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PERSPECTIVE

Hybrid bidentate phosphorus ligands in asymmetric catalysis: Privileged ligand approach *vs.* combinatorial strategies

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In this perspective the development of chiral phosphorus ligands for asymmetric catalysis is discussed, with a special focus on hybrid bidentate phosphorus ligands, in particular phosphine-phosphoramidites. An attempt is made to compare privileged ligand and combinatorial approaches to ligand development – for which the class of phosphine-phosphoramidite ligands is well suited – highlighting differences, similarities and their complementary use.

Introduction

Homogeneous transition metal catalysis has become a widespread synthetic tool in contemporary organic chemistry and its relevance continues to increase. The majority of total syntheses of natural products and process routes to pharmaceuticals published nowadays contain at least one transition metal catalyzed step.[1,2] The main advantages arise from increased selectivities and a higher atom economy when using catalysis compared to conventional methods. Moreover, transition metals allow for unprecedented transformations and functional group interconversions, which enable chemists to 'skip' a number of steps in an existing total synthesis or process route or even establish an entirely new route. However, finding a good catalyst for a given transformation often represents a challenge. The key element in catalyst optimization is finding the right ligand offering high activity and (*enantio*-)selectivity for the desired substrate. Numerous strategies have been reported in recent decades to speed up this ligand discovery process, including the use of high-throughput automated catalyst screening and analysis,[3,4] mass-spectrometric techniques,[5–7] iterative library deconvolution,[126] and dynamic combinatorial libraries of ligands.[8,9] For these high throughput experiments one can use libraries of existing ligands, preferably using privileged ligand scaffolds, or decide to make a unique new library with sufficient ligand diversity, preferably based on leads to have a proper starting point. In either case, design and synthesis of new ligands lies at the heart of this discovery process and efforts towards novel systems, which improve existing reactions or even enable new transformations, are ongoing and still in high demand.

This perspective focuses on recent developments in the area of chiral phosphorus ligands and aims to dissect the wide variety of ligand design concepts into two major classes, *i.e.* privileged *versus* combinatorial ligands. To put these recent developments into perspective, the discovery of chiral phosphorus ligands for asymmetric hydrogenation is discussed briefly. Moreover, the emerging class of hybrid bidentate phosphorus ligands is discussed in more detail here as they display characteristics of both the privileged as well as the combinatorial approach. It should be noted that this perspective is not a comprehensive review but intends to conceptually order a number of recent approaches to phosphorus ligand design.

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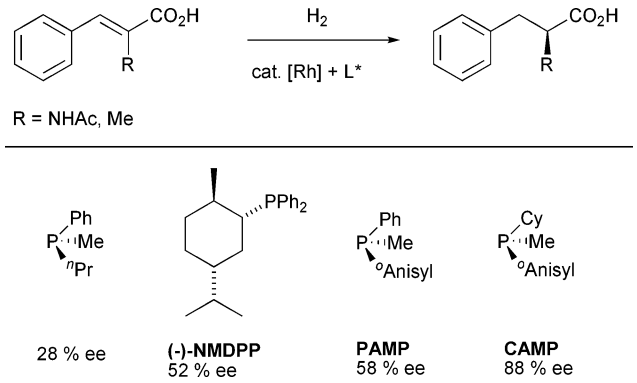
Monodentate P-chirogenic phosphines

The evolution of chiral phosphorus ligands is strongly coupled to the development of asymmetric hydrogenation.[127] In fact, it was only after the discovery of chiral phosphorus ligands that efficient asymmetric hydrogenations became feasible. In 1968, the first ligands that were found to induce enantioselectivity in asymmetric hydrogenations were optically active tertiary phosphines,[128–130] introduced by Horner[10] and Knowles.[11] The neutral rhodium catalysts based on (*R*)-methyl-n-propylphenylphosphine gave low *ee* values up to 28% in the hydrogenation of α-acylaminoacrylic acid derivatives (Scheme 1).[12] These selectivities were improved to up to 52% *ee* soon afterward by the group of Morrison and co-workers using a monodentate phosphine derived from (–)-menthol (NMDPP), which contains the chiral information on carbon instead of phosphorus.[13] Incorporation of *o*-anisyl and cyclohexyl substituents in PAMP and CAMP on the P-chiral ligand of Knowles resulted in enantioselectivities up to 88% *ee*.[14] In addition, cationic rather than neutral Rh-complexes were used that gave more active and selective catalysts. The potential of the, in that time, novel asymmetric hydrogenation reaction was demonstrated in the industrial synthesis of L-DOPA using the complex [Rh(**CAMP**)$_2$(cod)]BF$_4$.[15] However, the initial successes of these monodentate phosphines were soon overshadowed by their bidentate analogues and it took almost thirty years



Scheme 1 Rh-catalyzed asymmetric hydrogenation of cinnamic acid derivatives with chiral monodentate phosphines.

until chiral monodentate phosphorus ligands were rediscovered (*vide infra*).

Bidentate phosphines

Kagan made an important breakthrough in 1971 with the development of a chiral bidentate phosphine based on tartaric acid, DIOP (Fig. 1).[16] Catalysts based on this ligand achieved up to 72% *ee* for the hydrogenation of acylaminocinnamic acids, which he ascribed to two factors. Firstly, rigidity and stronger binding is enforced by bidentate coordination, minimizing conformational ambiguity. Secondly, a C_2-symmetric catalyst reduces the number of possible catalyst-substrate complexes by a factor two.[17] Today we know, however, that neither bidentate coordination nor C_2 symmetry are prerequisites for highly enantioselective catalysts (*vide infra*).

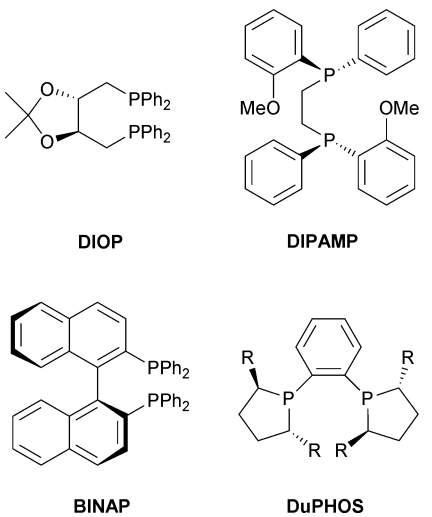


Fig. 1 Privileged bidentate phosphorus ligands.

Knowles took advantage of bidentate coordination and chirality at phosphorus, resulting in the synthesis of DIPAMP.[18] This ligand achieved for the first time enantioselectivities above 90% *ee* and quickly replaced CAMP in the synthesis of *L*-DOPA giving the optically active drug in up to 95% *ee*, an achievement for which Knowles was awarded the Nobel prize in chemistry in 2001.[15] The next breakthrough in the field was realized by Noyori (who shared in the 2001 Nobel prize) and Takaya with the development of BINAP.[19] By virtue of the axial chirality of the binaphthyl moiety, the conformation of the phenyl rings on the phosphorus donor atoms is locked and the chirality is efficiently transmitted to the metal. Its rhodium complexes catalyze the enantioselective reduction of α-acylaminoacrylic acids in up to 99.9% *ee*. In addition, this ligand proved to be extremely versatile and is used nowadays as a benchmark ligand in almost every asymmetric transition metal catalyzed reaction.[20] One more example worth mentioning in this context is the DuPHOS ligand class, developed by Burk and co-workers at Dupont.[21,22] The chiral information in these ligands is contained in the phospholane rings positioned in close proximity to the metal when coordinated. Together with the rigid backbone, this leads to catalysts that can handle a broad substrate scope requiring only minor variations on the R-substituents. Many more chiral diphosphine ligands have been reported up to now and are discussed in detail in a large number of reviews.[23–26]

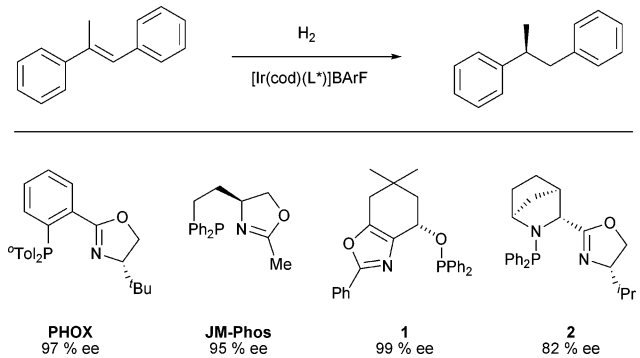
The ligands displayed in Fig. 1 all feature C_2 symmetry and a high degree of rigidity. Jacobsen[27] and Pfaltz[28] identified these structures as privileged ligands for asymmetric catalysis. Even though they were designed for asymmetric hydrogenation reactions, these ligands, or analogues thereof, provide excellent enantioselectivities in many reactions such as asymmetric hydroformylation,[131] allylic substitution,[132] hydroamination,[133] hydrosilylation,[134] *etc.* Below we will compare these privileged examples to recent combinatorial approaches in ligand development.

Hybrid bidentate phosphorus ligands

The use of two inequivalent donor atoms in a chiral bidentate ligand introduces a second handle to control the steric and electronic properties of the coordination sphere around the metal. This may be beneficial when regioselectivity is required and it can potentially lead to higher enantioselectivities due to specific binding of the substrate. Hybrid ligands can be composed of a phosphorus atom and a second metal binding heteroatom such as sulfur or nitrogen (P-S, P-N), or composed of two phosphorus atoms that are inequivalent *e.g.* phosphine-phosphite or phosphine-phosphoramidite. Here we will briefly discuss P-X type ligands and focus on the hybrid ligands with two inequivalent phosphorus donors.

P-N and P-S ligands

Chiral P-N ligands were initially designed for asymmetric allylic alkylation reactions and subsequently used as chiral bidentate analogues of Crabtree's catalyst [Ir(cod)(Pyridine)PCy_3]PF_6 for the asymmetric hydrogenation of unfunctionalized alkenes.[29] Pfaltz reported the first successful example of enantioselective hydrogenation of non-heteroatom containing alkenes using the so-called PHOX ligand, which is based on a phosphine-functionalized chiral oxazoline. It was also independently synthesized by Helmchen *et al.* (Scheme 2).[30–32] Many derivatives of the PHOX ligand have been reported by Pfaltz's group based on the same design concept.[33,34] Examples by other groups include JM-Phos developed by Burgess, which contains the chiral information in the backbone rather than in the side-arm of the ligand.[35–37] Andersson and co-workers reported chiral P-N ligands based on a bicyclic backbone and an oxazole (**1**) or thiazole moiety.[38,39] Later they also reported 2-azanorbornane derivative **2**,[40] which also proved

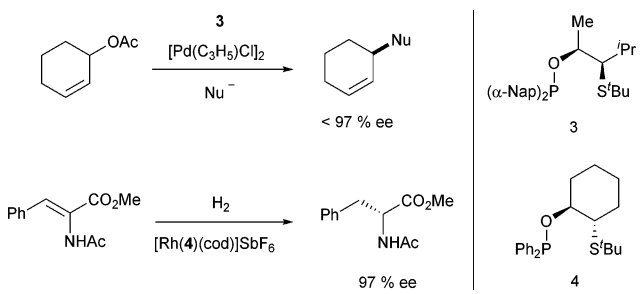


Scheme 2 Chiral P,N ligands in the Ir-catalyzed asymmetric hydrogenation of α-methylstilbene.

effective in the hydrogenation of fluorinated olefins and enol phosphinates.[41,42] For more examples the reader is referred to the comprehensive review by Cui and Burgess.[43]

P-N ligands show a great diversity in structure and are easy to derivatize as they are synthesized in a small number of steps. However, the successful examples all contain a six-membered coordination cycle and a bulky substituent close to the metal. Even though developed mainly for the hydrogenation of unfunctionalized substrates, the P-N ligand based Ir-catalysts prove to be efficient for a range of alkenes, including α,β-unsaturated esters, furans, imines and pyridines. In addition, many have shown to be also active in other reactions such as allylic substitution, in which the difference in *trans*-influence of the two inequivalent donor atoms aids to obtain high *enantio*- and regioselectivities.[29] More examples and other types of P-N ligands containing amino and imino donor groups are reviewed elsewhere.[44]

Compared to P-N ligands, their sulfur analogues remain a rarity in asymmetric catalysis. However, a particularly interesting and efficient C_1 symmetric P-S ligand family has been reported by the laboratory of David Evans (Scheme 3).[45,46] Ligands **3** and **4** have been used for highly enantioselective Pd-catalyzed allylic substitution and Rh-catalyzed hydrogenation. It was shown that the Rh-complex of **4** is able to bind the substrate selectively at only one enantiotopic face. The thus formed major substrate-catalyst complex leads to the product after oxidative addition of molecular hydrogen, migratory insertion of the olefin into the Rh–H bond, and reductive elimination. This mode of enantioselection is very different from the anti-lock-and-key mechanism observed for C_2 symmetric diphosphines in which the minor substrate-catalyst complex leads to the product.[47]



Scheme 3 Asymmetric allylic alkylation and hydrogenation using chiral P-S ligands **3** and **4** (α-Nap = α-naphthyl).

Phosphine-phosp(on)ite ligands

The discovery of Binaphos and its excellent enantioselectivities in Rh-catalyzed asymmetric hydroformylation by Nozaki and Takaya was a major breakthrough, and stimulated the development of this hybrid ligand class.[48,49] The controlled spatial arrangement of two chiral Bisnaphthol backbones in conjunction with the difference in electronic properties of phosphine and phosphite, result in a well-defined hydroformylation catalyst giving more than 90% *ee* using styrene as a substrate (Fig. 2, Scheme 4). However, the lengthy synthesis and low **b**/**l** (branched aldehyde/linear aldehyde) ratios motivated further research in this area. Van Leeuwen and co-workers reported ligand **5** that is based on a *tropos* biphenyl backbone connected to a P-chiral phosphine by a flexible linker.[50] The configuration of the biphenyl group is controlled by the adjacent stereocenter. Enantioselectivities up to 63% were achieved in the asymmetric hydroformylation of styrene, significantly lower than with Binaphos. Ruiz and Claver introduced sugar backbones, as a linker unit between phosphine and phosphite, but this additional chirality did not prove beneficial for hydroformylation reactions as moderate *ee*'s up to 38% were achieved with ligand **6**.[51]

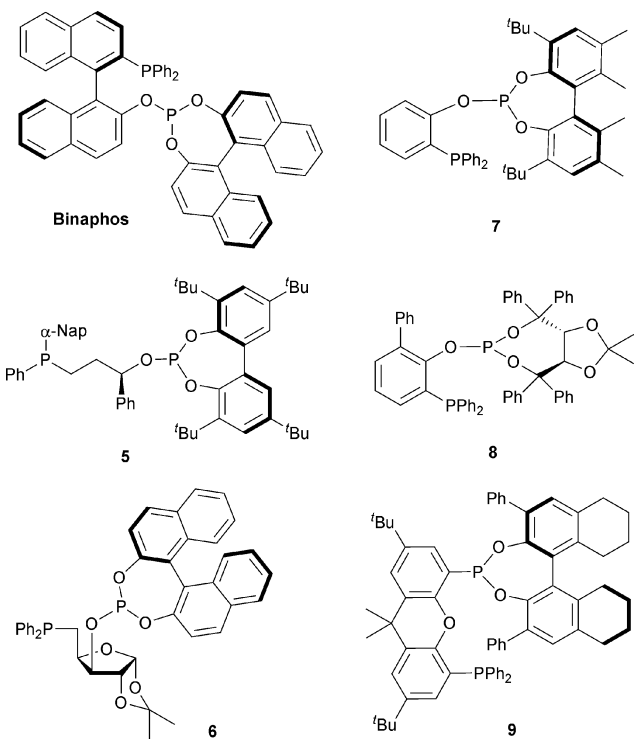
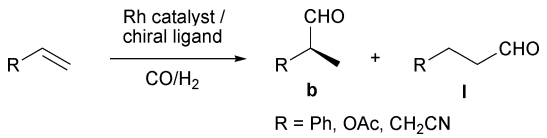
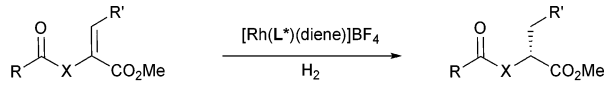


Fig. 2 Phosphine-phosph(on)ite ligands for Rh-catalyzed asymmetric hydroformylation.



Scheme 4 Asymmetric Rh-catalyzed hydroformylation.

Table 1 Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate (dmi), methyl 2-acetamidoacrylate (maa) and methyl 2-acetamidocinnamate (mac) using phosphine-phosphoramidite ligands[a]



dmi: R = OMe, R' = H, X = CH_2
maa: R = Me, R' = H, X = NH
mac: R = Me, R' = Ph, X = NH

Entry	Ligand (config. Binol)	Substrate	% Conv.	% *ee* (config.)
1[b]	**Quinaphos** (*R*)	**dmi**	> 99	99 (*R*)
2	**IndolPhos** (*S*)	**dmi**	> 99	98 (*S*)
3[c,d]	**10** (*R*)	**dmi**	> 99	99 (*R*)
4	**THNAPhos** (*R*)	**dmi**	> 99	99 (*R*)
5[c]	**Me-AnilaPhos** (*R*)	**dmi**	> 99	96 (*R*)
6	**11** (*S*)	**dmi**	> 99	99 (*S*)
7	**12** (*S*)	**dmi**	> 99	99 (*S*)
8	**PEAPhos** (*S*)	**dmi**	> 99	99 (nd)
9[b]	**Quinaphos** (*R*)	**maa**	> 99	98 (*S*)
10	**IndolPhos** (*S*)	**maa**	> 99	98 (*R*)
11[c,e]	**10** (*R*)	**maa**	> 99	99 (*R*)
12	**THNAPhos** (*R*)	**mac**	> 99	99 (*S*)
13	**HY-Phos** (*S*)	**mac**	> 99	98 (*R*)
14[c]	**Me-AnilaPhos** (*R*)	**mac**	> 99	98 (*S*)
15	**11** (*S*)	**maa**	> 99	99 (*R*)
16	**12** (*S*)	**mac**	> 99	99 (*R*)
17	**PEAPhos** (*S*)	**mac**	> 99	99 (*R*)

[a] Reactions were performed at Rh/L ≤ 1 : 1.1, Rh/substrate ≤ 1 : 100, at 25 °C, 10 bar H_2 in CH_2Cl_2 for ≤ 24 h using $[Rh(nbd)_2]BF_4$ or $[Rh(cod)_2]BF_4$ as metal precursor. [b] 30 bar H_2. [c] 1 bar H_2. [d] TFE (trifluoroethanol) as solvent. [e] acetone as solvent.

The groups of Pizzano and Schmalz took advantage of a more rigid phenyl scaffold to link the inequivalent donor atoms in ligands **7** and **8**. Ligand **7** was initially developed for asymmetric hydrogenation of dehydro amino acid esters and enol ester phosphonates, giving selectivities up to 95% *ee*.[52,53] The *ee*'s in hydroformylation reactions did not exceed 71% for styrene.[54] Higher selectivities, up to 85% *ee*, were obtained using the Taddol functionalized ligand **8**,[55] which was initially used for hydroboration reactions.[56] The *ortho*-substituent next to the phosphite moiety proved to be pivotal in order to obtain high *ee*'s. Only with *t*-Bu and Ph substituents, *ee*'s over 80% were achieved, again indicating the importance of rigidity and control over the coordination sphere. Our group took advantage of these concepts in the design of Xantphos derivative **9**. The rigid xanthene backbone was equipped with a diphenylphosphine and a bulky octahydrobinol derived phosphonite. High enantioselectivities (up to 91% *ee*) were obtained in the hydroformylation of dihydrofuran substrates.[57]

In addition to the examples discussed above, other chiral phosphine-phosphite ligands were reported based on the Binaphos platform by Zhang *et al.*,[58] and ferrocene derivatives by Chan *et al.*[59] Phosphine-phosphite ligands made most impact on the field of asymmetric hydroformylation, however, they have also been successfully employed in allylic alkylation,[60,61] conjugate addition,[62] hydroboration, and hydrogenation.[63] Again, the difference in *trans*-influence between the donor atoms facilitates regioselective reactions and specific binding of prochiral substrates. From the examples reported up to now, it seems that rigidity is a key element in this ligand class. Furthermore, combinatorial synthesis of some of these ligands allows for fine-tuning,[56,61] which is necessary as subtle changes in the ligand structure can have dramatic effects on the efficiency of enantioselection.[55]

Phosphine-phosphoramidite ligands

Notwithstanding the fact that phosphoramidite ligands are electronically very similar to phosphites, the steric properties show some marked differences. The nitrogen atom in a phosphoramidite is trivalent *versus* a bivalent oxygen in a phosphite. This makes phosphoramidites slightly more congested and also offers additional opportunities for derivatization for a more precise control over the positioning of the steric bulk. Moreover, it also enables the incorporation of the nitrogen in a cyclic framework, leading to a higher degree of rigidity. Introduction of an additional phosphine-coordinating group further increases the rigidity.

In the review of Crévisy, phosphine-phosphoramidites are divided into four classes based on their amine building blocks: cyclic amines, ferrocene, benzyl/aryl-amines, and chiral-pool diphenylphosphino-amines.[64] In order to reduce ambiguity, we would like to introduce an alternative classification based on the linker unit between phosphine and phosphoramidite. The linker can be a rigid cyclic amine (*class 1*), rigid (bi)cyclic moiety (*class 2*), or a flexible chain containing at least one non-cyclic sp_3-hybridized carbon atom (*class 3*). We believe that this classification is able to cover all examples reported up to now and differentiates clearly in the degree of rigidity, which is a key element in the ligand design.

Class 1. In 2000, Leitner reported the first example of a phosphine-phosphoramidite ligand, Quinaphos, which was used for highly enantioselective Rh-catalyzed hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate (hereafter dmi and maa, Fig. 3 and Table 1).[65] A pronounced matched/mismatched effect was observed for the configuration of the two stereocenters. Moreover, this versatile class of ligands was also used successfully in Ru-catalyzed hydrogenation of ketones with *ee*'s up to 94%.[66] Quinaphos ligands are synthesized from

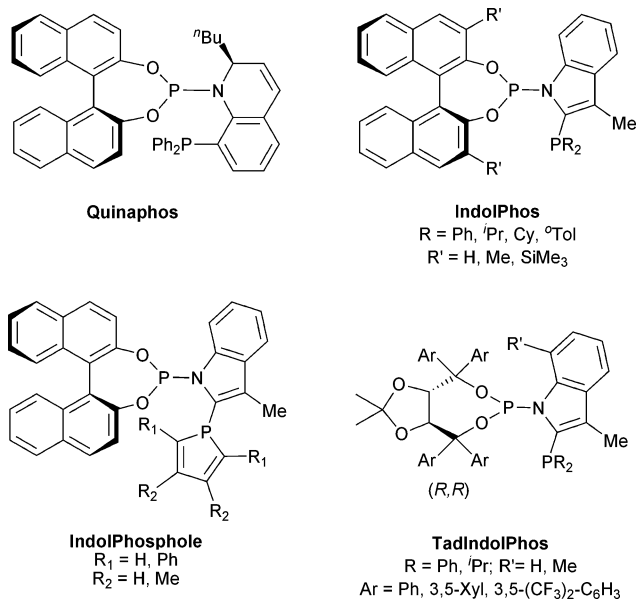
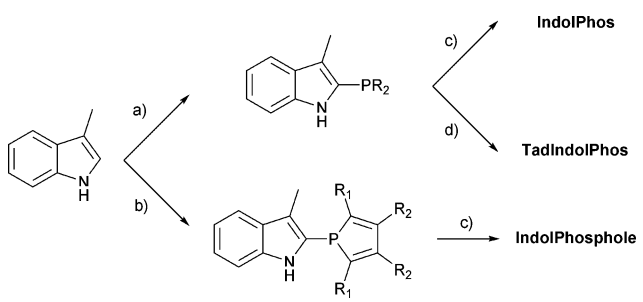


Fig. 3 Cyclic amine containing phosphine-phosphoramidites Quinaphos, IndolPhos, IndolPhosphole, and TadIndolPhos.

8-bromoquinoleine in two consecutive lithiation steps, followed by separation of the two diastereomers formed. This separation results in a low yield for the desired diastereomer that displays high *ee* in catalysis. However, recently Leitner and co-workers reported a more efficient diastereomer separation protocol that allows the isolation of gram-scale quantities of the ligand.[65b]

The second example in this class is the IndolPhos ligand and its derivatives. These ligands are conveniently synthesized in two steps from 3-methylindole in a modular fashion (Scheme 5). Selective lithiation in the 2-position of the indole is achieved by *in situ* protection of the nitrogen with CO_2, which concurrently acts as a directing group. Addition of the corresponding phosphorus chloride gives the desired indolylphosphine.[67,68] Alternatively, addition of a cyanophosphole gives the corresponding indolylphosphole.[69] The NH functionality of these intermediates can be, after deprotonation with a strong base like *n*-BuLi, derivatized with a phosphorochloridite of Binol or Taddol to arrive at the hybrid ligands IndolPhos, TadIndolPhos and IndolPhosphole.[70]



Scheme 5 Modular syntheses of IndolPhos-type ligands. *Conditions*: a) 1. *n*-BuLi, THF, –78 °C, 2. CO_2, 3. *t*-BuLi, 4. $ClPR_2$; b) 1. *n*-BuLi, THF, –78 °C, 2. CO_2, 3. *t*-BuLi, 4. Cyanophosphole; c) *n*-BuLi, (*S*)-Binol-PCl, THF, –78 °C; d) *n*-BuLi, (*R*,*R*)-Taddol-PCl, THF, –78 °C.

IndolPhos and TadIndolPhos ligands were successfully applied in asymmetric hydrogenation reactions. In addition to the benchmark substrates maa and dmi, also other α-dehydroamino acid esters, β-dehydroamino acid esters, 2-hydroxymethylacrylates, arylenamides, α-enamido and α-enol phosphonates, and cinnamic acid derivatives are hydrogenated at high rates in up to 99% *ee*.[68,70] We also investigated the mechanism of enantioselection effected by IndolPhos ligands and found that, similar to Evans' P-S ligand, the most stable catalyst-substrate complex leads to the product (lock-and-key mechanism).[71] We propose that this mechanism may be generally operable for hybrid C_1 symmetric ligands in asymmetric hydrogenation reactions (*vide infra*).

Asymmetric hydroformylation of styrene, vinyl acetate and allyl cyanide also proceeds with moderate to good enantioselectivity using these ligands up to 72, 74, and 63% *ee*, respectively.[72] The small bite angle of the ligand favors equatorial-apical coordination in the hydridobiscarbonyl rhodium intermediate, which leads to high **b/l** ratios of over 100. Interestingly, in the case of TadIndolPhos ligands it was found that for vinyl acetate and allyl cyanide the opposite enantiomer of the product was obtained when employing different Ar-substituents even though the absolute configuration of the Taddol moiety remains the same. The effect is proposed to stem from a difference in reaction mechanism. Whereas for smaller substituents (Ar = Ph), the reaction proceeds *via* the equatorial-apical hydridobiscarbonyl rhodium species in which the phosphine occupies the apical position, large substituents (Ar = 3,5-Xyl) favor coordination of the phosphoramidite on the apical position. This alters the chiral environment significantly and hence the enantioselectivity is reversed. Furthermore, IndolPhos and IndolPhosphole ligands have also been applied in Pd-catalyzed asymmetric allylic alkylations leading to high enantioselectivities up to 90% *ee*.[69]

Class 2. Xumu Zhang and co-workers replaced the oxygen linker for an ethylamino group in Binaphos to obtain its phosphoramidite analogue YanPhos (Fig. 4).[73] The increased rigidity compared to Binaphos and the slight change in the ligand's conformation imposed by using nitrogen instead of oxygen was beneficial for the application of the ligand in asymmetric hydroformylation of styrene, vinyl acetate and allyl cyanide giving *ee*'s of 99, 98, and 96%, respectively.[74] These enantioselectivities even surpass Binaphos but the **b/l** selectivity was moderate. The synthesis of the ligand is, as in the case of Binaphos, long, laborious, and low yielding (> 10 steps). Triphosphorus phosphine-phosphoramidite ligand **10**, also developed by Zhang *et al.*, coordinates to Rh and Pd in a bidentate fashion leaving one PPh_2 group uncoordinated.[75] The ligand is obtained in four steps from commercially available Binol in good overall yield. It gives rise to highly enantioselective hydrogenation of arylenamides, dehydroamino acid esters, and itaconic acid derivatives (up to 99% *ee*). A remarkable solvent effect was observed in the hydrogenation of these itaconates, switching the absolute configuration of the product when the reaction was performed in ketonic solvents.[76] The reason for this enantioreversal remains unclear.

The group of Zhuo Zheng reported the synthesis of tetrahydronaphtalene- and naphthalene-bridged phosphine-phosphoramidites THNAPhos and HY-Phos, respectively.[77,78] The phosphine was introduced by directed lithiation of (*R*)-1,2,3,4-tetrahydro-1-naphthylamine or 1-aminonaphtalene followed by condensation with a bisnaphthol phosphorochloridite. Even though the synthesis is short, the yields for the directed lithiation are moderate (30–52%). Both ligands proved to be highly efficient

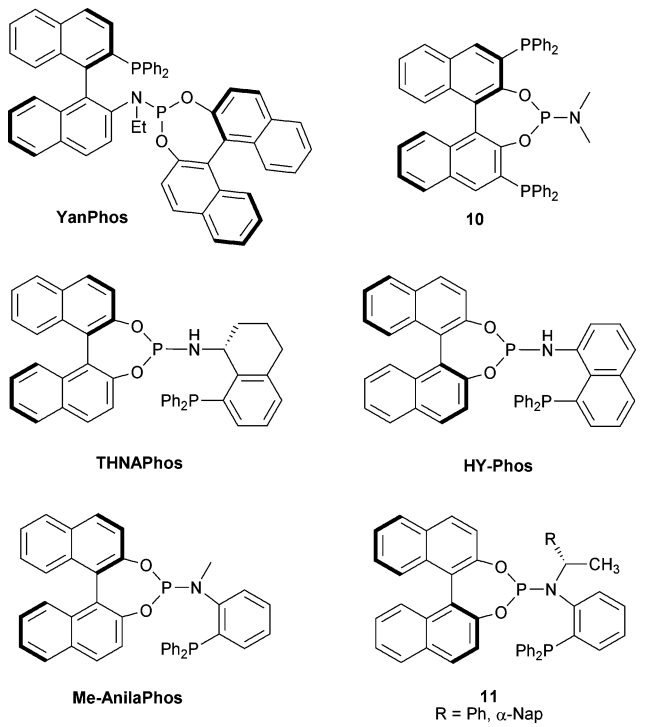


Fig. 4 Phosphine-phosphoramidite ligands connected by a rigid (bi)cyclic linker.

for Rh-catalyzed hydrogenation. Over 95% *ee* was obtained for a variety of prochiral olefins, including α-enol phosphonates, dehydroamino acids, arylenamides, hydroxymethylacrylates, and α-dehydroamino acid esters.[79,80]

Kostas and Börner described the synthesis of Me-AnilaPhos that is obtained in a single step from 2-diphenylphosphino-*N*-methylaniline. It can be considered as the phosphoramidite analogue of ligand **7**, which gave rise to the formation of good hydrogenation catalysts. Indeed, the Rh-complex of Me-AnilaPhos is highly active for the hydrogenation of methyl 2-acetamidocinnamate (mac) and dmi giving selectivities of 98 and 96% *ee*, respectively.[81] Derivatives of this ligand containing chiral substituents on the phosphoramidite (**11**), were successfully applied in the asymmetric hydrogenation of olefins, β-ketoesters, and quinolines.[82]

Class 3. Ferrocenylphosphine derived ligands **12** were independently reported by the groups of Chan and Zheng (Fig. 5).[59,83] They are prepared in a four-step synthesis from commercially available Ugi's amine, *N*,*N*-dimethyl-1-ferrocenylethylamine, in moderate overall yield. Application of ligand **12** in asymmetric hydrogenation reactions leads to highly active and selective catalysts. Excellent enantioselectivity up to 99.9% *ee* was obtained for a broad range of substrates, including β-dehydro amino acid esters.[84] Moreover, the catalyst loading could be lowered to 0.01 mol% while full conversion was obtained within 30 min. The outstanding performance of these catalysts may be seen as the result of combining two privileged chiral scaffolds, *i.e.* the Bisnaphthol and chiral ferrocene fragment of the very successful ligands BINAP and Josiphos,[85] respectively. Similar results were obtained using the H_8-Binol derivative.[86]

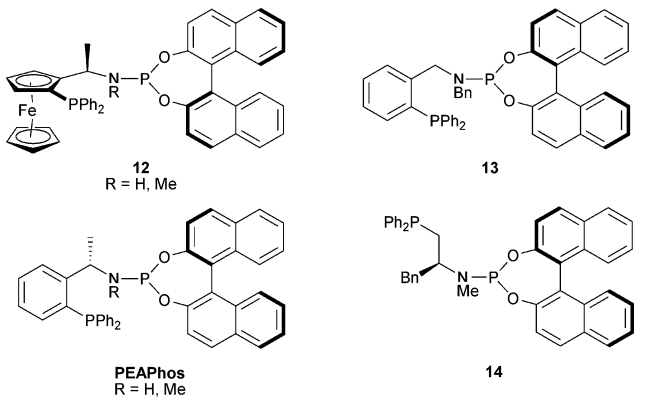


Fig. 5 Hybrid phosphine-phosphoramidites based on a more flexible linker.

Phenylethylamine-based ligands, PEAPhos reported by Zheng *et al.*,[87] feature a similar linking unit as ferrocenyl-based ligands **12**. Replacing the ferrocene moiety with a benzene unit significantly shortens the synthesis, starting from commercially available phenylethylamine. The ligands were evaluated in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters, arylenamides and dimethyl itaconate, generating up to 99.9% *ee*. Crévisy and co-workers reported a similar ligand **13**,[64] which does not contain a chiral center in the linker. This ligand is obtained from *o*-diphenylphosphinobenzaldehyde that is converted to the aminophosphine by reductive amination. Subsequent treatment with PCl_3 and (*S*)-Binol furnishes the hybrid phosphine-phosphoramidite. Unfortunately, no application of this ligand in catalysis has been reported, which would give valuable information on the importance of the chiral center in the linker. Ligand **14**, containing a short fully aliphatic linker, was prepared in five steps from Boc-protected phenylalaninol. Up to now, this ligand was only evaluated in Cu-catalyzed conjugate additions, resulting in poor *ee* values not exceeding 5%.[88]

Assymmetric hydrogenation of benchmark substrates. Comparison of the catalytic properties of the phosphine-phosphoramidites discussed above may give valuable insight into the structure-reactivity/selectivity relationship within this class of ligands. Unfortunately, not all ligands have been applied in the same reaction, prohibiting direct comparison of all ligands. However, results in asymmetric hydrogenation have been reported for most examples and are summarized in Table 1 for dmi and maa. When results for maa were unavailable, results obtained with mac, a structurally similar substrate, are included.

For these substrates, all ligands give full conversion and enantioselectivities range between 96 and 99%. In nearly all cases, the absolute configuration of the bisnaphthol backbone determines the absolute configuration of the product. This indicates a similar mechanism of enantioselection for the whole class of phosphine-phosphoramidites. We propose a quadrant diagram based on mechanistic work with IndolPhos ligands as depicted in Fig. 6.[71] At the side of the phosphoramidite, the upper and lower quadrant are sterically very different, whereas on the phosphine side, upper and lower quadrant are equivalent. This C_1 symmetric environment may enforce specific substrate coordination, which would lead to a mechanism in which the major catalyst-substrate complex leads to the product as also observed for P-S ligands[46] and

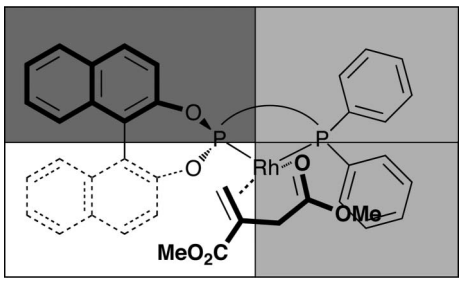


Fig. 6 Quadrant diagram for the enantioselection imposed by hybrid bidentate phosphoramidite ligands. The case is shown for a ligand containing the *S* configuration of the Bisnaphthol moiety and dmi as substrate, giving rise to the formation of the *S* enantiomer of the product.

phosphine-phosphites[53] (*vide supra*). Ligand **10** does not follow this empirical rule. This exception can be understood as in this case the bisnaphthol moiety is the linking unit, whereas in all other cases it is not involved in connecting the phosphine and phosphoramidite.

In summary, the excellent activities and enantioselectivities obtained in asymmetric hydrogenation reactions illustrate the practical potential of phosphine-phosphoramidites. For example, the activity was studied in more detail.[65,83] It was found that phosphine-phosphoramidite give unusually active hydrogenation catalysts, which may be explained by a perfect synergy between the electron-donating properties of the phosphine and π-acidic character of the phosphoramidite. Especially ligands that are synthesized in only two or three synthetic steps are promising candidates to be applied in fine-chemical synthesis on an industrial scale.

Next generation chiral monodentate and supramolecular phosphorus ligands

In 2000, the groups of Reetz, Feringa and de Vries, and Pringle independently reported the use of Binol-based phosphites (**15**),[89] phosphoramidites (**16**),[90] and phosphonites (**17**),[91] respectively, as ligands in Rh-catalyzed asymmetric hydrogenation reactions (Fig. 7).[92,93] These ligands are attractive as their metal complexes can induce high enantioselectivities up to 99% *ee* and the ligands are easy to prepare; just one or two steps from cheap commercially available starting materials. The active Rh-species is found to be coordinated by two monodentate ligands.[94] This opens up the possibility of mixing monodentate ligands in order to increase the number of successful catalysts.[95] This combinatorial approach has significantly contributed to the success of this class of ligands enabling asymmetric hydrogenation of a broad range of substrates

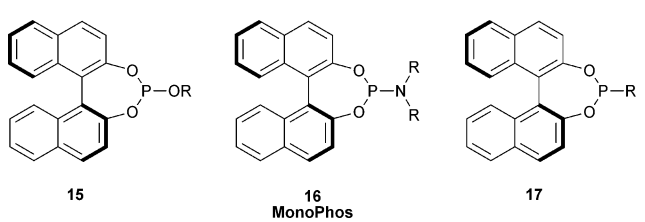


Fig. 7 Next generation monodentate Binol-based phosphites, phosphoramidites and phosphonites.

and application in many other reactions such as Cu-catalyzed conjugate additions.[96]

Application of mixtures of monodentate ligands is an attractive strategy to generate large ligand libraries but also has the inherent drawback that the homocombinations, which are likely present, have a detrimental effect on the enantioselectivity. By tuning the ratios between the two different ligands, this problem can be circumvented, however, at the expense of inefficient use of rhodium as part is captured in an inactive complex.[97]

An interesting new way to make bidentate ligands takes advange of complementary supramolecular recognition groups build into monodentate building blocks. By simple mixing these building blocks in the presence of a metal precursor, a supramolecular bidentate ligand forms upon self-assembly. Early examples based on metal–ligand interactions were reported by our group[98–101] and Takacs *et al.*[102,103] Even though excellent catalytic results were obtained with these ligands, their lengthy synthesis and high molecular weight hampers commercial applications. More recently, hydrogen-bonding interactions are being used to obtain supramolecular bidentate ligands, which are prepared in a few synthetic steps only and do not exceed molecular weights of classic bidentate ligands. Breit and co-workers took advantage of nature's hydrogen-bonding pattern in DNA in the supramolecular bidentate ligand composed of **19a** and **19b** (Fig. 8).[104] The power of this binding motif is that the aminopyridine and isoquinoline building blocks bind cooperatively. Even though they are self-complementary in the absence of a metal, coordination of the phosphines preorganizes the binding motifs, which leads to exclusive formation of supramolecular heterobidentate ligands. Achiral versions of these catalysts have been shown to generate high **l/b** ratios in the hydroformylation of linear olefins, which are normally only achieved with wide bite-angle diphosphine ligands, thus indicating the bidentate character of these supramolecular ligands.[105] Heterobidentate ligands containing a chiral Binol

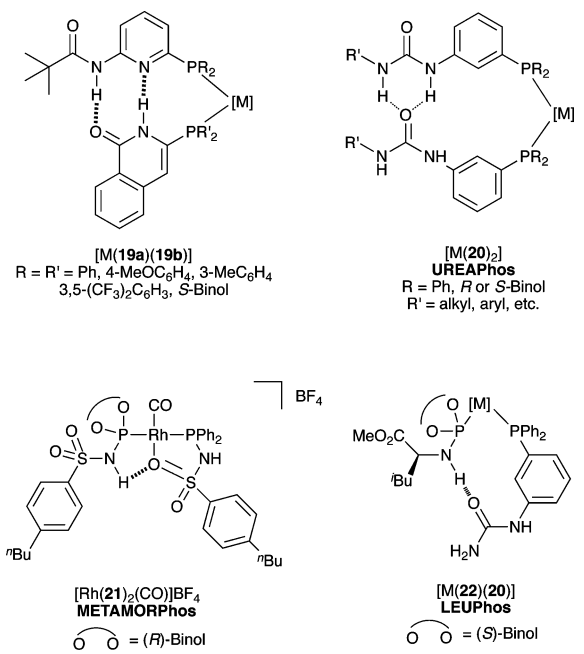


Fig. 8 Supramolecular approaches towards chiral bidentate ligands based on hydrogen-bonding interactions.

derived phosphonite, were shown to give high enantioselectivities (up to 99% *ee*) for the asymmetric hydrogenation of dmi and maa.[106]

The exclusive formation of heterobidentate metal complexes allows for novel catalyst screening approaches. Breit reported a deconvolution strategy: mixtures of catalysts derived from a library of self-assembled bidentate ligands were screened simultaneously in a small number of sub-groups, nine combinations per reactor. By selecting the best-performing sub-group for further deconvolution in new smaller sub-groups (four and then individual), the best catalyst is identified in an iterative fashion. Using this technique, Breit and co-workers were able to identify three highly active and selective hydrogenation catalysts from a library of 120 possible ligand combinations in just 17 experiments.[126]

Our group contributed to self-assembled hydrogen-bonded bidentate ligands with UREAPhos (**20**), which has shown excellent efficiencies in asymmetric hydrogenation reactions of industrially relevant substrates.[107,108] Initially, these ligands were applied as supramolecular homobidentate ligands, but more recently they have been successfully used as supramolecular heterobidentates by combination of an ureaphosphite with an ureaphosphine.[109,110] We also reported the use of sulfonamido-functionalized phosphines, METAMORPhos (**21**), to form supramolecular bidentate ligands (Fig. 8).[111] The adaptive character of the ligand allows the formation of purely heterobidentate complexes that show excellent activity and selectivity (up to 99% *ee*) in the hydrogenation of maa. In the presence of cationic Rh-precursors the Bisnaphthol-based METAMORPhos ligands give rise to the formation of dinuclear species that show unprecedented selectivities (up to 99% *ee*) for tetrasubstituted prochiral olefins.[112]

A second recent example of hydrogen-bonded supramolecular phosphorus ligands, LEUPhos, is based on the complementary interaction of an amino acid derived phosphoramidite (**22**) with an UREAPhos phosphine (**20**).[113] The self-assembled catalyst was shown to be highly active for the synthesis of Roche ester derivatives by means of asymmetric hydrogenation. In this particular example it was proposed that interactions between the substrate and the functionalized ligand contribute to the high selectivity displayed by the catalyst. By now, many more examples of supramolecular ligands have been reported based on metal–ligand interactions, hydrogen bonding, and ion pairing,[114] which are reviewed elsewhere.[103,104,115–119]

Privileged *vs.* combinatorial ligands

Since the introduction of the term 'privileged ligand', this classification is found widespread in the literature concerning ligand design. Since the definition is subject to changes, we redefine it for the current contribution: *A privileged ligand is a single chiral structure that provides highly active and enantioselective catalysts for a broad range of substrates and reactions*. Privileged ligands exhibit a high degree of generality, which opposes the specificity found in enzymes and also general findings within combinatorial catalyst development. In the last approach, for each substrate in a particular reaction a tailor made ligand is provided. In this section, we will provide a personal view on both strategies and highlight their complementarities.

We will illustrate differences based on two different cases. In the case of a new asymmetric reaction, which is not yet mechanistically fully understood such as asymmetric hydroamination with Rh or Pd,[120] the application of different privileged ligands is often a good starting point. Their rigidity and bidentate coordination result in well-defined complexes, which is often advantageous when not all reaction parameters are optimized. Most likely, one of the privileged ligands will provide a catalyst that displays significant *ee*'s for a small number of model substrates. In the scenario that a reaction is well-known and has demonstrated its value (*e.g.* asymmetric hydrogenation), and is to be applied for commercially interesting substrates of which the products are to be used as *e.g.* pharmaceutical intermediates, the privileged ligand approach may not offer a catalyst with the desired selectivity. Fine-tuning of the catalyst is required in those cases, which can be achieved through modular ligand synthesis (hybrid ligands) giving access to 10–20 similar ligands or combinatorial approaches (monodentate and supramolecular ligands) leading to large catalyst libraries.

Another important observation when comparing combinatorial strategies to ligand libraries and the privileged ligand approach is the use of rigidity *versus* flexibility in ligand design. An analogy can be made to diversity oriented synthesis for drug discovery where more flexible structures can cover a larger volume of the conformational space.[121–125] Most privileged ligands feature a very high degree of rigidity to reduce conformational ambiguity and offer precise control over the chiral space around the transition metal. However, they explore a very small volume of the conformational space, which limits catalyst discovery to only a few structures that are known to be highly selective. Combinatorial ligands may be able to reach beyond these boundaries and new privileged structures and ligands may be discovered in the future. For example, monodentate combinatorial ligands allow for more flexibility as the ligands can rotate individually, thereby covering a large number of conformations. Many of these conformations may give low selectivities but if the most reactive is also selective, this should not be an impairment. As we are to this date unable to exactly predict how the chiral space around the metal has to be arranged in order to achieve high enantioselectivities, rigid and flexible design concepts essentially face the same challenge: Finding this optimal arrangement of the chiral space for a particular substrate.

Privileged ligand and combinatorial ligand approaches are therefore complementary strategies for catalyst optimization. Whereas privileged ligands will be valuable in the early stages of reaction discovery, optimization and application for real-life substrates necessitates fine-tuning provided by combinatorial approaches. Hybrid ligands bridge the gap between these to approaches, as they offer possibilities for fine-tuning but still display a high degree of generality.

Conclusions

In conclusion, it is in our opinion impossible to ever find one ligand that will be suitable for all substrates in a specific reaction, let alone multiple reactions. Privileged and combinatorial approaches to ligand design are therefore highly complementary. New ligands for new applications will therefore always be required. It is important, however, that these new ligands are able to also transform real-life, non-benchmark substrates. We therefore would like to encourage all researchers in this field to think about new ligands and evaluate their new ligands for challenging substrates next to some

benchmark substrates, as it is hard to judge the potential of a new ligand solely on the results obtained for benchmark substrates. The class of hybrid ligands is highly interesting in this regard and has demonstrated its potential in terms of activity and selectivity for various industrially important reactions.

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