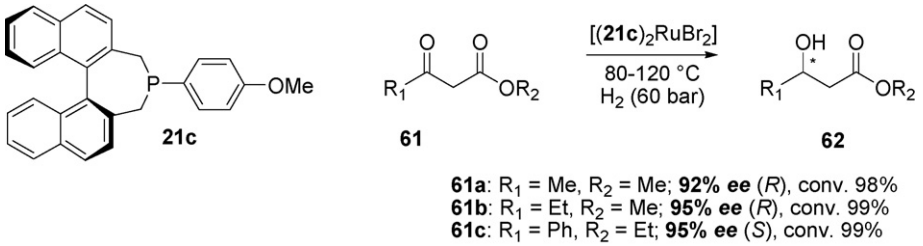
The Rh complex of CAMP **1e** has been as well exploited in the reduction of cyclopentanetrione into an α-ketol, intermediate of total synthesis of prostaglandin E_1, with modest enantioselectivity (68%) [78].

In 2004 we described the first successful application of monodentate phosphines to the catalytic hydrogenation of β-ketoesters [79]. Monodentate phosphepine **21** formed efficient Ru catalyst for the enantioselective reduction of a number of β-ketoesters into β-hydroxyesters. Even at high temperatures (100–120 °C) enantioselectivities up to 95% were practicable [80]. Interestingly, other monodentate ligands of excellence in hydrogenation such as phosphites, phosphonites and phosphoramidites give inferior performances than phosphines in this reaction (Scheme 41).

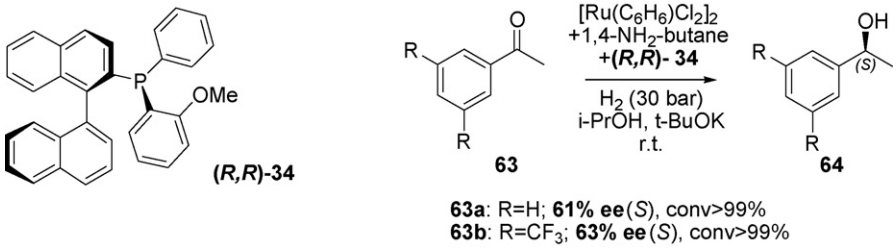
Very recently monodentate ligands were successfully employed in the hydrogenation of simple aromatic ketones. Ligands **21** were associated to chiral pyridinebisimidazoline ligands in the transfer hydrogenation of prochiral ketones yielding



Scheme 40. Hydrogenation of acetamido cinnamic acid AH or ester AMe catalyzed by Rh complexes of ligands **21a** and **33b**.



Scheme 41. Ruthenium-catalyzed hydrogenation of β-ketoesters in the presence of phosphepine **21c**.



Scheme 42. Hydrogenation of aromatic ketones in the presence of ligand **34**.

enantioselectivities up to 95% ee [81]. This result is nevertheless of little relevance since the chiral induction is equal or lower than for the sole pyridinebisimidazoline ligand with an achiral triphenylphosphine. More significant achievement was gained by ruthenium complexes of P-chirogenic atropisomeric ligand **34** for the hydrogenation of acetophenone [38]. Interestingly, the presence of an achiral diamine was crucial for the activity and moderate enantioselectivities could be obtained (Scheme 42).

4. Conclusion

In comparison to diphosphines, chiral monophosphine ligands still play a minor role with regard to highly enantioselective transformations in the field of asymmetric hydrogenation. This is, however, not due to a general lack of providing a chiral environment to the metal center, but rather explained by the initial failure of matching the triumph of bidentate ligands. In light of the recent results, it is now proven that monophosphines are able to provide extremely high enantioselectivity, in some cases even higher than their bidentate counterparts, while being often advantageous with regard to synthesis. The success of monophosphines in C=C hydrogenation has consequently been accompanied by an observable shift of attention towards this ligand class, in spite of the so far disappointing results for the synthesis of amine and alcohols from ketones or imines.

A major direction for the future is therefore to expand the scope of applications. Recent results seem to point to a favorable synergic effect when combining different synthetic approaches, i.e. different combinations of chirality (atropisomerism/stereocenters). Here, novel monodentate ligands might allow for more difficult benchmark reactions, e.g. asymmetric reductive amination, hydrogenation of prochiral allylic alcohols, etc. The inherent flexibility of monodentate ligands furthermore holds the promise of improving catalytic systems by heterocombination of ligands (chiral–chiral as well as chiral–achiral), a decisive advantage which distinguishes monodentate systems from bidentates. Thus, we expect that this class of ligands will attract more research groups in the incoming years and that novel asymmetric catalytic reactions will be developed.

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