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Libraries of Bidentate Phosphorus Ligands; Synthesis Strategies and Application in Catalysis

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Combinatorial chemistry in combination with high-throughput screening technologies is an important way of finding new successful catalyst systems. The design of ligand libraries of bidentate phosphorus ligands and the application of their transition-metal complexes in homogeneous (asymmetric) catalysis reactions will be described in this review. Till now three different approaches were developed to arrive at such libraries of bidentate phosphorus ligands: 1) modular synthesis of bidentate ligands 2) the solid support synthesis of bidentate ligands and 3) the self-assembly of ligand building blocks into bidentate ligands. The scope and limitations of these strategies will be discussed on the basis of a limited number of articles that dealt with the synthesis of at least 15 bidentate phosphorus ligands.

1. Introduction

Transition-metal catalysis has found wide-spread application and is a subject of intensive research both in industry and academia. Initially transition-metal catalysis was mainly applied to the synthesis of bulk chemical synthesis,[1] but its application in fine-chemical industry is steadily increasing.[2] The main reason for the recent increase is undoubtedly its potential in asymmetric catalysis, although there are several other advantages of homogeneous catalysts compared to noncatalytic routes, such as the reduction of waste and potential shortcuts in lengthy total syntheses.[3] Despite the enormous progress in the area of asymmetric transition-metal catalysis, suitable catalysts are still lacking for many reactions and processes. This is related to the challenge involved in this type of selectivity; without catalyst the energy barriers of the competing reaction paths leading to the (*R*) and (*S*) product are by definition the same. For a reaction that leads to 95% *ee* the chiral catalyst should induce a difference in these energy barriers of 2 kcal/mol. Although computational techniques have evolved enormously since Knowles' pessimistic statement in 1983 concerning the use of theoretical methods for the development of asymmetric catalysts, even today the necessary accuracy is lacking to predict selectivity of catalysts.[4] The intensive research of the past decades in the area of asymmetric catalysis has resulted in very few privileged ligands[5] that form catalysts able to convert a wide range of substrates with high enantioselectivity and that are applicable for several reactions. This has driven researchers to other strategies to find catalytic solutions to certain problems and as such combinatorial approaches and high-throughput experimentation, initially applied in biotechnology, has been explored and identified as an indispensable tool for catalysis research. This approach involves two scientific challenges:[6] 1) strategies and methods have to be developed for the preparation of large libraries of chiral ligands and/or catalysts displaying high degrees of structural diversity, 2) methods have to be developed for the high-throughput screening of such catalysts. For reviews on screening-techniques that can be used for high-throughput screening the reader is referred to other reviews and papers.[6] In this overview we discuss the developments in the field of ligand library development for (hetero-)bidentate phosphorus ligands. In contrast to monodentate phosphorus ligands,[7] the libraries of (chiral) bidentate phosphorus ligands are scarce, despite the importance of bidentate phosphorus ligands in (asymmetric) transition-metal-catalyzed reactions. This is attributed to the intrinsically more complicated synthesis of bidentate ligands compared to that of monodentate ligands. This is especially true for hetereobidentate ligands as two different groups need to be introduced to the ligand backbone. In this microreview we show the strategies developed to arrive at bidentate phosphorus libraries and discuss the applicability of the routes, evaluating both the size and diversity of the generated libraries. The applied strategies to arrive at ligand libraries can be divided in three different approaches: (1) modular synthesis, i.e. the use of intermediates from which various ligands can be synthesized in a few steps, (2) the

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use of solid support synthesis, and (3) the application of supramolecular strategies to prepare self-assembled ligands. Often the term library or combinatorial chemistry is not used in the development of a series of ligands. In our overview of bidentate phosphorus ligand libraries we selected articles that dealt with the synthesis of 15 or more bidentate phosphorus ligands.

2. Synthesis of Libraries of Bidentate Phosphorus Ligands Using Modular Compounds

One of the routes explored to arrive at ligand libraries is the use of modular ligand structures. A (optically pure) compound is prepared in one or more steps, which is subsequently used to prepare a series of ligands that consequently belong to a ligand class of structural similarity.[6a] This approach is sometimes also referred to as "divergent synthesis". The modular ligand structure facilitates both the preparation of a ligand library and the modification of a successful structure in attempts for further optimization.

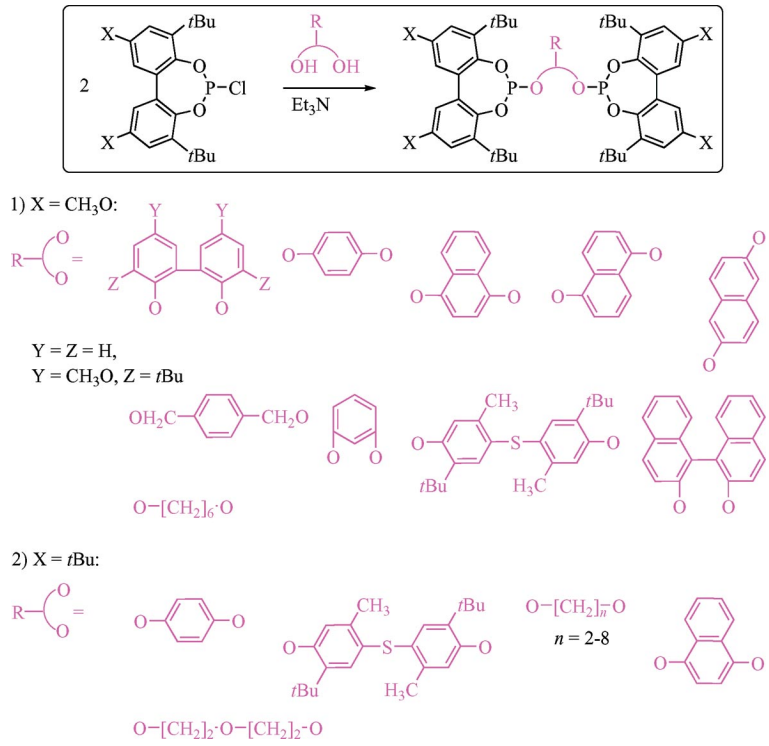
The first report on the modular approach to ligand libraries can be found in the patent literature. Billig et al. devised a synthetic route that facilitated the preparation of, among other phosphites, 22 different chiral diphosphites, using the building blocks depicted in Scheme 1.[8] The ligands were varied in the backbone that connected the two donor atoms as well as in the phosphite ligand themselves. These diphosphites, and also the diphosphites **1**–**4** shown in Scheme 2, were applied in the Rh-catalyzed hydroformylation of alkenes. In Table 1 the results of the hydroformylation of 1-butene by Rh complexes based on the diphosphites **1**–**4** are displayed. The introduction of substituents in the ligand backbone changed the *l*:*b* ratio only from 3.2 to 6.3 (Entries 1 and 2). Variation of the phosphite units has a much stronger influence on the regioselectivity. Whereas a Rh-**3** catalyst was active and induced a high selectivity (*l*:*b* ratio of 50.5, Entry 3), the Rh-**4** catalyst did not promote the reaction (Entry 4) at all under these conditions. Presumably, all ligands have been studied in this reaction, but the patent literature does not allow further interpretation of ligand effects.

Elsbeth Goudriaan obtained her HLO diploma (Bachelor degree) in 2002 in Utrecht. She then worked as a research technician in the group of Prof. Dr. H. Hiemstra and Dr. J. H. van Maarseveen in the field of cyclic peptide synthesis at the University of Amsterdam. In 2003 she started as a PhD student in the Homogeneous and Supramolecular Chemistry group of Prof. Dr. J. N. H. Reek and Prof. Dr. P. W. N. M. van Leeuwen. In 2007 she finished her PhD Thesis, which concerned the development of supramolecular ligand libraries and the application of these libraries in asymmetric catalysis. This NWO supported project was performed in collaboration with DSM Research. Currently she is working at Mercachem B.V. in Nijmegen.

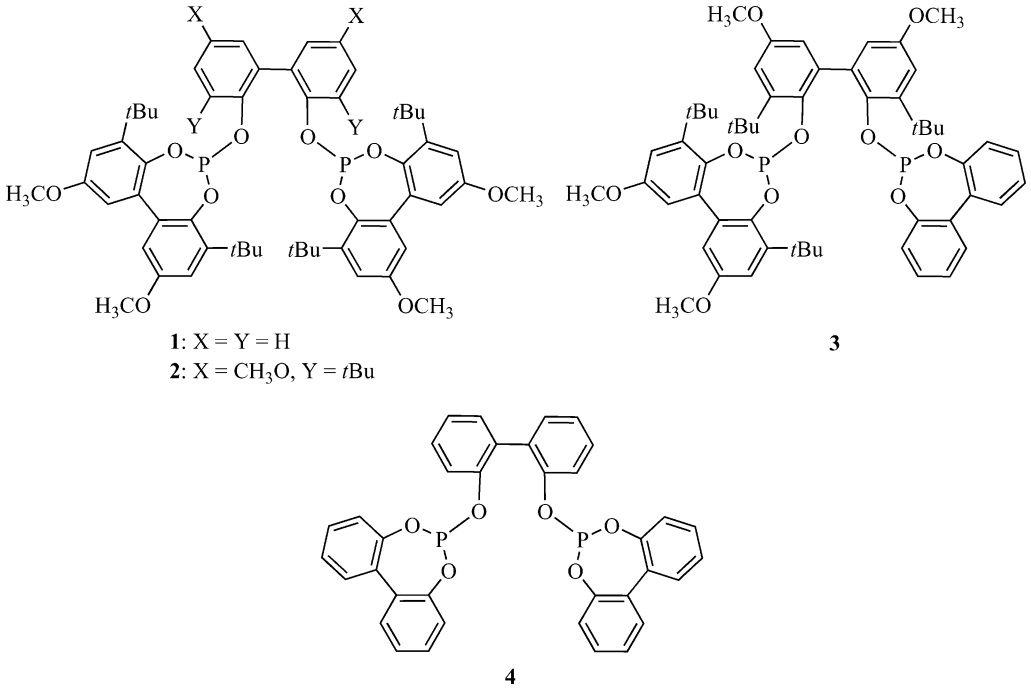
Piet van Leeuwen headed a group working on homogeneous catalysis during many years in the Shell research laboratory in Amsterdam. He started as a part-time professor of Homogeneous Catalysis at the University of Amsterdam in 1989. After leaving Shell in 1994 he became a full-time professor. He was Head of Education and Head of Department for a number of years. From 2002 till 2005 he was part-time professor of Industrial Homogeneous Catalysis at the Technical University Eindhoven and Director of the National Research School Combination Catalysis. In 2004 he became group leader in the newly started ICIQ in Tarragona, Spain. In 2005 he received a Marie Curie Chair of Ecellence in Tarragona and the Holleman Prize (for organic chemistry), granted every five years by the royal Dutch academy of sciences.He has worked on many aspects of homogeneous catalysis using especially rhodium and palladium with the assistance of many co-workers, in particular with his co-supervisors Profs. Paul Kamer and Joost Reek, and Drs. Gino van Strijdonck and Zoraida Freixa.

Mandy-Nicole Birkholz (née Gensow) was born in Schwerin (Germany) in 1979. She received her diploma in chemistry from the University of Rostock (Germany) in 2003. She obtained her PhD from the University of Rostock in 2006, working under the guidance of Prof. Börner in cooperation with the BASF AG on the synthesis of chiral self-assembling rhodium catalysts for the enantioselective catalysis. In 2007 she joined the group of Prof. Reek and Prof. van Leeuwen at the University of Amsterdam, in which she has been working on the synthesis of supramolecular catalysts.

Joost Reek finished his masters at the University of Nijmegen in 1991 and received his PhD in 1996 at the same university. His PhD research was done in the group of Prof. R. J. M. Nolte and dealt with the synthesis, supramolecular binding properties and catalytic activity of molecular clips. He attended the group of Prof. M. J. Crossley in Sydney as a postdoctoral fellow in 1996, where he became experienced in porphyrin chemistry. In January 1998 he became lecturer (senior lecturer in 2003) in the group of Prof. van Leeuwen at the University of Amsterdam with research activities focusing on transition-metal catalysis, supramolecular chemistry and supramolecular catalysis, catalyst immobilization and dendritic transition-metal catalysis. He started several collaborations with other research groups and companies and received numerous grants among which a prestigious CW-VICI grant. In 2005 he became a young member of royal Dutch academy of sciences (KNAW) and in January 2006 he was appointed full professor (chair supramolecular catalysis) at the University of Amsterdam. In September 2006 he started a company, Cat-fix, to commercialize some of the inventions in the area of supramolecular catalysis. Since 2007 he is member of the International advisory board of the European journal of inorganic chemistry. Most of his current activities are focused on the development of novel concepts in (supra)molecular transition-metal catalysis.



Scheme 1. Building blocks used for the synthesis of diphosphites, in red we have displayed the backbones that were used to make the diphosphites.



Scheme 2. Ligand library of diphosphites applied in the hydroformylation of 1-butene.

Further early examples of modular ligands involve the ferrocenyl-based ligands developed by Togni and co-workers (some examples: Scheme 3).[9] In 1994, they published several different ferrocene-ligands that were synthesized from one modular compound: the intermediate (diphenylphosphanyl)ferrocenylamine (Scheme 1) could be transformed into either P-P, P-N or P-allyl ligands using different reagents and conditions. This approach was extended in the following years and resulted finally in the well-known Josiphos ligand series. For a specific review on the development of this ligand the reader is referred to an excellent review.[9e]

Table 1. Selected results from the rhodium-catalyzed hydroformylation of 1-butene to C_5 aldehydes in the presence of in situ prepared $[Rh(CO)_2(\mathbf{1}–\mathbf{4})]$ precatalysts.

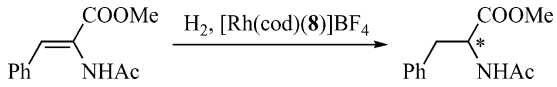
Entry	Ligand	Ligand/Rh	TOF [g mol/L/h]	*l*:*b*
1	**1**	4.3	3.7	3.2
2	**2**	4.0	0.4	6.3
3	**3**	4.1	6.0	50.5
4[a]	**4**	–	–	–

[a] No reaction was observed and the reaction conditions were not given.

In the area of modular bidentate ligands, phosphite-related ligands are well represented. Hydroxy- and amino-functionalized compounds, the starting compounds to prepare phosphite and phosphoramidite ligands, are readily available, often also in chiral forms as they are derived from natural products. Additionally, the preparation of phosphite compounds is relatively easy compared to for instance phosphane ligands.

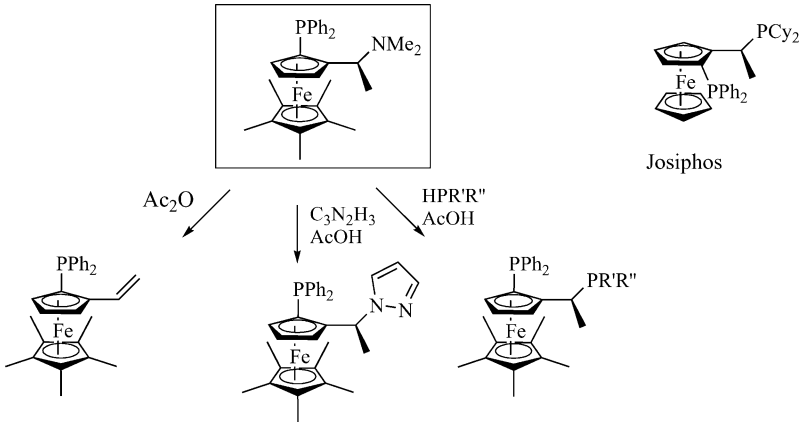
Jugé and co-workers developed a 17-membered ephedrine-based library of aminophosphane-phosphonite ligands,[10] referred to as AMPP ligands. Several members of this library have P-donor atoms that possess P chirality. The ligands were prepared from the intermediate oxazaphospholidine **5** (Scheme 4) in two steps.[11] Reaction of **5** with the lithium reagents provided intermediate **6**, which was trapped with a chlorophosphane. Subsequent addition of BH_3 yields the protected compounds **8a**–**l** (in 30 to 79% yield), which, after deprotection with dabco, provided the aminophosphane-phosphonite ligands. The intermediate **6** also reacted with the P-stereogenic phosphorus chloride compound **7** to deliver aminophosphane-phosphonites **8m**–**p** in which both phosphanes are P-stereogenic. The obtained ligands were diastereomerically pure.

The ligands were applied in the asymmetric hydrogenation of methyl α-acetamidocinnamate (Scheme 5), in which both the ligand structure and the solvent influence was investigated (Table 2).

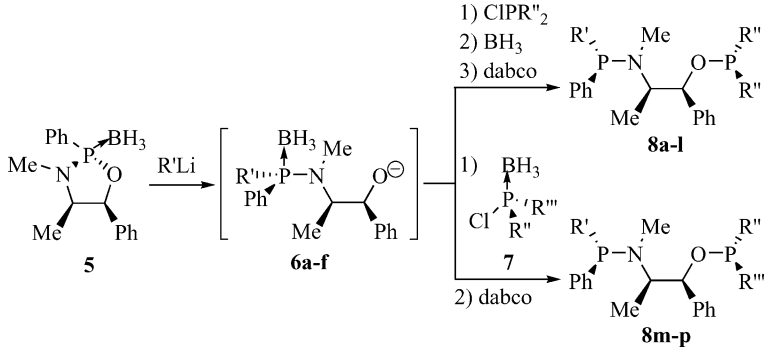


Scheme 5. Asymmetric hydrogenation of methyl α-acetamidocinnamate.

With exception of one ligand yielding 60% of the product, all catalysts based on these ligands provide the product in 91% yield or higher. The *ee* value of the obtained product varied from 0 to 99%. An *ee* value of 99% was obtained with two ligands of type **8a**–**l**, with either R′ = *o*-An or *o*-MEMPh, R′′ = Ph; both ligands also gave >90% yield (Table 2, Entries 5 and 6). Small changes in the ligand structure resulted in very different selectivities. For instance the catalyst based on the ligand **8d**, containing a 1-naphthyl group, resulted in 88% *ee* in dichloromethane (Table 2, En-



Scheme 3. The ferrocene-based ligand Josiphos and some related ligands, prepared from one modular intermediate.



Scheme 4. Synthesis of AMPP ligands.

Table 2. Selected results from the rhodium-catalyzed hydrogenation of methyl α-acetamidocinnamate with [Rh(cod)(**8**)]BF_4, containing AMPP ligands **8** (see Scheme 4).

Entry	**L**, R′, R″, R‴	*t* [h]	Yield [%]	*ee* [%]
1[a]	**8d**: 1-Np, Ph, Ph	4	99	88 (*S*)
2[a]	**8f**: 2-Np, Ph, Ph	4.5	96	16 (*S*)
3[b]	**8o**: Ph, *o*-An, Ph	24	95	62 (*R*)
4[b]	**8p**: *o*-An, Ph, *o*-An	21	95	75 (*S*)
5[b]	**8b**: *o*-An, Ph, Ph	20	98	99 (S)
6[b]	**8c:** *o*-MEMPh, Ph, Ph	36	94	99 (S)

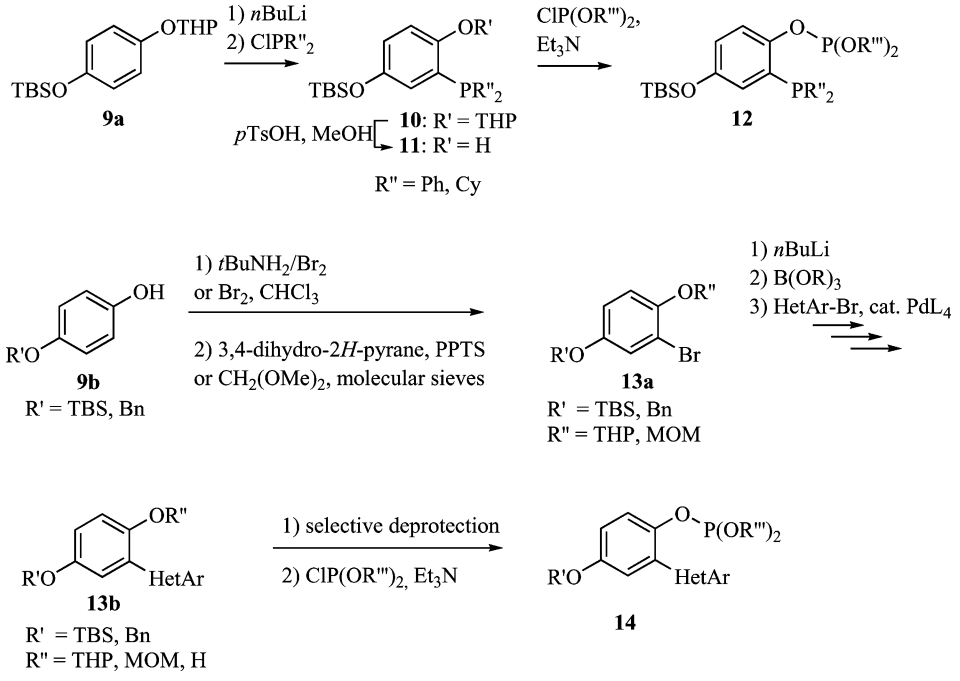
[a] In dichloromethane. [b] In benzene.

try 1), whereas the catalyst based on ligand **8f**, containing a 2-naphthyl group, converted the same substrate with only 16% *ee* (Entry 2). The experiments further demonstrated that the chirality at the phosphorus centre was of major importance. Whereas almost all AMPP ligands were prepared from (+)-ephedrine, both the (*R*)- and (*S*)-enantiomer of the product could be obtained with excellent *ee* values. For example ligands **8o** and **8p** provide the products with opposite enantioselectivity, whereas the backbone is the same (Entry 3 and 4 of Table 2). These results clearly demonstrate the value of the application of ligand libraries.

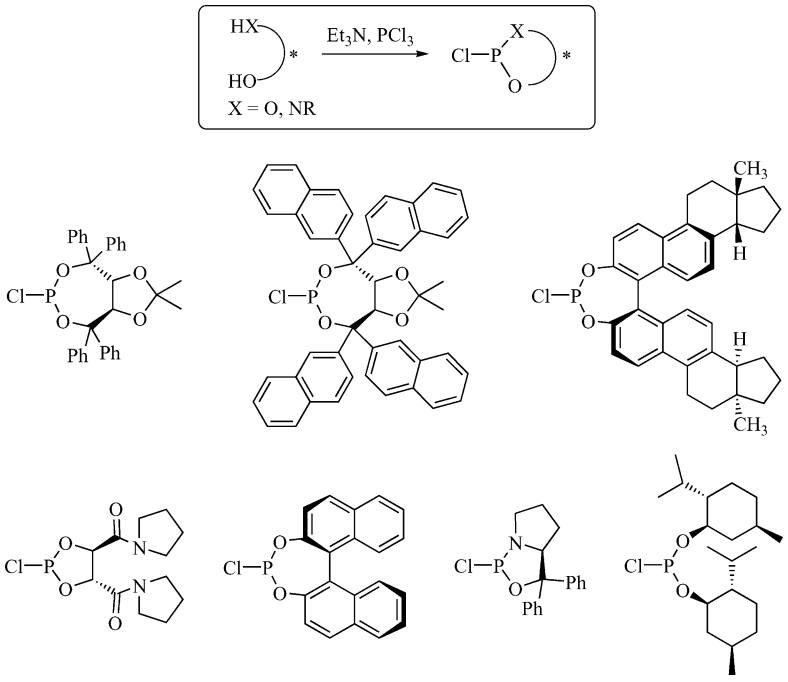
Another library of (potentially) chelating ligands synthesized from modular building blocks was published by Schmalz and co-workers, consisting of P/P (14), P/N (3), P/S (2) and P/Se (1) ligands.[12] The key building block in the synthesis is the orthogonally doubly protected hydroquinone (**9a**, Scheme 6), that could be functionalized with several different donor ligands. The first donor moiety was introduced using different methodologies, depending on the desired donor ligand. Phosphane donor ligands were introduced by lithiation of **9a** and subsequent reaction with electrophiles (e.g. chlorophosphanes), yielding the protected compound **10**. For the heteroaryl donor ligands (i.e. pyridine, thiophene etc.), building block **9b** was converted to an aryl bromide **13**, which was converted into the functionalized ligand **14** by palladium-catalyzed cross-coupling reactions (Scheme 6).

After selective deprotection of one alcohol (**10** → **11**), the second coordinating group was introduced by reacting the phenolic OH moiety with a phosphorus chloride reagent. The diversity of the ligands, apart from the different donor atoms like phosphorus, sulfur or nitrogen, was essentially in the structure of the phosphite part (Scheme 7).

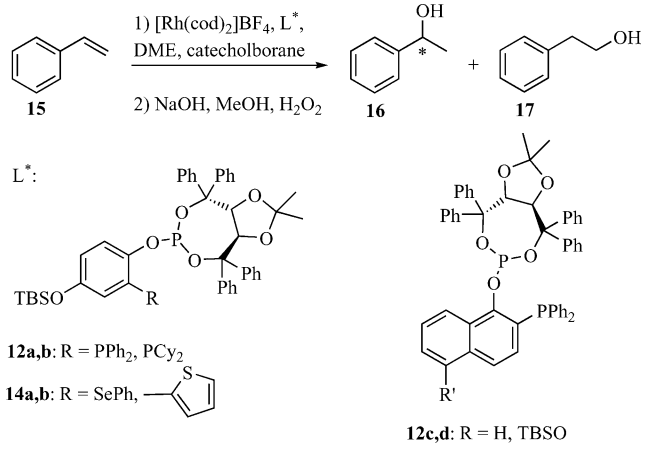
The activity and selectivity of the ligands were investigated in the hydroboration of styrene (**15**) (Scheme 8). The yields varied between 7 and 98% and the *ee* value between 3 and 91% (Table 3). The highest *ee* values were obtained with the bis-phosphorus ligands **12c** and **12d** (Scheme 8, Table 3 Entries 5, 6). Only the bis-phosphorus ligands gave *ee* values above 60%. For instance, changing the diphenylphosphane group in the phosphane-taddolphosphite ligand **12a** for a phenylselenium (**14a**) resulted in a decrease of *ee* from 81% (*R*)-enantiomer) to 3% (*S*)-enantiomer, Table 3, Entries 1 and 2). The corresponding thiophene-analogue **14b** provided the product in only 5% *ee* (*S*)-enantiomer, Entry 3). Furthermore, large differences in performance for the different phosphanes were observed. Whereas the aforementioned diphenylphosphane-taddolphosphite ligand **12a** provided 81% *ee* of the (*R*)-enantiomer, the dicyclohexylphosphane-taddolphosphite ligand **12b** resulted only in 49% *ee* of the (*S*) product (Entry 4).



Scheme 6. Synthesis of modular ligands as published by Schmalz and co-workers. Only the synthesis of the biphosphorus ligands is displayed.



Scheme 7. Overview of phosphorus chloride compounds applied in library synthesis.



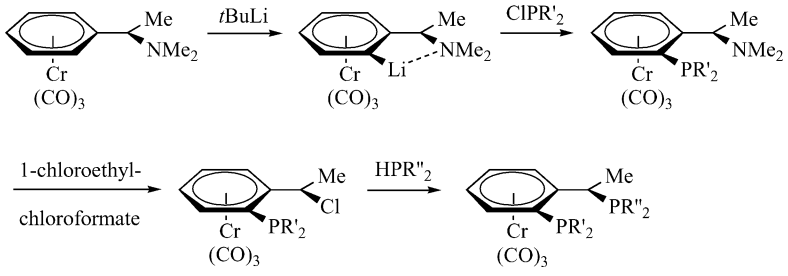
Scheme 8. Asymmetric hydroboration of styrene (**15**).

Salzer and co-workers synthesized 20 different planar chiral diphosphane ligands based on an arene(tricarbonyl)-chromium backbone (Scheme 9).[13] Different phosphorus donor moieties were introduced: aliphatic, alicyclic and aromatic groups. A (*R*,*R*)-2,5-dimethylphospholane moiety was also included.

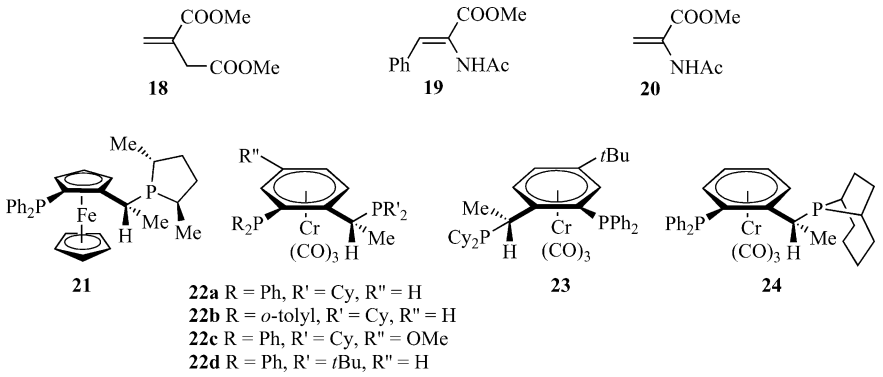
Table 3. Selected results displayed by some ligands from the library of Schmalz in the rhodium-catalyzed hydroboration of styrene (**15**).

Entry	Ligand	Time [h]	**16/17**	Yield [%]	*ee* **16** [%]
1	**12a**	2.5	98:2	98	81 (*R*)
2	**14a**	2	64:36	31	3 (*S*)
3	**14b**	5	83:17	25	5 (*S*)
4	**12b**	2.5	97:3	92	49 (*S*)
5	**12c**	3.5	95:5	63	91 (*R*)
6	**12d**	3.5	96/4	97	88 (*R*)

The ligands were applied in the rhodium-catalyzed asymmetric hydrogenation of various alkenes, an imine-substrate and a ketone substrate (Scheme 10). The substitution pattern of the ligands appeared to be extremely important, both for the activity and the selectivity of the catalysts, demonstrating the power of library screening. For instance, in the hydrogenation of dimethyl itaconate (Table 4, **18**) *tert*-butylphosphanes (e.g. Scheme 10, **22d**) generally resulted in disappointingly low selectivities, whereas the suc-



Scheme 9. Synthesis of $Cr(CO)_3$-based diphosphane ligands.



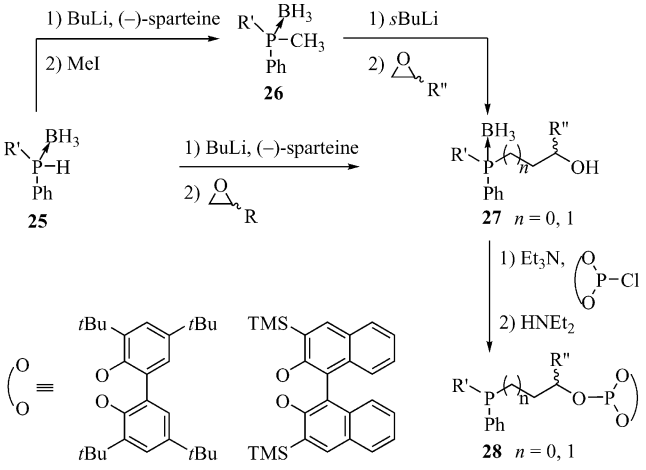
Scheme 10. Substrates and planar chiral ligands from Salzer and co-workers for the asymmetric hydrogenation.

cess of catalysts based on arylphosphanes varied substantially. Two closely related ligands, differing only in the substituents on the phosphorus (phenyl- or *o*-tolyl-phosphane; **22a** and **22b**, Table 4) gave rise to catalysts with very different selectivities. The catalyst based on ligand **22a** provides the product in 70% *ee*, whereas the analogue based on **22b** gives only 1.0% *ee*. The catalyst prepared from ligand **21**, that converts dimethyl itaconate with full conversion and >99% enantioselectivity, provides the hydrogenation product of methyl acetamidocinnamate (**19**) with only 12% *ee* and 45% conversion. Also in the hydrogenation of methyl 2-acetamidoacrylate (**20**) this catalyst performs moderately: 31% *ee* with full conversion. A similar substrate-dependent performance is observed with the catalyst formed from ligand **22c**: 7.1% *ee* in the dimethyl itaconate hydrogenation, 77% *ee* in the hydrogenation of methyl acetamidocinnamate and 87% *ee* for the product of hydrogenated methyl 2-acetamidoacrylate. It is important to note that for every substrate the highest *ee* is obtained with a different ligand: **21** for substrate dimethyl itaconate, **24** for methyl acetamidocinnamate and **23** for methyl 2-acetamidoacrylate.

Table 4. Hydrogenation of several alkenes with (tricarbonyl)chromium-functionalized ligands.

Entry	Substrate	Ligand	Conversion [%]	Yield [%]	*ee* [%]
1	**18**	**21**	100	100	>99 (*S*)
2		**22a**	37	37	70 (*S*)
3		**22b**	23	2	1.0 (*S*)
4		**22c**	85	85	7.1 (*S*)
5	**19**	**21**	45	45	12 (*R*)
6		**22c**	21	21	77 (*S*)
7		**24**	99	99	87 (*S*)
8		**22d**	38	38	1.2 (*R*)
9	**20**	**21**	100	100	31 (*R*)
10		**22c**	90	90	87 (*R*)
11		**22d**	33	33	7.6
12		**23**	100	100	91 (*S*)

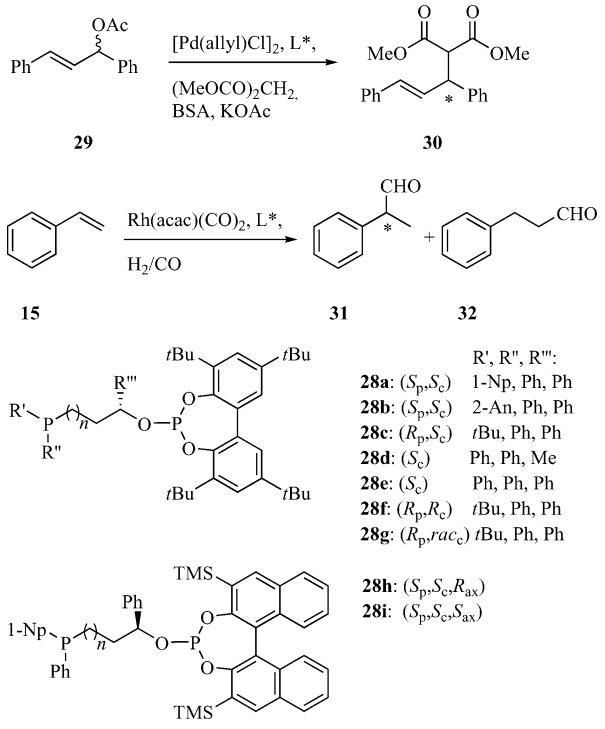
A series of 15 P-stereogenic bidentate phosphane-phosphite ligands has been prepared in our group.[14] Starting from a racemic secondary phosphane (**25**) chiral hydroxy-functionalized phosphanes were prepared via (–)-sparteine-mediated enantioselective lithiation. Subsequent reaction of the P-stereogenic hydroxy-functionalized phosphanes **27** with phosphorus chloridite reagents yields the bidentate phosphane-phosphite ligand **28** (Scheme 11).



Scheme 11. The preparation of a series of P-stereogenic phosphane-phosphite ligands by van Leeuwen and co-workers.

The performance of transition-metal catalysts based on these ligands was investigated in several asymmetric transformations, among which the rhodium-catalyzed hydroformylation and the allylic alkylation (Scheme 12). Some selected ligands and the performance of their catalysts are reported in Table 5 and Table 6.

The conversions obtained in the allylic alkylation varied between 40–100% and the *ee* values between 11 (ligand **28g**) and 83% (ligand **28e**). Especially the chirality at the carbon atom appeared to be important to achieve high *ee*. The catalyst based on ligand **28c**, which has the (*R*)-configuration at phosphorus and (*S*) at carbon, provides the product of the allylic alkylation in 78% *ee* at almost full conversion (Table 5, Entry 1). The catalyst based on its diastereomer, **28f** [(*R*) configuration at phosphorus and (*R*) at carbon], provides the product in approximately the same *ee* (77%, Entry 2), but the opposite enantiomer. The mixture of these two diastereoisomeric ligands (**28g**), which have the same chirality at the phosphorus atom and opposite at carbon, delivers the product in nearly racemic form (11% *ee*, Entry



Scheme 12. Conditions and ligands from van Leeuwen and co-workers for the asymmetric allylic alkylation and hydroformylation.

Table 5. Performance of several transition-metal complexes based on phosphane-phosphite in the allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate (**29**).

Entry	Ligand	Conversion [%]	*ee* [%]
1	**28c**	95	78 (*S*)
2	**28f**	86	77 (*R*)
3	**28g**	99	11 (*S*)
4	**28h**	61	21 (*S*)
5	**28i**	74	79 (*R*)
6	**28e**	100	83 (*S*)

Table 6. Performance of several transition-metal complexes based on phosphane-phosphite in the hydroformylation of styrene (**15**).

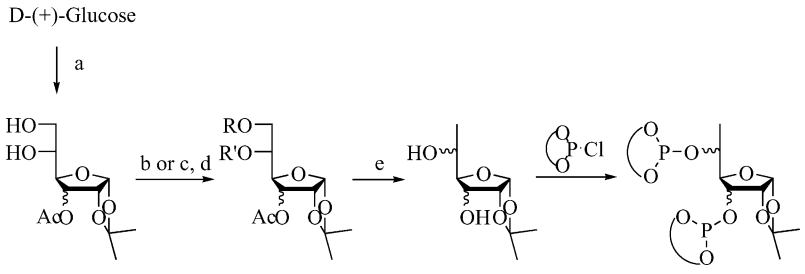
Entry	Ligand	Time [h]	Conversion [%]	**31**:**32**	*ee* [%]
1	**28a**	24	55	11	63 (*S*)
2	**28b**	25	24	20	57 (*S*)
3	**28d**	17	41	18	9 (*R*)
4	**28e**	25	69	2	18 (*S*)
5	**28h**	18	95	9	40 (*S*)
6	**28i**	19	26	8	4 (*S*)

3). The chirality at the P-stereogenic center is apparently unimportant, which can be explained by the fact that the nucleophilic attack at the palladium-allyl intermediate takes place *trans* with respect to the phosphane. This is also clear from the *ee* values obtained from the catalysts based on **28h** and **28i**. These ligands are similar at the phosphane, but possess opposite chirality at the phosphite (derived from the axially chiral binol), resulting in respectively 21% *ee* of the (*S*) product and 79% *ee* of the (*R*) product (Entries 4 and 5). In contrast, the chirality at the phosphane is very important in the hydroformylation (Table 6): the catalysts based on the ligands **28d** and **28e**, possessing no chirality at the phosphane part, induce almost no enantioselectivity (9 and 18% respectively, Entry 3 and 4), whereas the catalysts based on the P-stereogenic phosphanes **28a** and **28b** result in reasonable *ee* values (resp. 63, the highest *ee* obtained in this study, and 57%; Entries 1 and 2). In contrast to some privileged ligands[5] the performance of these catalysts are reaction specific. For instance ligand, **28i** gives 79% *ee* in the palladium-catalyzed allylic alkylation (Table 5, Entry 5), whereas in the rhodium-catalyzed hydroformylation of styrene only 4% *ee* is reached (Table 6, Entry 6). It is interesting to note that in the allylic alkylation the chirality around the phosphite is very important, whereas in the hydroformylation the stereoselectivity seems to be steered by the phosphane part.

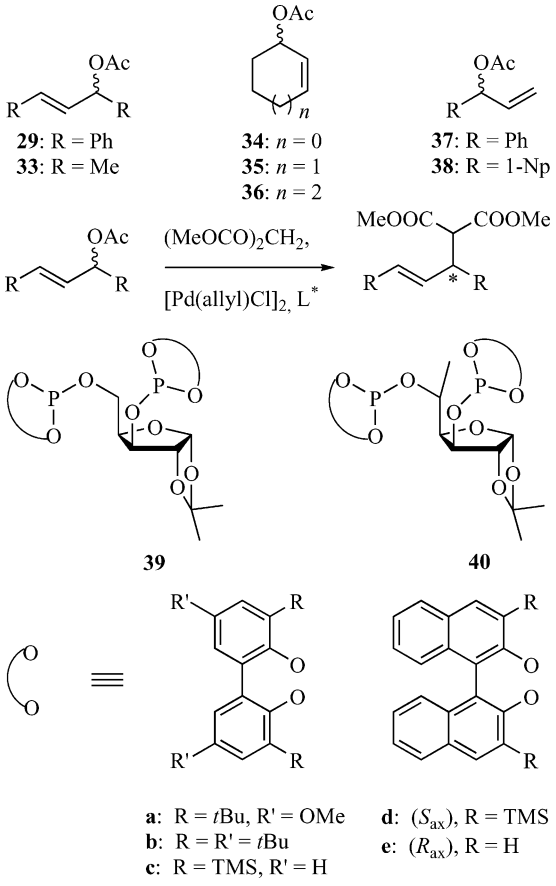
An example of a larger library synthesized through a modular approach is reported by Diéguez and co-workers. They reported the synthesis of 33 furanoside-based diphosphite ligands (Scheme 13),[15] which were pioneered previously by Buisman who developed 13 sugar-based phosphite ligands.[16]

The ligands were investigated in several asymmetric reactions, among which the rhodium-catalyzed hydroformylation,[15a] the rhodium-catalyzed asymmetric hydrogenation of various alkenes[15b] and the palladium-catalyzed allylic substitution.[17] Several substrates were investigated in the allylic alkylation: symmetric disubstituted linear substrates (**29** and **33**), cyclic substrates **34**–**36** and monosubstituted linear substrates **37** and **38** (Scheme 14, Table 7).

Except for the monosubstituted substrate **37**, for every substrate a catalyst based on a furanoside ligand could be identified that provides the product with moderate to high *ee* (68% or more; Table 7). The catalyst based on ligand **40b** showed high selectivities for several substrates, especially for the disubstituted linear substrates and the cyclic substrates



Scheme 13. Synthesis of furanoside-based diphosphane ligands.



Scheme 14. Conditions and furanoside-based ligands for the asymmetric allylic alkylation.

Table 7. Selected results of catalysts based on furanoside-biphosphite ligands in the allylic alkylation.

Entry	Substrate	Ligand	Conversion [%]	*ee* [%]
1	**29**	**39b**	100	97 (*S*)
2		**39d**	11	97 (*S*)
3		**40b**	100	98 (*S*)
4	**33**	**39b**	100	59 (*R*)
5		**40b**	100	78 (*R*)[c]
6		**40e**	61	4 (*S*)
7	**34**	**40b**	100	68 (*R*)
8	**35**	**40b**	100	74 (*S*)
9	**36**	**40b**	100	87 (*S*)[d]
10[a]	**37**	**40b**	100	29 (*S*)[e]
11[b]	**38**	**40b**	100	95 (*S*)

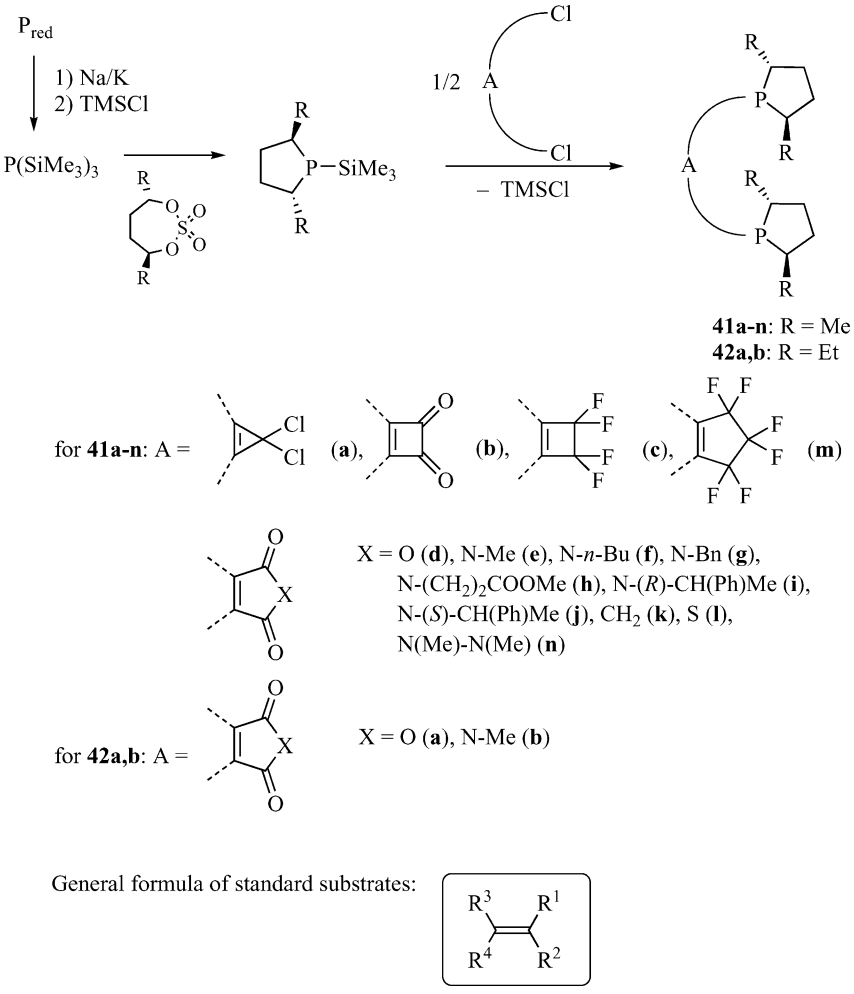
[a] Branched to linear selectivity: 24:76. [b] Branched to linear selectivity: 34:66. [c] 85% *ee* At –20 °C, 12% conversion in 1 h, vs. full conversion in 10 min at 20 °C (highest *ee* obtained for this substrate in this study). [d] 96% *ee*, 13% Conversion in 90 min at –20 °C (100% conversion in 30 min at 20 °C). [e] The highest *ee* for this substrate, 33%, was obtained with a ligand resembling **39b**, differing only in the chirality at the 3-position of the furanoside: (R) instead of (S).

(Table 7, Entries 3, 7 and 9). The catalyst based on this ligand also induced high enantioselectivity for the monosubstituted linear substrate **38**, 95% (Entry 11), although the regioselectivity was strongly in favour of the (achiral) linear product. The same catalyst displayed similar regioselectivity in the alkylation of substrate **37**, but only 29% *ee* was obtained for the branched product (Entry 10). These results also illustrate the strong sensitivity of catalysts for relatively small changes in the substrate. The authors also discuss the influence of substituents of the ligands on the activity and selectivity for some substrates. The alkylation of **29** required bulky ligands based on a *xylo*- (**39a**–**d**) and *gluco*-furanoside (**40a**–**d**), containing substituents at the *ortho*-positions of the biaryl moieties. In addition, the stereocenters at C3 and C5 showed a cooperative effect, which was not explained.

Holz, Monsees, Börner and co-workers synthesized 16 bis(phospholane) ligands by coupling 1,2-dichloroalkenes with a trimethylsilylphospholane intermediate, which was prepared in two steps starting from red phosphorus. The ligands were investigated in the asymmetric Rh-catalyzed hydrogenation of di- and trisubstituted olefins (Scheme 15/Table 8).[18] The library provided a selective ligand for every substrate (Table 8). For most of the studied substrates the ligands **41b**, **41d**, and **41e** turned out to be the best of this so-called cat*AS*ium® M ligand family. The ligand backbone had a pronounced influence on the selectivity of the catalysts. For most substrates, catalysts based on a bisphospholane with a five-membered backbone, like **41d**, **41e** and **41k**, provided the product in moderate to high *ee* (>70%). Large differences in *ee* were observed for the catalyst formed from ligand **41a**, containing the cyclopropene backbone: almost 80% *ee* was obtained for the methyl (*Z*)-*N*-acetamido cinnamate, whereas hardly any *ee* is observed in the hydrogenation of dimethyl itaconate. Generally the best catalyst for a certain conversion gave the highest *ee* in a range of solvents, although the absolute *ee* changed considerably with the solvent. One of the most striking examples in this context are the results obtained with Rh(**41n**) in the hydrogenation of ethyl (*E*)-2-acetamido-3-methylbutenoate; in methanol around 20% *ee* is obtained whereas the *ee* is over 95% when the reaction was carried out in dichloromethane.

This demonstrates that not only the ligands should be varied, but also the condition for the catalytic reactions. This obviously leads to large matrices of experiments to be carried out, which can only be handled with high throughput experimentation.

From the results described in this section we can conclude that modular ligand synthesis enables the preparation of series of analogous bidentate phosphorus ligands. Generally, the backbone of the ligands is invariant within a series, and the diversity stems from different substituents on the phosphorus atom. In some examples also easily variable substituents on the backbone were modified. The size of the libraries of bidentate phosphorus ligands synthesized with covalent synthetic techniques is generally small to modest. These examples show that these relatively small ligand libraries using classical synthetic techniques can already lead to very selective catalysts. The chances of finding new hits for challenging substrates, however, will be small if only small libraries are subjected to screening.



Scheme 15. Highly tunable family of chiral bisphospholanes for the Rh-catalyzed enantioselective hydrogenation of standard substrates.

Table 8. Rh-catalyzed hydrogenation of several olefins with cat*AS*-ium® M ligands.

R^1	R^2	R^3	R^4	Ligand	Solvent	*ee* [%]
CO_2Me	NHAc	H	Ph	**42b**	THF	99
CH_2CO_2Me	CO_2Me	H	H	**41e**	CH_2Cl_2	99
CO_2Me	H	Me	NHAc	**41e**	CH_2Cl_2	99
H	CO_2Me	Me	NHAc	**41b**	CH_2Cl_2	94
CO_2Bn	H	Me	NHAc	**41b**	CH_2Cl_2	>99
H	CO_2Bn	Me	NHAc	**41d**	MeOH	90
CO_2Et	H	*i*Pr	NHAc	**41d**	CH_2Cl_2	>99
H	CO_2Et	*i*Pr	NHAc	**41j**	CH_2Cl_2	90

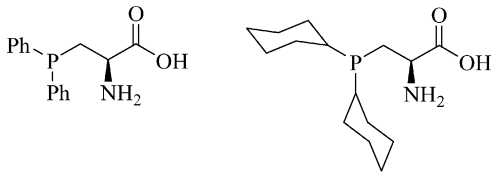
3. Libraries of Diphosphorus Ligands Developed Using Solid Phase Synthesis

A widely used approach in combinatorial chemistry is the use of solid phase synthesis techniques for the development of a large number of compounds.[19] Synthesis on support has the advantage that excess reagents can be used, which may drive the reaction to completion, and the purification of intermediates is simple as it generally involves a filtration and washing step only. One can use solid-phase techniques for parallel synthesis (one compound per vessel) or for a so-called split-and-pool strategy. In a split/pool strategy, the supported intermediates are isolated, divided over various vessels and combined with other intermediates and reacted to form the next intermediate. The supported compounds are divided into portions, each portion is subjected to reaction with a single building block. After reaction these portions are pooled, resulting in a single batch of solid support bearing a mixture of components. Repetition of the divide, couple, recombine processes results in a library where each polymer particle of solid support carries a single library member, and the number of members is equal to the product of the number of building blocks incorporated at each step.[20] Generally split-and-pool libraries are orders of magnitude larger than those obtained with parallel synthesis. However, for the preparation of ligand libraries this approach has not been applied, as catalyst screening on mixtures of catalysts is difficult, especially when selectivity is an issue. The parallel synthesis of ligands allows the evaluation of the performance of single catalysts, providing accurate and reliable data.

Parallel synthesis, in which each library member has its own spatially addressable site, can also take advantage from

the application of solid phase techniques. The reaction with supported building blocks can often be driven to completion by addition of (large) excesses of reagents. These reagents can easily be removed after synthesis by simple washing steps.[19] An additional advantage of ligands on a support is the possibility of easy recycling, provided that the ligands remain on the support during the synthesis route and are not susceptible to degradation.

The first example of a library of bidentate phosphorus ligands on support (being also the first example of combinatorial synthesis in ligand development) was given by Gilbertson and co-workers in 1996. Using solid phase peptide synthesis techniques, they developed a 63-membered library of bidentate phosphorus ligands by incorporating two different amino-acid-derived phosphane ligands (Figure 1) in different peptide chains.[21]



43 **44**

Figure 1. Amino-acid functionalized phosphanes for incorporation in peptide chains.

In the initial work, only two different phosphorus ligands were used, whereas the variation was found in the amino-acid sequence and the position of the phosphanes in the sequence (*i*, *i* + 4 and *i*, *i* + 1). Thanks to the helical structure of the peptide chain all di-phosphane systems prepared were able to form a chelating bidentate with the rhodium (Figure 2).[22]

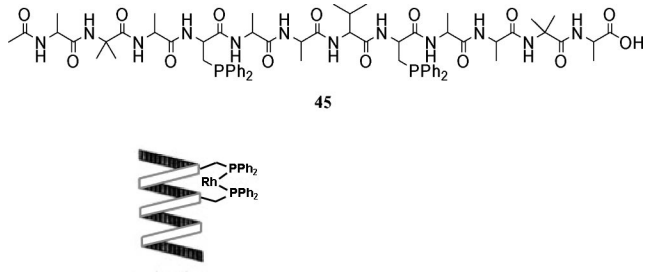


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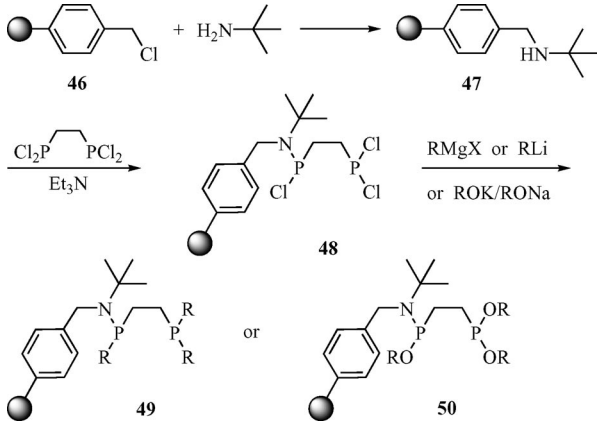
Figure 2. Chelating diphosphane-functionalized peptide that forms a rhodium complexes active in hydrogenation.

Every peptide was synthesized separately using solid-phase strategies, allowing separate screening of the ligands. The ligands were applied in the asymmetric rhodium-catalyzed hydrogenation of methyl 2-acetamidoacrylate (**20**), resulting in *ee* values varying between 0 and 18% and conversions between 1 and 100%.[21]

Although the highest enantioselectivity obtained was only moderate to low, some trends could be observed. For instance, all *ee* values above 10% were obtained when using peptides containing at least one (dicyclohexylphosphanyl)-serine. The influence of the support on the catalysis, as well as the nature and position of the peptide were reported in a subsequent paper.[23] A second-generation library, containing the phosphanes in either the *i* + 1, *i* + 3 or *i* + 4 position, already gave up to 37% *ee*, although at the expense of activity (<10%). Repeating some experiments in homogeneous phase (after cleaving the ligands from the support), demonstrated that the solvent has a large effect. For instance, the catalyst that provides the product with 36% *ee* on the support using THF as a solvent, shows less than 10% *ee* in THF when applied in the homogeneous phase, and around 8% of the other enantiomer was obtained in dichloromethane. The origin of the difference in selectivity obtained between the supported phase and the homogeneous phase in THF was not clear. Catalysis in water gave very similar results to those obtained with the solid phase catalyst in THF. The authors suggest that the hydrophobicity of the peptide plays a crucial role. Due to this hydrophobicity the peptides are likely aggregating in a tertiary structure in water, which might result in the formation of a similar structure as the peptides on the support. In the next years large libraries of phosphane-containing β-turn peptide secondary structures were developed and applied in the palladium-catalyzed alkylation.[24,25] In these libraries, both the phosphane substituents and the turn motifs were varied. Using this approach, high *ee* values (>80%) in, for instance, the alkylation of cyclopentenyl and cyclohexenyl acetate with dimethyl malonate have been obtained.

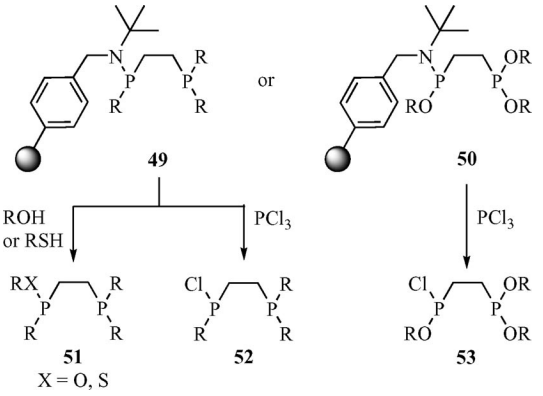
Li and co-workers made use of the solid-phase synthesis technology to prepare a library of 15 (achiral) bidentate phosphorus ligands. A polymer-supported secondary amine was formed by reaction of Merrifield's resin with an excess of *tert*-butylamine. Subsequent reaction with 1,2-bis(dichlorophosphanyl)ethane yielded the immobilized chlorophosphane that could be further functionalized by reaction with nucleophiles (Scheme 16).[26]



46 **47** **48** **49** **50**

Scheme 16. Synthesis of polymer-supported diphosphorus ligands.

The bidentate phosphorus ligands could be cleaved easily from the support by reaction with phosphorus trichloride, forming PCl compounds **52** and **53**, or by reaction with an alcohol or thiol (only for the phosphane analogues) (Scheme 17).

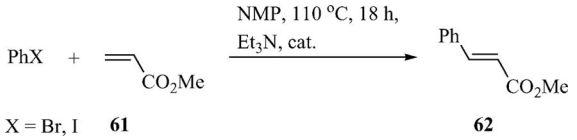


Scheme 17. Cleavage of the bidentate phosphorus ligands from support.

Whereas a variety of R groups can be introduced at the phosphorus atom by the use of different nucleophilic reagents in the last synthesis step, the diversity in this type of libraries is rather limited. The backbone is invariant (always C_2H_4) and at least three of the R groups around the phosphorus atoms are the same and there is no control over the P chirality.

A comparable methodology for the preparation of diphosphorus ligands was shown by Mansour and Portnoy. Resin-supported amino alcohols were used to synthesize a variety of supported monodentate (14) and bidentate (10) phosphorus ligands (Scheme 18).[27]

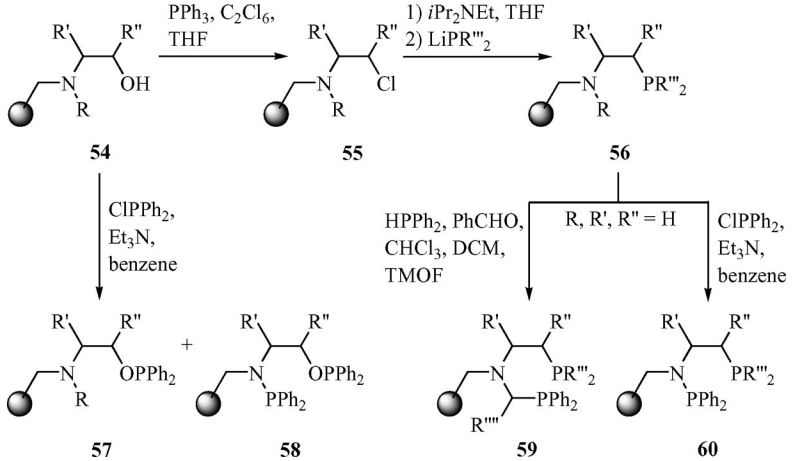
The alcohol **54** was first converted into the more reactive chloride **55** by reaction with triphenylphosphane/hexachloroethane. Subsequent reactions of the chloro intermediate with lithiophosphorus compounds yield the monophosphane derivatives **56**. The monophosphane ligands containing a secondary amine could be further functionalized by direct phosphorylation of the amine using diphenylphosphanyl chloride, leading to the aminophosphane-phosphane ligands **60**, or by Mannich condensation, resulting in the formation of α,β-diphosphanyl amine ligands **59**. Direct treatment of the supported (tertiary) amino alcohol with phosphorus chloride reagents resulted in the formation of a mixture of bidentate aminophosphane-phosphinite ligands (**58**) and monodentate phosphonite ligands (**57**). The ratio between the two products depended on the substituents on the carbon backbone and the amine. The ligands were applied in the palladium-catalyzed Heck reaction of bromobenzene and methyl acrylate (**61**), which resulted in the formation of the *trans*-alkene **62** (Scheme 19).



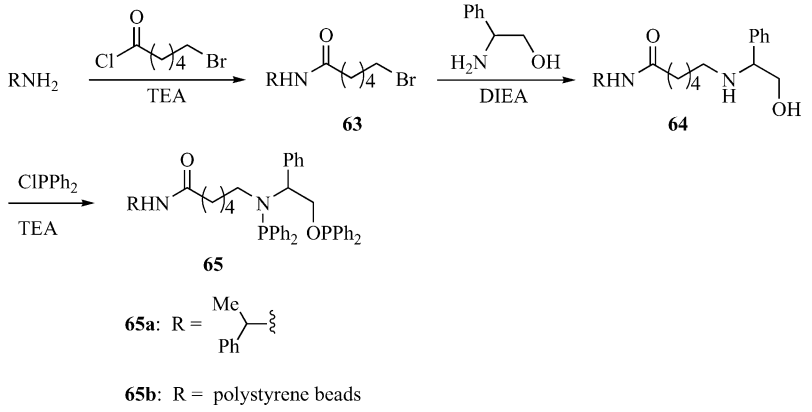
Scheme 19. Palladium-catalyzed Heck reaction of bromobenzene and methyl acrylate (**61**). Cat. = resin-bound ligand (see Scheme 18) precomplexed with $Pd(OAc)_2$.

The conversion varied between 8 and 63%, the yield of the desired product from 1 to 56%. The conversion and selectivity for the coupled product appeared to be strongly dependent on the ligands applied. Phosphane ligands performed better than phosphite ligands, and a positive effect of bidentate ligands was observed. The beneficial behaviour of bidentate ligands over monodentate ligands could be ascribed to the chelating effect, preventing the formation of palladium black. This is further supported by the observation that the coupling of the iodo analogue proceeds smoothly for all applied ligands. This seems a remarkable difference with respect to bromobenzene, but it is known that "naked" palladium(0) species, available from palladium clusters formed during the reaction as a consequence of catalyst decomposition, are amongst the most active catalysts for iodoarenes in the Heck reaction.[28]

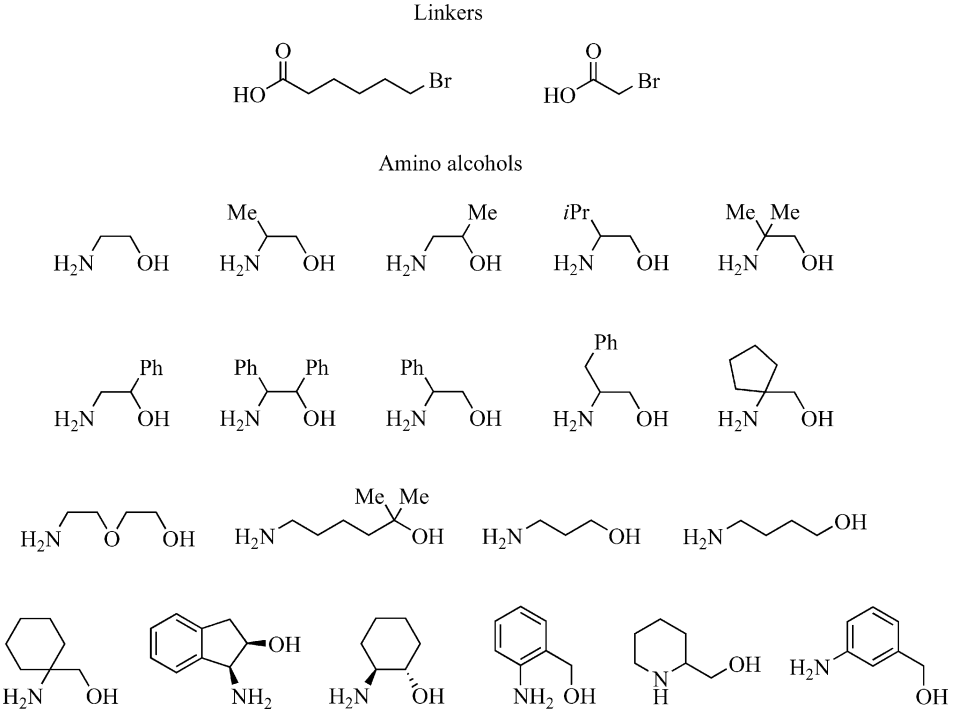
Lavastre and Morken developed a 40-membered library of aminophosphane-phosphonite ligands on polystyrene beads using the split-and-pool methodology.[29] Commercially available amino-functionalized polystyrene beads were functionalized with a linker. To this linker 63 different amino alcohols were attached. Subsequent reaction of the library with diphenylphosphanyl chloride yielded the bidentate phosphorus ligands **65** (Scheme 20).



Scheme 18. Synthesis of bidentate phosphorus ligands from a supported amino alcohol.



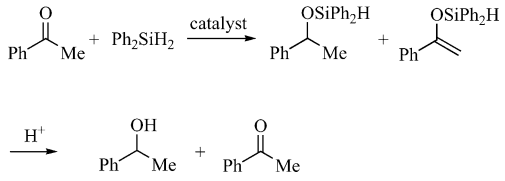
Scheme 20. The formation of aminophosphane-phosphonite ligands on polystyrene beads.



Scheme 21. Different linkers and amino alcohols applied for the combinatorial formation of aminophosphane-phosphonite ligands **65** on polystyrene beads.

Coupling with dialkylphosphanyl chloride reagents did not result in satisfactory yields of the bisphosphorus ligands and thus only diphenylphosphanyl chloride was used to prepare the ligands. The diversity in this library originates from the linker (2 different linkers) and the amino alcohols (20) (Scheme 21).

The beads were functionalized with specific photo-cleavable tags for every single bead in order to be able to identify the best catalysts by deconvolution.[30] 76 Beads containing the ligands were randomly selected and distributed in a 76-well plate for parallel screening. The library was applied in the rhodium-catalyzed hydrosilylation of acetophenone (Scheme 22), resulting in the identification of three amino alcohols, ethanolamine, 1-methylethanolamine and 2-(2-aminoethoxy)ethanol, that are the basis for active ligands for this reaction.[31]



Scheme 22. Hydrosilylation of acetophenone.

The conversion of the substrate ranged from 0 to 31%. Decoding of some beads that were not active showed that all inactive catalysts were formed from ligands derived from secondary amines, which lead to the formation of monodentate ligands.

From this section we can conclude that the application of standard solid phase synthetic strategies facilitate the

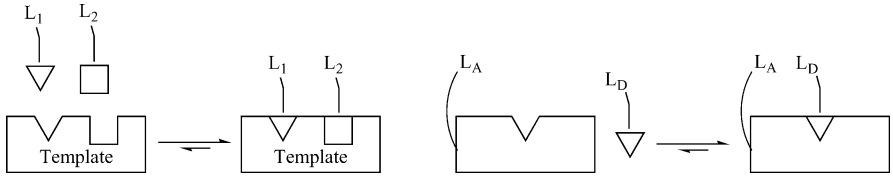
preparation of medium to large ligand libraries of bisphosphorus compounds. Generally the libraries are larger than those synthesized in solution using the modular approach. So far the number of examples is small and also the diversity of the ligand libraries reported so far is limited, but this is not an inherent limitation of the technique.

4. Development of Bidentate Phosphorus Ligand Libraries Using Supramolecular Chemistry

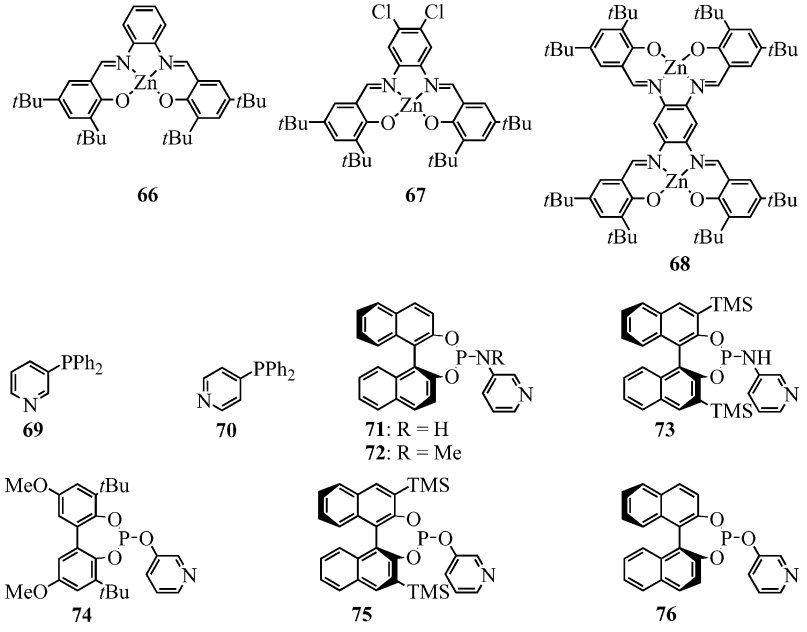
Very soon after the introduction of supramolecular bidentate phosphorus ligands,[32,33] the first libraries of these type of compounds were published. This already indicates the suitability of these types of ligands for combinatorial approaches. Supramolecular ligands are formed by the self-assembly of different building blocks. As a result, the preparation of these compounds deals with the synthesis of more easily accessible, smaller compounds (comparable to the synthesis of monodentate ligands). In addition to the easier synthesis, it benefits from the rapid growth of the number of ligands by the combination of building blocks. The development of supramolecular ligand libraries can be divided in two distinct approaches. One approach is the design of a template containing two binding sites, to which two ligands can assemble (Scheme 23, left). Another approach is the use of two monodentate ligands that are functionalized with complementary binding sites which result in the formation of a bidentate ligand upon mixing (Scheme 23, right). The assembly processes can be either via metal–ligand interactions, hydrogen bonds or ionic interactions.

The first example of bidentate phosphorus ligands formed via self-assembly using a template was shown by our group in 2003. Pyridyl phosphorus ligands were assembled to a bis[porphyrinatozinc(II)] template.[32a] Also tris[porphyrinatozinc(II)] phosphite ligands could be assembled to form bidentate ligands by the addition of ditopic nitrogen ligands.[32b] Love and co-workers[34] and our group[35] also showed independently the formation of bidentate ligands via anion-templation. An example of a real library based on the template approach was recently reported by our group.[36] A bis[salphenzinc(II)] template was developed, to which different pyridyl-functionalized phosphorus ligands were assembled (Scheme 24).

Unexpectedly, selective assembly of two different ligands to the bis[salphenzinc(II)] template was observed (most likely due to steric constraints). This facilitates the construction of large libraries, because also hetero-bidentate ligands can be formed from the same building blocks. A library of 17 different self-assembled bidentate phosphorus ligands was screened in the asymmetric hydroformylation of styrene (see Scheme 12, **15** → **31** and **32**). The library was relatively small, but rather diverse because it consisted



Scheme 23. Formation of bidentate ligands by self-assembly. Left: template approach; Right: direct approach.



Scheme 24. Building blocks for the formation of a supramolecular ligand library based on salphenzinc(II) templates and different nitrogen donor phosphorus ligands.

of bidentate phosphite, bidentate phosporamidite, phosphane-phosphite, phosphane-phosphoramidite and phosphite-phosphoramidite ligands. When applying templates **66** or **67** monodentate analogues of the templated bidentate ligands were formed, which were studied in catalysis as control experiments.

The conversion obtained with the catalysts based on these ligands varied between 0–100%, the *ee* between 0 and 72% (Table 9), demonstrating the influence of both steric and electronic ligand parameters. Large template effects were observed. For instance, the catalyst based on the ligands **69/71** on the mono-salphenzinc(II) template **67** resulted in 20% conversion and only 4% *ee* for the branched product (Table 9, Entry 5). On the contrary, if the same ligands were assembled on the bis[salphenzinc(II)] template **68**, a similar activity and regioselectivity but much higher *ee* (72%, Entry 6) was observed. Although less pronounced, the same trend is observed for the catalysts [$Rh(CO)_2$(**66**(**71**+**73**))] (Entry 7) and [$Rh(CO)_2$(**68**(**71**+**73**))] (Entry 8): 10 vs. 55% *ee* for respectively the monodentate and the bidentate ligand assembly. In addition, small differences in the building blocks used to assemble the catalysts resulted in huge differences in the outcome of the catalysis results. The catalyst based on [$Rh(CO)_2$(**68**(**71**+**73**))] (Entry 8) forms the branched product with 55% *ee*, a very similar complex [$Rh(CO)_2$(**68**(**72**+**73**))], only differing in the substituent on the nitrogen of the amidite (H or Me) only yields 4% *ee* (Entry 10).[36]

Table 9. Selected results of self-assembled biphosphorus ligands on a bis[salphenzinc(II)] template in the hydroformylation of styrene (**15**).

Entry	Ligand	Template	Conversion [%]	**31/32**	*ee* [%]
1	**71/71**	**66**	<1	–	–
2	**71/71**	**68**	<1	–	–
3	**73/73**	**66**	>99	12.5	11 (*S*)
4	**73/73**	**68**	>99	13.5	13 (*S*)
5	**69/71**	**67**	20	8.4	4 (*S*)
6	**69/71**	**68**	19	9.2	72 (*S*)
7	**71/73**	**66**	>99	12.3	10 (*S*)
8	**71/73**	**68**	66	9.9	55 (*S*)
9	**72/73**	**66**	93	12.4	3 (*S*)
10	**72/73**	**68**	21	5.3	4 (S)

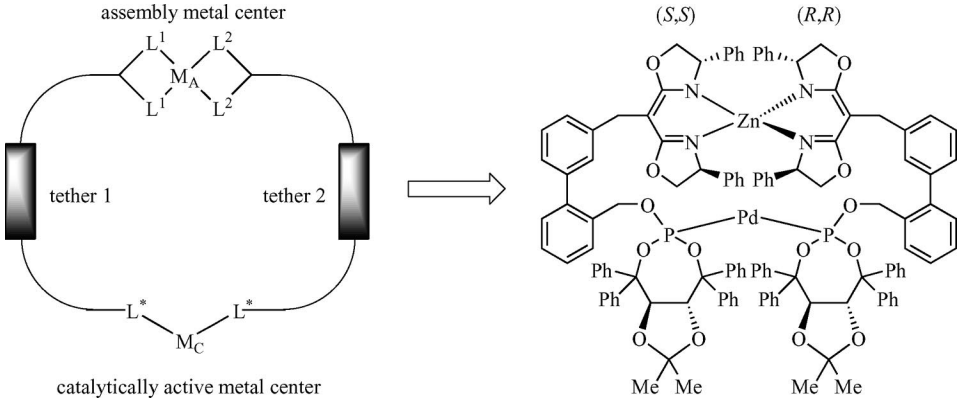
Another example of the template approach is described by Takacs and co-workers.[37] Zinc(II) was used as template metal ion to form heterobidentate ligands. Chiral phosphite ligands were equipped with chiral bisoxazoline ligands, which were used to form the bidentate self-assembled diphosphite ligand upon addition of zinc(II) acetate. The phosphites are available for coordination to the catalytic active metal (Scheme 25). The self-assembled ligands were formed as single enantiomeric species, because the heteroleptic complexes (*SS*, *RR*) are preferred over the homoleptic ones (*SS*, *SS* and *RR*, *RR*).[38]

In this way 50 different heteroleptic TADDOL-phosphite bidentate ligands were assembled from 13 different phosphite-functionalized bisoxazoline ligands (Scheme 26).

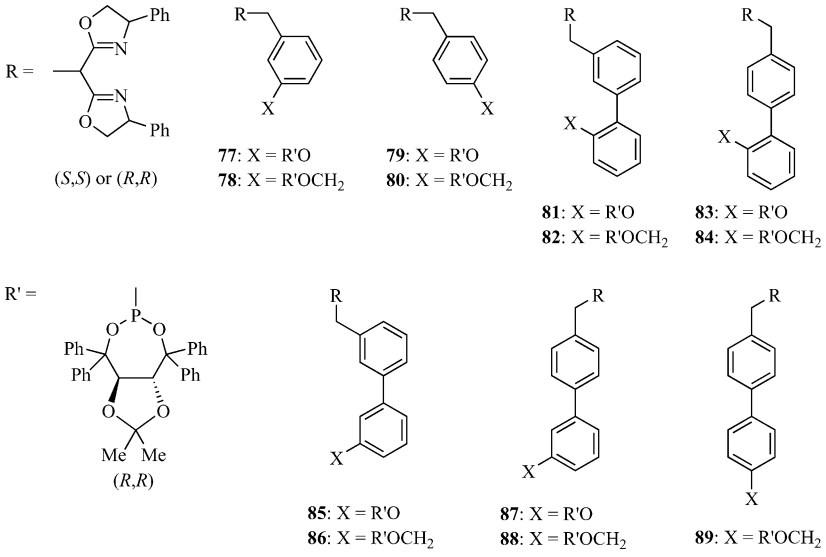
The ligands were applied in the asymmetric palladium-catalyzed allylic amination (Scheme 27), resulting in yields above 70% for all ligands and enantioselectivities ranging from 20 to 97% (with **82**–**84**).

The large variety in enantioselectivity obtained is remarkable, considering the fact that the phosphite part is the same for every ligand. The ligands vary only in the backbone, demonstrating the significant influence that subtle changes in backbone structure can have on the selectivity of a reaction. Because the influence of these small changes cannot be predicted in advance, this example clearly shows the importance of library screening in catalysis. More recently,[37e] the approach was successfully applied in the rhodium-catalyzed hydroboration. A library of around 160 self-assembled ligands was subjected to screening and the *ee* of the hydroborated products obtained is between the 96 and the –30% (minus stands for the other enantiomer). Importantly, catalyst optimization was mostly provided by scaffold modification.

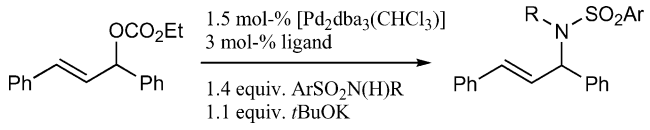
The direct approach has been applied more widely as a strategy to make bidentate ligands, and metal–ligand interaction, hydrogen bonds and ionic interactions have been applied as interactions for the assembly process. The first report of a platinum complex in which the ligands are connected through a hydrogen-bond interaction stems from 1957,[39a] though at this stage the relevance to supramolecular phenomena was not yet appreciated. Roundhill and coworkers reviewed the early history[39b] of the use of second-



Scheme 25. Palladium complex of a self-assembled bidentate phosphite ligand with a zinc(II) as template.



Scheme 26. Building blocks for supramolecular heteroleptic TADDOL phosphite ligands.

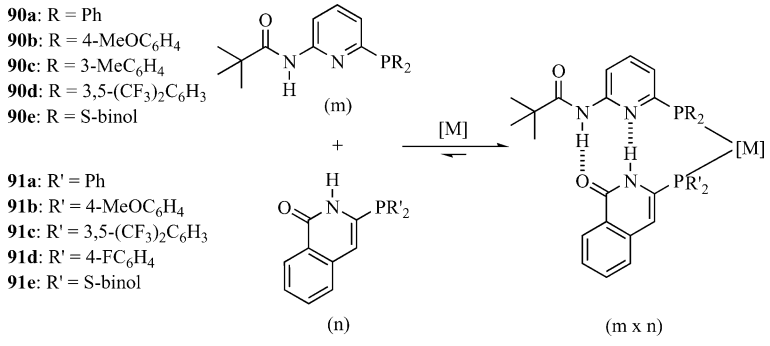


Scheme 27. Allylic amination.

ary phosphane oxides to form metal complexes, containing the phosphane oxide and the hydroxy form, which results in a strong hydrogen bond between the two ligands in the metal complex. Catalytic applications of one of their platinum complexes based on this ligand were reported by van Leeuwen et al.[40,41]

Newkome and Hager[42] published a tridentate ligand 6-(diphenylphosphanyl)-2-pyridone that forms hydrogen bonds in dinuclear palladium and platinum complexes, as was shown by Mashima, Nakamura and co-workers.[43] In the basis of this motif, Breit and Seiche reported the formation of the self-assembled bidentate phosphorus ligand in apolar solvents, and used these ligands in the rhodium-catalyzed hydroformylation.[32c] Similar binding motifs were used to prepare a ligand library based on[44a] heterobidentate phosphorus ligands, which were assembled through two hydrogen bonds of the aminopyridine/isoquinoline binding motif (Scheme 28).

Different phosphane- and phosphonite-functionalized aminopyridines and isoquinolines were synthesized, resulting in libraries containing up to 40 different self-assembled heterobidentate phosphorus ligands.[44,45] Application of a part of the library in the hydroformylation of 1-octene and the hydrogenation of methyl 2-acetamidoacrylate (**20**) revealed active and selective catalysts for both processes. The hydroformylation catalysts obtained rival catalysts based on covalent bidentates (such as Xantphos) in terms of activity and selectivity. In the hydrogenation of methyl 2-acetamidoacrylate (**20**, Scheme 10), conversions between 12 and 100% and *ee* values between 33 and 99% (with ligand **90e/91e**) were obtained. Also the hydrogenation of dimethyl itaconate (**18**, Scheme 10) displayed similar activity and selectivity ranges [conversions between 22 and 100%, *ee* values between 38 and 94% (again with ligand **90e/91e**)]. The variety of results obtained shows again the power of catalyst libraries.



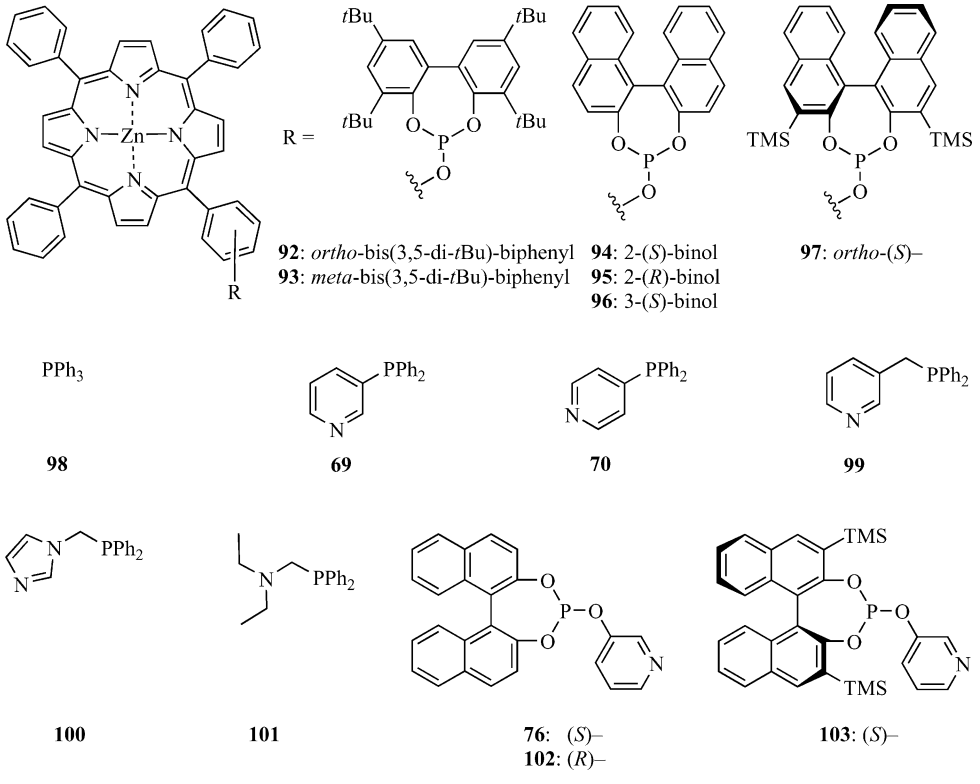
Scheme 28. Library of aminopyridine- and isoquinoline-functionalized phosphorus ligands for the formation of self-assembled bidentate ligands.

Our group recently reported UREAphos, a new class of ligand building blocks utilized with urea binding motifs. Because the urea group is a self-complementary hydrogen bond motif, initial focus has been on homobidentate ligands, and therefore only a small library (six bidentate phosphite ligands) was studied in the hydrogenation of several functionalized alkenes.[46] The selectivities obtained for various substrates were high and therefore this UREAphos represents an interesting new class of bidentate ligands, especially because the synthesis is simple and can be done using robotics. This work is currently extended to form very large ligand libraries, with homo and heterobidentate ligands.

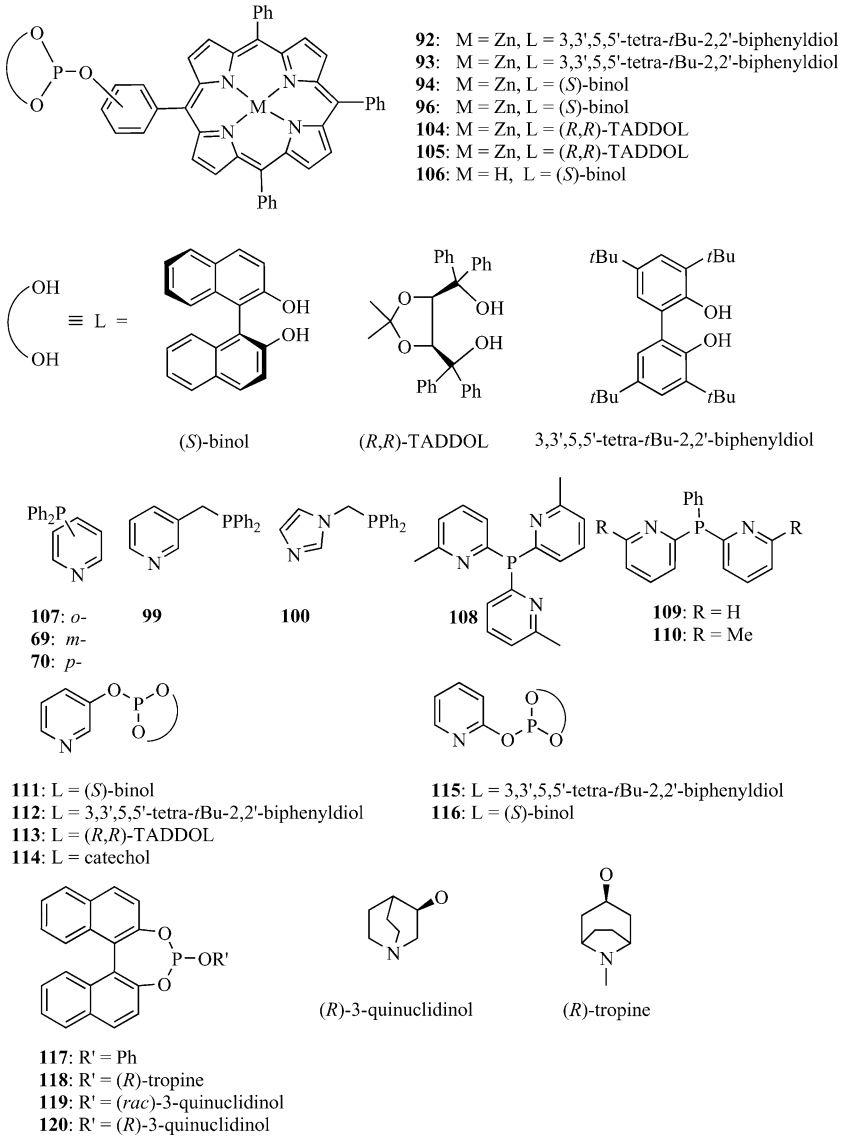
We also reported SUPRAphos, a class of self-assembled bidentate ligands based on porphyrinatozinc(II) and pyridine coordination.[47] Six phosphite-porphyrinatozinc(II) building blocks with 8 different pyridyl-functionalized phosphites or phosphanes resulted in a 48-membered library of bidentate phosphorus ligands (Scheme 29).

The bidentate character of the self-assembled ligands was proven by (high-pressure) NMR experiments and UV/Vis titrations. The library was applied in the asymmetric allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate (**29**) with dimethyl malonate. The enantiomeric excess in this reaction ranged from 87% of the (*S*) product to 86% of the (*R*) product. In these initial catalysis experiments the complex based on the monodentate ligands **94** and **95** gave, unexpectedly the highest selectivity. The selectivity for (*S*) product could even be improved to 97% *ee* (*S*) by applying the catalyst based on ligand **94** at –20 °C. The highest *ee* obtained with a complex based on a bidentate ligand **96·98** was 59% (*S*) at 25 °C and 70% of the (*S*) product at –20 °C. Importantly, small changes in ligand structure lead to large changes in selectivity and even in reversal of the *ee*. For instance, the catalyst based on ligand **94·98** resulted in 47% *ee* for the (*R*) product, whereas ligand **94·99**, containing only an additional CH_2 in the achiral pyridyl phosphane, resulted in 40% *ee* of the (*S*) product.

After the initial promising results the SUPRAphos library was extended and it currently consists of almost 400 bidentate ligands of which the most common ones are depicted in Scheme 30. A part of the library was studied in the asymmetric rhodium-catalyzed hydrogenation of trisubstituted cyclic *N*-(3,4-dihydro-2-naphthalenyl) acetamide,[48] a substrate that is inherently difficult and for which the best results with rhodium based catalysts gave only around 70% *ee*. Parallel high-throughput screening of 64 ligands showed that the substrate was converted between 0 and 100% and that the *ee* of the product obtained varied between –12 up to 94% *ee*. Interestingly, only one rhodium catalyst, based on ligand combination **94/69**, produced the product in high *ee* (94%, at 100% conversion) and the second best selectivity obtained was below 60%. This remarkable one hit in the library, which is the most selective catalyst reported to date in the literature, demonstrates that screening of large ligand libraries pays off.

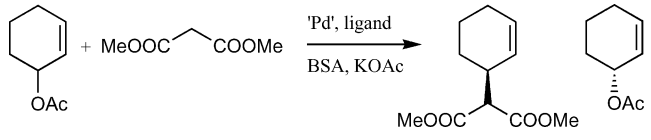


Scheme 29. The initial building blocks of the SUPRAphos ligand library that was applied in the hydroformylation and asymmetric allylic substitution.



Scheme 30. Building blocks of the SUPRAphos library that was partly applied in the asymmetric hydrogenation of a cyclic enamide and in the palladium-catalyzed kinetic resolution of cyclohexenyl acetate.

A comparable 56-membered library (4 × 14) (Scheme 30) was applied in the palladium-catalyzed kinetic resolution of racemic cyclohexenyl acetate (Scheme 31).[49]



Scheme 31. Kinetic resolution of cyclohexenyl acetate.

Conversions between 0 and 94% were obtained. Note that in an ideal kinetic resolution the conversion should not exceed 50%, providing the remaining starting material in high enantiomeric purity. The enantioselectivity for the product ranged from 0 to 65% (ligand **94**·**115**), whereas the *ee* for the remaining starting material ranged from 0 to as high as 99% (for ligand **94** in combination with **107**, **108**–**110**)! One clear trend could be distilled from the results. All catalyst systems that show good kinetic resolution (four from the 56 studied), with an *ee* of the starting material of >90%, were based on SUPRAphos ligands that contained an *ortho*-pyridylphosphane building block. The kinetic resolution (*S*-factor 12) is acceptable yielding high *ee* values of the (*S*) enantiomer above conversions of 60% at high rates (TOF 450 mol mol^{-1} h^{-1}). The combination of a high kinetic resolution and a low *ee* of the product is remarkable as usually a catalyst will lead to acceptable *ee* values of the product and a poor kinetic resolution. The transition state for the oxidative addition is similar to that of the nucleophilic attack, explaining why usually high kinetic resolution is accompanied with high *ee* of the product. The main difference of the current system with those reported in literature is the dynamic character of the ligand, enabling the

catalyst to change its coordination sphere during the various reaction steps. For instance, a decoordination of the achiral pyridylphosphane ligands from the zinc is envisioned, which could either coordinate to palladium or cause deracemization of the substrate attached to the palladium. This would explain the success of *ortho*-pyridylphosphanes, as these ligands are slightly weaker bound to the porphyrinatozinc(II) platform.

As is clear from this section, supramolecular approaches facilitate the preparation of large and diverse ligand libraries. So far, the inherent flexibility due to the noncovalent linkages does not seem to limit applications. The large ligand libraries demonstrate clearly the dramatic influence of small changes in the building blocks, being a strong push for the application of ligand library screening in catalysis research. So far, the application of supramolecular chemistry appears to be one of the most promising approaches to arrive at large and diverse libraries of bidentate phosphorus ligands.

5. Conclusions

Libraries of bidentate phosphorus ligands are in demand for all types of difficult catalytic reactions, and in particular for asymmetric transformations as accurate prediction of catalyst selectivity is beyond current potential of computation approaches. With ligand libraries of sufficient size and diversity and screening technologies currently available, proper catalysts for challenging conversions could be found within the limited time-frame that is given by the time-to-market restrictions. Currently, there is only limited technology to prepare chiral bidentate ligands and catalyst libraries thereof. This review shows that there are three main strategies to prepare such libraries:

1) *Divergent or modular synthesis*, which generally leads to a series of structurally related ligands (not so diverse), which can be a successful strategy for fine-tuning and optimization of catalysts. However, since still the ligands have to be prepared one by one, these libraries are generally rather small.

2) *The application of solid phase synthesis*, which potentially lead to larger libraries. The principle have been demonstrated but so far the libraries are not diverse and limited in size. Examples of larger and diverse libraries are expected to be reported in the nearby future.

3) *The formation of ligands by self-assembly*, which proved to be a very powerful method to provide large ligand libraries. The number of bidentate ligands grows exponentially with the number of building blocks used. The diversity of bidentate ligands can be large as well. So far the above strategies have not been combined yet, but one can imagine that if building blocks suitable for ligand assemblies are prepared using modular synthesis and/or automated (supported) synthesis the ligand libraries that become accessible are of sizes that dwarf current libraries. Efforts in this direction are currently pursued in our laboratory.

Acknowledgments

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