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Supported Chiral Monodentate Ligands in Rhodium-Catalysed Asymmetric Hydrogenation and Palladium-Catalysed Asymmetric Allylic Alkylation

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A family of monodentate polystyrene-supported phosphites, phosphoramidites and phosphanes has been prepared and evaluated as ligands in rhodium-catalysed asymmetric hydrogenation and palladium-catalysed asymmetric allylic alkylation. The supported ligands yielded active and enantioselective catalysts, which in selected cases match the performance of the nonsupported counterparts. As expected, the performance of the supported ligands in the rhodium-catalysed hydrogenation depends on the nature of the ligand, the type of polymeric support, as well as on the substrate. Additionally, the supported ligands have been applied in the monodentate ligand combination approach, by combining them with nonsupported monodentate ligands. The partially supported heteroligand combinations possess different catalytic properties than the related nonsupported combinations. The heteroligand species, however, are not formed selectively, and nonsupported homoleptic complexes also contribute to the overall activity.

Introduction

In the last decades chiral (monodentate) phosphorus ligands have proven their superiority in numerous transition-metal-catalysed asymmetric transformations.[1–3] Subtle changes in ligand structure can have a decisive influence on the stability, activity and selectivity of a catalyst. Not surprisingly, efficient (combinatorial) techniques for the preparation and evaluation of catalyst libraries in a time efficient manner are highly desirable.[2,4] The quest for efficient catalysts still relies heavily on the synthesis of ligand libraries. Several groups have successfully applied solid-phase techniques for the parallel and combinatorial synthesis of (supported) ligands.[3,5] Phosphorus based ligands are in general prone to oxidation and/or hydrolysis reactions and the major advantage of this approach is the easy purification, which can be achieved by a simple washing procedure. Waldmann and co-workers have shown that in copper-catalysed enantioselective conjugate addition reactions, polymer-bound phosphoramidites mirrored the performance of the soluble analogues.[5a] Application of solid-phase methods thus accelerates both the synthesis and the screening of ligand libraries. In addition, polymer-supported ligands allow recovery and reuse of both the transition metal and the ligand, while due to the swelling properties of the support, good mixing with the reactants can be maintained.[6–8] Illustrative are the good activities observed for a number of resin-supported chiral monodentate ligands in the rhodium-catalysed asymmetric hydrogenation.[9] The supported phosphite and phosphoramidite ligands studied so far, have been predominantly derived from the chiral BINOL moiety (BINOL = 1,1′-binaphthalene-2,2′-diol). Recently we synthesised a structurally diverse family of polymer-supported monodentate ligands[3a] and here we report their application in rhodium-catalysed asymmetric hydrogenation and palladium-catalysed asymmetric allylic alkylation reactions.

Results and Discussion

Figure 1 shows the structures of the resin-supported monodentate ligands studied. The immobilised ligands are referred to by a code, in which the letters specify the type of polymeric support, while the numbers indicate the substituents on the phosphorus atom.

Several resin-supported phosphites and phosphoramidites had been synthesised previously.[3a] We synthesised additional members by reaction of hydroxy-functionalised polystyrene (**1**) with the appropriate phosphorus chloride in the presence of a tertiary amine as a base (Scheme 1). Elemental analysis and ^{31}P gel-phase NMR[10] indicated that the ligands were formed in good yield (100–91%) and

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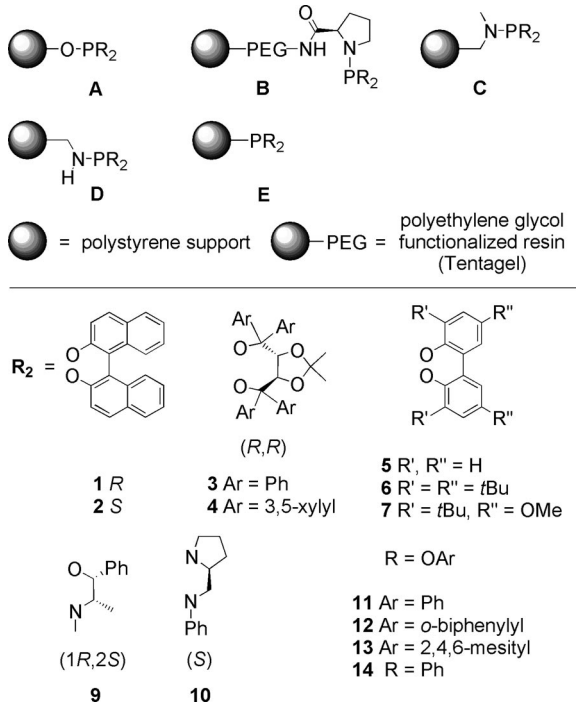
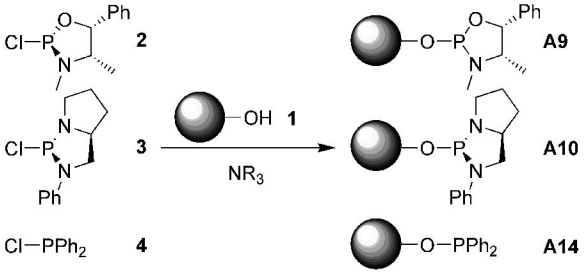


Figure 1. Structures of the supported ligands used in this study.

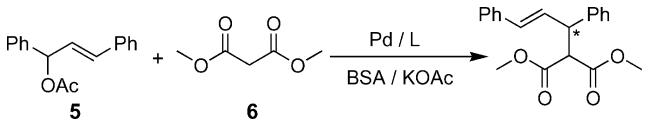
purity, with small amounts (<1%) of hydrolysis products as the major impurities. Chiral phosphoramidite **A9** was synthesised from (2*R*,4*S*,5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine (**2**) and displayed two signals in ^{31}P gel-phase NMR (141 and 135 ppm, 1:1.8) which has also been observed for nonsupported analogues[11,12] and can be assigned to the formation of the different diastereomers.[13] Chiral diamidophosphite **A10** was synthesised from (2*R*,5*S*)-2-chloro-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane (**3**).[14] It displayed a single resonance in ^{31}P gel-phase NMR at δ = 120 ppm, which, according to the observed chemical shift, indicates that the phosphorus stereocentre possesses an *R*-configuration.[15] The achiral diphenylphosphinite **A14** was prepared straightforwardly by reaction of the hydroxy-functionalised resin (**1**) with chlorodiphenylphosphane (**4**).



Scheme 1. Synthesis of **A9**, **A10** and **A14**.

Palladium-Catalysed Asymmetric Allylic Alkylation

Allylic substitution reactions are among the most widely studied catalytic reactions in organic synthesis. Asymmetric allylic alkylation is often regarded as a standard test to determine the efficiency of a ligand in asymmetric C–C bond formations.[16] Palladium, in combination with bulky monodentate phosphoramidite or phosphite ligands, yields highly active and enantioselective allylic alkylation catalysts.[17] Although a variety of polymer-supported chiral ligands have been studied in this reaction,[8b,18] resin-bound phosphite and phosphoramidite ligands have been largely neglected. We evaluated our family of supported monodentate ligands and chose the alkylation of 1,3-diphenyl-2-propenyl acetate (**5**) with dimethyl malonate (**6**) as a model reaction (Scheme 2). The results are summarised in Table 1.



Scheme 2. Palladium-catalysed alkylation of 1,3-diphenyl-2-propenyl acetate.

Table 1. Chiral monodentate polymer-supported ligands in the palladium-catalysed allylic alkylation. Reaction conditions: Pd/ligand/**5/6**/BSA = 1:2:100:300:300, [Pd] = 5 mM, CH_2Cl_2, room temp., pinch of KOAc added, catalyst precursor: $[Pd(allyl)Cl]_2$, catalyst incubation time: 15 min, reaction time: 16 h.

Entry	Ligand	Conversion[a]	*ee*[b]
1	**A1**	100	14 (*R*)
2	**A3**	100	31 (*S*)
3	**A9**	100	7 (*S*)
4	**A10**	100	0[c]
5	**B4**	84	58 (*S*)
6	**B7**	87	2 (*R*)
7	**C2**	100	32 (*R*)
8	**C4**	85	52 (*S*)
9	**L1**	99	89 (*S*)[d]
10	**L3**	100	25 (*S*)[e,f]
11	**L3**	100	29 (*S*)[e]

[a] Given in %, based on conversion of **5**. Determined by GC with *n*-decane as internal standard. [b] Given in %. Determined by HPLC (Daicel OD). [c] Pd/ligand, 1:1, immobilised catalyst purified prior to the reaction. [d] Taken from ref.[17]. [e] Pd/ligand/**5/6**/BSA = 1:2:20:60:60. [Pd] = 3.8 mM. [f] Pd/ligand, 1:1.

Application of two equivalents of phosphites **A1** and **A3**, phosphoramidites **A9**, **B7** and **C2** and diamidophosphite **A10** resulted in active catalysts, giving the products in quantitative yields (Entries 1–4 and 6–7). The ligands do not create an efficient chiral environment around the catalytic centre, as the enantioselectivities were low (0–32%). Supported phosphoramidites **B4** and **C4**, derived from the chiral TADDOL moiety gave the product in somewhat higher enantiomeric purities (58 and 52% *ee*, respectively), albeit displaying lower activities (84 and 85% conversion, Entries 5 and 8, TADDOL = α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol).[19] Interestingly, the type of polymeric support and the type of amido linker (**B** vs. **C**) appears to have a limited influence on the performance, as both the activity and enantioselectivity of **B4** and **C4** are comparable. Never-

theless, the support does clearly influence the performance. Compared to **L1** (Figure 2), the supported analogues **B4** and **C4** are far less efficient ligands (Entries 5, 8 and 9). Not only do they give the products in lower yields (84–85% vs. 99%), the immobilised ligands display far lower enantioselectivities (52–58% vs. 89% *ee*). Application of **A10** leads to racemic product (Entry 4) and its performance is in contrast to the nonsupported analogue **L2**, which induces up to 78% *ee*.[15] (*R*)-monophos (**L3**) and the related polymer-supported **C2**, display similar enantioselectivities (29 and 32% *ee*, Entries 7 and 10–11). Although only a limited number of supported ligands have been compared with their nonsupported analogues, it can be concluded that the performances of the supported catalysts do not meet those of their solution counterparts.

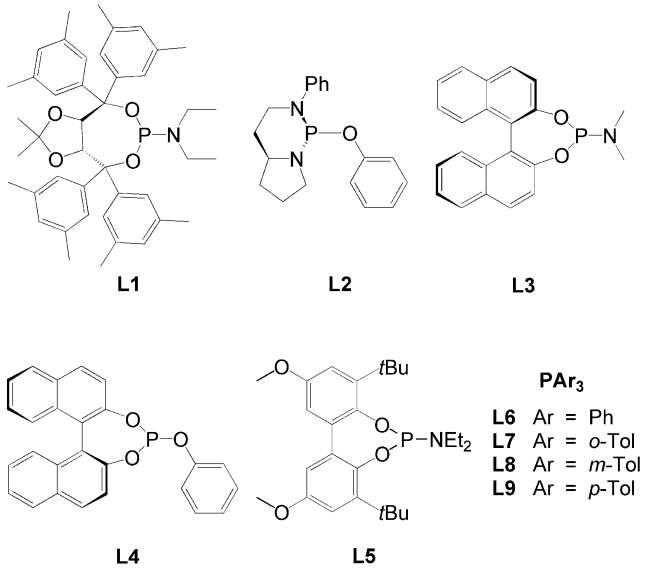
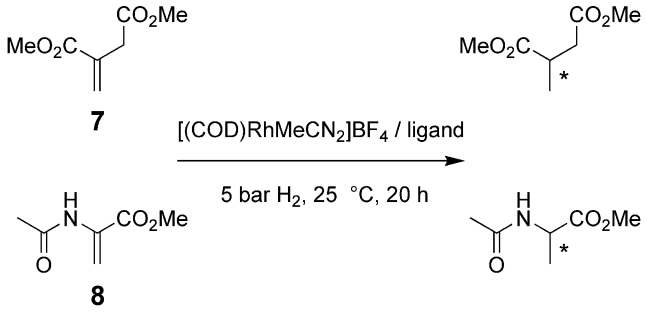


Figure 2. Nonsupported monodentate ligands applied in the studies.



Scheme 3. Rhodium-catalysed asymmetric hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate.

Table 2. Performance of resin-supported ligands in the hydrogenation of **7**. Reaction conditions: Rh/**7** 1:40, [Rh] = 2.8 mM, 5 bar H_2, CH_2Cl_2, room temp., catalyst formed in situ, catalyst precursor: $[(COD)Rh(MeCN)_2]BF_4$, catalyst incubation time: 30 min, reaction time: 20 h.

Entry	Ligand	Ligand/Rh	Conversion[a]	*ee*[b]
1	**A1**	1	100	11 (*R*)
2	**A1**	2	100	17 (*R*)
3	**A3**	1	100	24 (*R*)
4	**A3**	2	69	29 (*R*)
5	**A9**	1	100	24 (*R*)
6	**A9**	2	100	21 (*R*)
7	**B1**	1	100	41 (*R*)
8	**B1**	2	80	41 (*R*)
9	**C1**	2	16	16 (*R*)[c,d,e]
10	**C1**	2	21	24 (*R*)[c,d]
11	**C1**	1	100	77 (*R*)[c]
12	**C1**	2	100	70 (*R*)[c]
13	**D2**	1	98	> 97 (*S*)
14	**L3**	1	100	> 97 (*R*)
15	**L3**	2	100	> 97 (*R*)
16	**L4**	1	100	97 (*S*)[f]

[a] Based on conversion of **7**, determined by GC with *n*-decane as internal standard. [b] Determined by chiral GC. [c] Rh/substrate, 1:20, [Rh] = 5.0 mM. Catalyst precursor: $[Rh(COD)_2]BF_4$. [d] 1 bar H_2. [e] Reaction mixture shaken. [f] From ref.[20b]; Rh/**7** = 1:1000, 1.3 bar H_2.

Rhodium-Catalysed Hydrogenation

Chiral monodentate phosphites and phosphoramidites belong to the most efficient ligands known for rhodium-catalysed asymmetric hydrogenation of alkenes and carbon–element double bonds.[1a,1b,20] Resin-bound chiral ligands have proven their efficiency in asymmetric hydrogenation, but mostly BINOL derived phosphites or P-chiral phosphanes have been studied.[9] We evaluated our family of supported monodentate phosphites and phosphoramidites in the rhodium-catalysed hydrogenation of dimethyl itaconate (**7**, Scheme 3) and methyl 2-acetamidoacrylate (**8**), of which the results are summarised in Table 2.

First we studied in situ formed catalysts, for which we allowed the supported ligand and the catalyst precursor ($[(COD)Rh(MeCN)_2]BF_4$) to react for 30 min in DCM prior to the catalytic reaction (see Supporting Information for details). We applied both 1:1 and 1:2 metal to ligand ratios, as different coordination modes of the metal to the resin (e.g. monodentate vs. bidentate) may reflect on the catalytic performance.[21] Generally the catalyst displayed good activities, but gave the product in low to moderate enantioselectivities. Illustrative is the results obtained with supported phosphite **A1**, which is derived from the chiral *R*-BINOL moiety. With a metal to ligand ratio of 1:1, the ligand gave the product quantitatively in 11% *ee* (Entry 1). With a ligand to metal ratio of two, the enantiomeric excess (*ee*) increased slightly to 17% (Entry 2).[22] The low enantioselectivity is in sharp contrast to that observed for the related nonsupported phosphite **L4** (Figure 2), as this gives the product in 97% *ee* (Entry 16). Similar drastic drops in enantioselectivity as a result of the immobilisation on a (polymeric) support have been reported for other ligands.[9d] The low enantioselectivities induced by ephedrine derived phosphoramidite **A9** (21–24% *ee*, Entries 5–6) is comparable to related nonsupported oxazaphospholidines, for which up to 40% *ee* has been reported.[12] Application of TADDOL-derived phosphite **A3** resulted in active catalysts, but inducing only low enantioselectivities (Entries 3–4). Use

of two equivalents of **A3** resulted in a considerable drop in conversion (100 vs. 69%), while the *ee* increased slightly from 24 to 29% (Entry 3 vs. 4). We attribute this difference in performance to a lower percentage of uncoordinated rhodium as a result of the higher ligand to metal ratio. A comparable behaviour was observed for phosphoramidite **B1** (Entries 7–8). Increasing the ligand to metal ratio to two resulted in a drop in conversion (100 to 80%), although for this ligand the enantioselectivity was not affected (41% *ee*). Phosphoramidite **C1** was studied under various conditions and the results indicate that the performance of the catalyst is very sensitive to the reaction conditions (Entries 9–12).[23] Under one bar of hydrogen pressure and with a ligand to metal ratio of two the catalyst displayed a poor catalytic performance; i.e. both conversion and enantioselectivity were low (Entries 9–10). Increasing the hydrogen pressure to five bars resulted in a considerable increase of both activity and enantioselectivity (100% conversion, 70% *ee*, Entry 11). The enantioselectivity increased even further to 77% *ee* when the metal and ligand were applied in equimolar amounts (Entry 12). The nonsupported **L3** is, compared to **C1**, significantly more enantioselective (97% *ee*, Entries 14–15). A direct comparison of the performances of the related **B1**, **C1** and **L3** is, however, not possible, as the structure of the amido moiety of phosphoramidites has a profound influence on the catalytic performance.[24] With ligand **D2**, derived from a primary amine-functionalised resin,[23] the product was formed in nearly quantitative yield and in excellent enantiomeric purity (> 97% *ee*, Entry 13). This result is particularly interesting, as several groups have observed that the N–H proton in primary amine derived phosphoramidites has a crucial influence on both the stability of the ligand and the performance of the hydrogenation catalyst.[9d,25,26] The latter effect has been attributed to hydrogen bonds, but since phosphoramidite **D2** is immobilised on a polymeric support, which restricts the occurrence of these interactions, our data indicate that other factors also play a role.[26] Nonsupported rhodium species may contribute to the activity of the in situ formed catalysts and as a result will lower the overall enantioselectivity. We therefore determined the performance of purified resins. To this purpose, the resin and the catalyst precursor (1:1) were allowed to react in DCM for 14 h, followed by removal of the solvent phase and washing of the resin. For ligand **A1**, the purified catalyst displayed a considerably lower activity (54 vs. 100% conversion) and proved to be less enantioselective (7 vs. 17% *ee*) than the in situ generated catalysts (Entry 1, Table 3 vs. Entries 1–2, Table 2). This suggests that in the purified and the in situ generated catalysts, the catalytic centre is present in different environments.[27] Generally, the solvent has a profound influence on the activity and enantioselectivity of rhodium hydrogenation catalysts.[1a] Furthermore the type of solvent determines the swelling of polystyrene resins and thereby influences the accessibility of the catalytic centre.[8d,9a,28] We therefore studied the performance of preformed **A1**-based catalysts in methanol and toluene (Entries 2–3, Table 3). The enantioselectivities in these solvents are very comparable to those observed for dichloromethane (7–9% *ee*). The conversions showed somewhat more variation (54–71%). Surprisingly, the highest activity (71% yield) was observed in methanol, a solvent in which the resins swell poorly. The purified catalysts derived from **A10** displayed good activity in dichloromethane (100% conversion), but gave the product as a racemate (Entry 4). Finally, we evaluated the performance of preformed catalysts in the hydrogenation of methyl 2-acetamidoacrylate (**8**, Scheme 3). Again good activities were observed, giving the product in almost all cases in quantitative yields (Entries 5–9). The product was formed in good enantiopurity when BINOL derived ligands **A1** and **C2** were applied (78 and 80% *ee*, Entries 5 and 7). Application of TADDOL derived phosphite **A3** gave nearly racemic product (5% *ee*, Entry 6).

Table 3. Performance of purified resin-supported hydrogenation catalysts. Reaction conditions: Rh/ligand/substrate = 1:1:62, [Rh] = 2.8 mM, 5 bar H_2, CH_2Cl_2, room temp., catalyst precursor: [(COD)Rh(MeCN)$_2$]BF_4, catalyst formed for 14 h prior to purification, reaction time: 24 h.

Entry	Ligand	Substrate	Solvent	Conversion[a]	*ee*[b]
1	**A1**	**7**	CH_2Cl_2	54	7 (*R*)[c]
2	**A1**	**7**	MeOH	71	7 (*R*)[h]
3	**A1**	**7**	toluene	67	9 (*R*)[h]
4	**A10**	**7**	CH_2Cl_2	100	0
5	**A1**	**8**	CH_2Cl_2	100	78 (*S*)[d]
6	**A3**	**8**	CH_2Cl_2	100	5 (*R*)[d]
7	**C2**	**8**	CH_2Cl_2	96	80 (*R*)[e]
8	**L3**	**8**	CH_2Cl_2	100	> 97 (*S*)[e,f]
9	**L4**	**8**	CH_2Cl_2	100	81 (*R*)[f,g]

[a] Based on conversion of the substrate, determined by GC with *n*-decane as internal standard. [b] Determined by chiral GC. [c] [Rh] = 6.3 mM. Reaction time = 14 h. [d] [Rh] = 8.8 mM. [e] [Rh] = 1.3 mM. [f] Catalyst formed in situ. [g] From ref.[20b]; Rh/**8** = 1:1000, 1.3 bar H_2. [h] Rh/ligand = 1:2, [Rh] = 6.3 mM. Catalyst preformed in CH_2Cl_2. Reaction time: 20 h.

Interestingly, for methyl 2-acetamidoacrylate the enantioselectivities obtained with the supported **A1** and the related nonsupported **L4** are comparable (78 vs. 81% *ee*), while for dimethyl itaconate as the substrate the performances of the supported and nonsupported ligands are considerably different (7% *ee* for **A1** and 97% for **L4**). In contrast, for both substrates **L3** induced considerably higher *ee* values (roughly 97%) than **C1** or **C2** (roughly 80% *ee*). Although only two substrates have been applied, the results indicate that the complex relationship between the catalytic properties of polymer-supported catalysts and their homogeneous analogues is also dependent on the type of substrate.

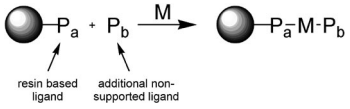
Application of Polymer-Supported Ligands in the Heterocombinations of Ligands

The discovery that heterocombinations of chiral monodentate ligands can yield more active and enantioselective catalysts than the homocombinations has been an important breakthrough in asymmetric catalysis.[2] The methodology allows the screening of very large libraries of ligand

combinations, with only limited synthetic effort.[29] NMR studies have revealed that homocombinations, e.g., $(P_a)_2M$; see Equation (1), are present in the mixture and these species can lower the overall catalytic performance of the system.[30]

$$P_a + P_b + M \rightarrow (P_a)_2M + P_aP_bM + (P_b)_2M \quad (1)$$

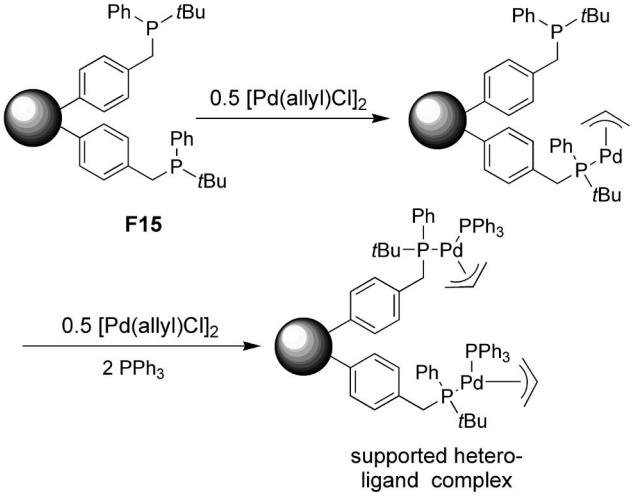
The site isolation of polystyrene-bound monodentate ligands, as a result of the immobilisation on the support, can inhibit the formation of bis-ligated species.[21,31] We anticipated that, as a result of the site isolation offered by the polymeric support, resin-supported monodentate ligands would lead to the selective formation of the desired heteroligand complex (Scheme 4).



Scheme 4. Selective formation of supported heteroligand complexes.

Preliminary results indicate that the approach indeed leads to the formation of supported palladium heteroligand complexes. When a (*tert*-butyl)(benzyl)(phenyl)phosphane-based resin (**F15**, Scheme 5)[32] was in situ reacted with 0.25 equiv. $[Pd(allyl)Cl]_2$ (**F15**/Pd, 2:1, solvent = THF/C_6D_6, 8:1), two broad signals were observed in the ^{31}P gel-phase NMR spectrum (Figure 3, spectrum **I**). The upfield signal at roughly 9 ppm corresponds to the uncoordinated phosphane (marked in Figure 3 with ^), while the palladium complex displays a signal at roughly 46 ppm (marked with *). The integral corresponds to the involvement of approximately 50% of the phosphanes in coordination to the metal centre, indicating that the metal is not coordinated in a bis-ligated manner (Scheme 5). The resin was subsequently allowed to react with 0.25 equiv. $[Pd(allyl)Cl]_2$ and 1 equiv. PPh_3 (**F15**:Pd:PPh_3 1:1:1). In the ^{31}P gel-phase NMR spectrum (**II**), the signal corresponding to uncoordinated **F15** was virtually absent, indicating that all resin-supported phosphanes are coordinated to the metal. No phosphorus containing species were observed in the solution phase above the resin (spectrum **III**). This signifies that the PPh_3 was immobilised on the resin as a result of coordination to the palladium centre, thus the formation of a supported heteroligand complex (Scheme 5).

Although supported heteroligand catalysts have been reported,[33] to the best of our knowledge the methodology has not yet been applied in a combinatorial approach. For the catalytic reactions, we turned our attention to the rhodium-catalysed hydrogenation. This reaction has been extensively studied in the heteroligand approach, giving vital information on the performance and behaviour of (related) nonsupported heteroligand catalysts. We started by studying in situ generated catalyst, formed by reaction of equimolar amounts of the resin (P_a), the nonsupported ligand (P_b) and the catalyst precursor in DCM. The structures of the supported and nonsupported ligands are depicted in Figures 1 and 2. The performance of a selection of hetero-



Scheme 5. Stepwise formation of a supported heteroligand palladium complex. Chloride anions and charges have been omitted for clarity.

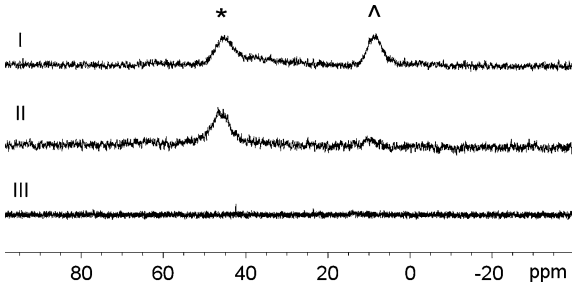


Figure 3. NMR spectra corresponding to the stepwise formation of a supported heteroligand palladium complex.

ligand combinations is given in Table 4 (see Exp. Section for the full set of data). The performances of the combination ranged from good (100% conversion and 73% *ee* for the **E14/L3** combination, Entry 8) to very poor (9% conversion and 9% *ee* for the **C2/L7** combination, Entry 5). The influence of the type of nonsupported ligand on the catalytic performance is particularly evident if the performances of the related **C2/L7**, **C2/L8** and **C2/L9** systems are compared (Entries 5–7). The most active system is formed by combining **C2** with **L9** (88% yield), while **C2/L7** is roughly ten times less active (9%) and the activity of **C2/L8** is in between (50%). The enantioselectivity follows a different trend; with **L8** inducing the highest *ee* (43%), while **L9** results in almost racemic product. Typical heteroligand effects become evident by comparing the performance of a hetero-system with the performances of the two parent ligands. For example, for **A9** full conversion and 24% *ee* was observed (Entries 5–6, Table 2). For the **A9/18** combination the conversion drops to 80% and the *ee* increases to 40% (Entry 1, Table 4). Thus, in the presence of the achiral tris-*ortho*-tolylphosphane (**L7**) the *ee* observed for **A9** increases, indicating that the supported heteroligand catalyst is formed successfully. Similarly, for **B1/L5** the results indicate that the heteroligand catalyst is formed. Ligand **B1** gives the product in 41% *ee* (*R*) (Entries 7–8, Table 2). In combination

with the achiral phosphoramidite **L5**, the *ee* increases to 53% (Entry 2, Table 4). Combining **B1** with the achiral phosphane **L7**, results in 46% *ee*, but now predominately as the *S*-isomer (Entry 3, Table 4). Thus, a switch in chirality of the product can be induced by addition of an appropriate achiral monodentate phosphane. Similar effects have been observed by others for related nonsupported systems.[29]

Table 4. Performance of heteroligand combinations in the hydrogenation of **7**. Reaction conditions: Rh/**7** = 1:40, [Rh] = 2.8 mM, 5 bar H_2, CH_2Cl_2, room temp., catalyst formed in situ, catalyst precursor: $[(COD)Rh(MeCN)_2]BF_4$, catalyst incubation time: 30 min, reaction time: 20 h.

Entry	P_a	P_b	Conversion[a]	*ee*[b]
1	**A9**	**L7**	80	40 (*R*)
2	**B1**	**L5**	60	53 (*R*)
3[c]	**B1**	**L7**	86	46 (*S*)
4	**C2**	**L5**	25	5 (*R*)
5[c]	**C2**	**L7**	9	9 (*S*)
6[c]	**C2**	**L8**	50	43 (*S*)
7[c]	**C2**	**L9**	88	1 (*R*)
8	**E14**	**L3**	100	73 (*R*)
9	**L6**	**L3**	100	> 97 (*R*)

[a] Based on conversion of **7**, determined by GC with *n*-decane as internal standard. [b] Determined by chiral GC (Betadex 325). [c] Reaction mixture was not stirred.

Interestingly, resin **C2** in combination with the achiral **L5** and **L7** displayed considerably lower activities and enantioselectivities than the **B1/L5** and **B1/L7** combinations (Entries 2 vs. 4 and 3 vs. 5). Because both resins are BINOL-based, this fact indicates that the type of support (resin **B** vs. **C**) has a decisive influence on the performance of the heteroligand system. This can be attributed to the differences in amido linker (proline vs. *N*-methylbenzylamine), but the different microenvironments supplied by the two polymeric supports may be equally important. The influence of the microenvironment is also evident from the different performance of **E14/L3** and **L6/L3** (Entries 8–9). In these related systems, triphenylphosphane is either present in its supported form (**E14**) or as a nonsupported ligand (**L6**). The immobilisation of the triphenylphosphane results in a significant decrease in enantioselectivity (73% *ee* for **E14/L3** vs. > 97% *ee* for **L6/L3**). We attribute this difference to the site isolation offered by the polymer, influencing the ratios in which the various homo- and heteroligand complexes are formed.[34] On the basis of this result, it can not be confirmed that the supported heteroligand species is formed selectively. The presence of nonsupported species was confirmed by experiments in which the activity of the solution and resin phases were determined independently, for which the data are given in Table 5.[35] When after 40 min reaction time the solution phase of **E14/L3** was separated from the polymeric phase and allowed to react for another 19 h, the product was obtained in >97% *ee* (Entry 5). For the heteroligand combination in which the phases were not separated the product was obtained in a lower *ee* of 73% *ee* (Entry 4). This indicates that (highly enantioselective) **L3**-based species are present in the solution phase of the **E14/L3** system. Similarly, for the **A2/L3** combination the product is formed quantitatively in >97% *ee* (Entry 1). The solution phase, separated from the resin prior to the catalytic reaction, displays a similar activity; although the enantioselectivity is lower (67% *ee*, Entry 2). The resin phase, which was also applied as a catalyst, proved equally active, but gives the product in only 5% *ee* (Entry 3). Thus, nonsupported species (of **L3**) are present in the solution phase. The fact that the resin and solution phases do not match the performance of the combined phases indicates that in the in situ system the heteroligand catalyst is formed and contributes to the overall activity. Thus, although the polymeric support does influence the ratio of the homo- and heteroligand species (and thereby the catalytic performance), the site isolation offered by the resin is not sufficient for the selective formation of the immobilised heteroligand rhodium complexes.[36,37]

Table 5. Catalytic performance of the solution and polymeric phase of in situ generated heterocombinations in the hydrogenation of **7**. Reaction conditions: Rh/**7** = 1:40, [Rh] = 2.8 mM, 5 bar H_2, CH_2Cl_2, room temp., catalyst formed in situ, catalyst precursor: $[(COD)Rh(MeCN)_2]BF_4$, catalyst incubation time: 30 min, reaction time: 20 h.

Entry	P_a	P_b	Phase	Conversion[a]	*ee*[b]
1	**A2**	**L3**	both	100	> 97 (*R*)
2	**A2**	**L3**	solution	100	67 (*R*)[c]
3	**A2**	**L3**	resin	100	5 (*R*)[c]
4	**E14**	**L3**	both	100	73 (*R*)
5	**E14**	**L3**	solution	100	> 97 (*R*)[d]

[a] Based on conversion of the substrate, determined by GC with *n*-decane as internal standard. [b] Determined by chiral GC (Betadex 325). [c] Solution and resin phase separated prior to catalysis after incubation time of 14 h. [d] Solution and resin separated after 40 min reaction time. Solution phase returned to autoclave for an additional 19 h reaction time.

Conclusions

In conclusion, polystyrene-supported (chiral) monodentate phosphites and phosphoramidites have been studied as ligands for transition-metal-catalysed asymmetric reactions. In the palladium-catalysed asymmetric allylic alkylation, moderate to good activities and enantioselectivities were observed. In the rhodium-catalysed hydrogenation, the polymers yielded active and enantioselective catalysts. Several supported ligands induced lower activities and enantioselectivities than their homogeneous analogues. A general correlation between the catalytic performance of the supported and nonsupported analogues was not found. Moreover, it turned out that the relationship between the catalytic properties of the two counterparts is highly dependent on the type of substrate. In addition, we applied the polymer-bound ligands in the heteroligand combination approach by combining them with nonsupported monodentate ligands. We anticipated that the site isolation offered by the polymeric support would yield the heteroligand complex selectively. The results, however, indicate that the systems consist of mixtures of supported and nonsupported homo- and heteroligand species.

Experimental Section

General Remarks: All reactions were carried out under strictly oxygen and water free conditions, using standard Schlenk techniques under an atmosphere of purified nitrogen or argon. Chemical were purchased in highest commercially available purity from Acros Chimica, Aldrich Chemical Co., Biosolve, Fluka and Merck and were used as received, unless indicated otherwise. Toluene and C_6D_6 was distilled from sodium, diethyl ether and THF from sodium/benzophenone, tertiary amines, dichloromethane and methanol were distilled from calcium hydride. Chlorodiphenylphosphane was freshly distilled prior to use. (2*R*,4*S*,5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine (**2**) was synthesised according to a literature procedure.[38] Dr. N. Vautravers and Prof. D. Cole-Hamilton are greatly acknowledged for a generous gift of (2*R*,5*S*)-1,3-diaza-2-chloro-3-phenyl-2-phosphabicyclo[3.3.0]octane (**3**). 4-hydroxyphenol, polymer-bound (**1**, 1% DVB-PS, 50–100 mesh, 0.91 mmol/g) was purchased from Aldrich. Polymer-supported triphenylphosphane (**E14**, 1% DVB-PS, 100–200 mesh, 1.2–1.5 mmol/g) was purchased from Acros Chimica and with the exeption of **A9**, **A10**, **A11** and **A14**, all other resin-bound ligands were synthesised according to literature procedures.[3a] The monodentate phosphites were synthesised according to literature procedures.[3a] NMR spectra were recorded at room temperature on a Bruker Avance 300, a Bruker Avance 400 NMR, a Varian Mercury 300 or a Varian Inova 500 spectrometer. Positive chemical shifts (δ) are given (in ppm) for high-frequency shifts relative to an 85% H_3PO_4 in D_2O reference (^{31}P). Gel-phase ^{31}P NMR spectra of the resins suspended in THF (using a D_2O inner tube) or THF/C_6D_6 (8:1) were recorded using standard NMR techniques. Elemental analyses were carried out by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany.

Preparation of A9: 545 mg (0.50 mmol) 4-hydroxyphenol polymer-bound resin (**1**) was washed with THF (3 × 5 mL) and suspended in 10 mL toluene. After 1 h 1.0 mL *i*Pr_2NEt (3.8 mmol, 7.6 equiv.) was added, followed by 236 mg (2*R*,4*S*,5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine (**2**; 1.03 mmol, 2.07 equiv.). A gentle flow of argon was bubbled through the mixture for several 5 min periods within 3 h, after which the reaction was allowed to proceed for an additional 14 h. The suspension was filtered and the resin washed with subsequently toluene, THF, DCM, Et_2O, DCM and Et_2O (5 mL each) and dried under a gentle flow of argon, followed by drying under vacuum. ^{31}P NMR (THF/C_6D_6, 8:1): 141 ppm (broad singlet), 135 ppm (broad singlet); (10:18). Microanalysis: found P 2.17%.

A10, A11 and A14: Were prepared in a similar manner, replacing **2** with the appropriate phosphorus-chloride reagent. **A10**: ^{31}P NMR (THF): 120 ppm. **A11**: ^{31}P NMR (THF/C_6D_6, 8:1): 128 ppm. Microanalysis: found P 1.14%. **A14**: ^{31}P NMR (THF/C_6D_6, 8:1): 112 ppm. Microanalysis: found P 2.46%.

Supporting Information (see also the footnote on the first page of this article): ^{31}P NMR spectra for supported ligands **A9**, **A10**, **A11** and **A14** and for the supported palladium allyl heteroligand complex, procedures for the catalytic reactions and the full data for the performance of the heteroligand combinations studied.

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[1] a) M. van den Berg, A. J. Minnaard, R. M. Haak, M. Leeman, E. P. Schudde, A. Meetsma, B. L. Feringa, A. H. M. de Vries, C. E. P. Maljaars, C. E. Willans, D. Hyett, J. A. F. Boogers, H. J. W. Henderickx, J. G. de Vries, *Adv. Synth. Catal.* **2003**, *345*, 308–322; b) M. T. Reetz, A. Meiswinkel, G. Mehler, K. Angermund, M. Graf, W. Thiel, R. Mynott, D. G. Blackmond, *J. Am. Chem. Soc.* **2005**, *127*, 10305–10313; c) S. Alexakis, J. Burton, J. Vastra, C. Benhaim, X. Fournioux, A. van den Heuvel, J.-M. Leveque, F. Maze, S. Rosset, *Eur. J. Org. Chem.* **2000**, 4011–4027; d) G. J. H. Buisman, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Tetrahedron: Asymmetry* **1993**, *4*, 1625–1634; e) M. Baker, P. G. Pringle, *J. Chem. Soc., Chem. Commun.* **1991**, 1292–1293. For a review see: M. van den Berg, B. L. Feringa, A. J. Minnaard, in: *Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, Germany, **2007**, vol. 3, P995–1028.

[2] a) M. T. Reetz, *Angew. Chem. Int. Ed.* **2008**, *47*, 2556–2588; b) D. Peña, A. J. Minnaard, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Org. Biomol. Chem.* **2003**, *1*, 1087–1089; c) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem. Int. Ed.* **2003**, *42*, 790–793.

[3] a) B. H. G. Swennenhuis, R. Chen, P. W. N. M. van Leeuwen, J. G. de Vries, P. C. J. Kamer, *Org. Lett.* **2008**, *10*, 989–992; b) R. den Heeten, B. H. G. Swennenhuis, P. W. N. M. van Leeuwen, J. G. de Vries, P. C. J. Kamer, *Angew. Chem. Int. Ed.* **2008**, *47*, 6602–6605.

[4] a) C. Gennari, U. Piarulli, *Chem. Rev.* **2003**, *103*, 3071–3100; b) M. Reetz, *Angew. Chem. Int. Ed.* **2001**, *40*, 284–310; c) K. Ding, H. Du, Y. Yuan, J. Long, *Chem. Eur. J.* **2004**, *10*, 2872–2884; d) J. G. de Vries, L. Lefort, *Chem. Eur. J.* **2006**, *12*, 4722–4734; e) C. J. Jäkel, R. Paciello, *Chem. Rev.* **2006**, *106*, 2912–2942; f) L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, *Org. Lett.* **2004**, *6*, 1733–1735.

[5] a) O. Huttenloch, E. Laxman, H. Waldmann, *Chem. Eur. J.* **2002**, *8*, 4767–4780; b) A. Agarkov, S. J. Greenfield, T. Ohishi, S. E. Collibee, S. R. Gilbertson, *J. Org. Chem.* **2004**, *69*, 8077–8085; c) S. C. Gilbertson, S. E. Collibee, A. Agarkov, *J. Am. Chem. Soc.* **2000**, *122*, 6522–6523; d) Y. Kobayashi, D. Tanaka, H. Danjo, Y. Uozumi, *Adv. Synth. Catal.* **2006**, *348*, 1561–1566.

[6] For reviews on polymer-supported catalysts, see: a) *Chem. Rev.* **2002**, *102*, issue 10; b) M. Guinó, K. K. Hii, *Chem. Soc. Rev.* **2007**, *36*, 608–617; c) J. Lu, P. H. Toy, *Chem. Rev.* **2009**, *109*, 815–838; d) D. E. Bergbreiter, J. Tian, C. Hongfa, *Chem. Rev.* **2009**, *109*, 530–582; e) I. Tóth, P. C. van Geem, in: *Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, vol. 3, p. 1421–1470.

[7] a) *Chiral Catalysts Immobilization and Recycling* (Eds.: D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim, Germany, **2000**; b) A. F. Trindade, P. M. P. Gois, C. A. M. Afonso, *Chem. Rev.* **2009**, *109*, 418–514.

[8] a) B. Clapham, T. S. Reger, K. D. Janda, *Tetrahedron* **2001**, *57*, 4637–4662; b) C. R. Landis, T. P. Clark, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5428–5432; c) C. E. Song, J. W. Yang, E. J. Roh, S. G. Lee, J. H. Ahn, H. Han, *Angew. Chem. Int. Ed.* **2002**, *41*, 3852–3854; d) S. R. Gilbertson, S. Yamada, *Tetrahedron Lett.* **2004**, *45*, 3917–3920.

[9] a) W. Chen, S. M. Roberts, J. Whittall, *Tetrahedron Lett.* **2006**, *47*, 4263–4266; b) X.-P. Hu, J.-D. Huang, Q.-H. Zeng, Z. Zheng, *Chem. Commun.* **2006**, 293–295; c) A. Mandoli, M. Calamante, B. L. Feringa, P. Salvadoria, *Tetrahedron: Asymmetry* **2003**, *14*, 3647–3650; d) S. Doherty, E. G. Robins, I. Pal, C. Newman, C. Hardacre, D. Rooney, D. A. Mooney, *Tetrahedron: Asymmetry* **2003**, *14*, 1517–1527.

[10] a) F. Bardella, R. Eritja, E. Pedroso, E. Giralt, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2193–2196; b) C. R. Johnson, B. Zhang, *Tetrahedron Lett.* **1995**, *36*, 9253.

[11] a) N. Oka, T. Wada, K. Saigo, *J. Am. Chem. Soc.* **2003**, *125*, 8307–8317; b) G. Delapierre, J. M. Brunel, T. Constantieux, G. Buono, *Tetrahedron: Asymmetry* **2001**, *12*, 1345–1352.

[12] M. T. Reetz, M. Surowiec, *Heterocycles* **2006**, *67*, 567–574.
[13] a) J. M. Brunel, O. Chiodi, B. Faure, F. Fotiadu, G. Buono, *J. Organomet. Chem.* **1997**, *529*, 285–294; b) O. Legrand, J. M. Brunel, T. Constantieux, G. Buono, *Chem. Eur. J.* **1998**, *4*, 1061–1067.
[14] S. Breeden, M. Wills, *J. Org. Chem.* **1999**, *64*, 9735–9738.
[15] V. N. Tsarev, S. E. Lyubimov, A. A. Shiryaev, S. V. Zheglov, O. G. Bondarev, V. A. Davankov, A. A. Kabro, S. K. Moiseev, V. N. Kalinin, K. N. Gavrilov, *Eur. J. Org. Chem.* **2004**, *10*, 2214–2222.
[16] a) B. M. Trost, M. R. Machacek, A. Aponick, *Acc. Chem. Res.* **2006**, *39*, 747–760; b) Z. Lu, S. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297; c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2944; d) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336–345; e) T. Hayashi, M. Kawatsura, Y. Uozomi, *Chem. Commun.* **1997**, 561–562; f) C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron: Asymmetry* **1992**, *3*, 1089–1122.
[17] See for instance: a) E. Raluy, M. Dieguez, O. Pamies, *J. Org. Chem.* **2007**, *72*, 2842–2850; b) B. D. Chapsal, I. Ojima, *Org. Lett.* **2006**, *8*, 1395–1398; c) M. D. K. Boele, G. P. F. van Strijdonck, P. C. J. Kamer, M. Lutz, A. L. Spek, J. G. de Vries, P. W. N. M. van Leeuwen, *Chem. Eur. J.* **2004**, *10*, 6232–6246; d) A. I. Polosukhin, O. G. Bondarev, S. E. Lyubimov, A. V. Korostylev, K. A. Lyssenko, V. A. Davankov, K. N. Gavrilov, *Tetrahedron: Asymmetry* **2001**, *12*, 2197–2204; e) H. Pellissier, *Tetrahedron* **2008**, *64*, 10279–10317; f) K. N. Gavrilov, S. E. Lyubimov, S. V. Zheglov, E. B. Benetsky, P. V. Petrovskii, E. A. Rastorguev, T. B. Grishina, V. A. Davankov, *Adv. Synth. Catal.* **2007**, *349*, 1085–1094; g) B. D. Chapsal, Z. Hua, I. Ojima, *Tetrahedron: Asymmetry* **2006**, *17*, 642–657.
[18] a) Y. Uozumi, *Catalysis Surveys from Asia* **2005**, *9*, 269–278; b) O. Belda, S. Lundgren, C. Moberg, *Org. Lett.* **2003**, *5*, 2275–2278; c) Y. Uozumi, K. Shibatomi, *J. Am. Chem. Soc.* **2001**, *123*, 2919–2920; d) S.-H. Kim, G.-J. Kim, *J. Ind. Eng. Chem.* **2006**, *12*, 643–647; e) B. M. Trost, Z. Pan, J. Zambrano, C. Kujat, *Angew. Chem.* **2002**, *114*, 4885–4887.
[19] During the preparation of this manuscript, comparable results were reported with related supported ligands: Z.-D. Jiang, Z.-H. Meng, *Chin. J. Chem.* **2007**, *25*, 542–545.
[20] a) J. Ansell, M. Wills, *Chem. Soc. Rev.* **2002**, *31*, 259–268; b) M. T. Reetz, G. Mehler, *Angew. Chem. Int. Ed.* **2000**, *39*, 3889–3890; c) W.-J. Tang, Y.-Y. Huang, Y.-M. He, Q.-H. Fa, *Tetrahedron: Asymmetry* **2006**, *17*, 536–543.
[21] H. Danjo, D. Tanaka, T. Hayashi, Y. Uozumi, *Tetrahedron* **1999**, *55*, 14341–14352.
[22] Generally it was observed that the rhodium black formation decreased considerably when a ligand to metal ratio of 2 instead of 1 was applied.
[23] Note that, resins **Cx** and **Dx** contain at least two phosphorus compounds; see ref.[3a] for details.
[24] See for instance: a) H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. De Vries, B. L. Feringa, *J. Org. Chem.* **2005**, *70*, 943–951; b) A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc. Chem. Res.* **2007**, *40*, 1267–1277.
[25] a) L. Panella, A. M. Aleixandre, G. J. Kruidhof, J. Robertus, B. L. Feringa, J. G. De Vries, A. J. Minnaard, *J. Org. Chem.* **2006**, *71*, 2026–2036; b) L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, *Org. Lett.* **2004**, *6*, 1733–1735; c) D. Peña, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2002**, *124*, 14552–14553.
[26] a) Y. Liu, C. A. Sandoval, Y. Yamaguchi, X. Zhang, Z. Wang, K. Kato, K. Ding, *J. Am. Chem. Soc.* **2006**, *128*, 14212–14213; b) Hu, X. Ping, Z. Zheng, *Org. Lett.* **2005**, *7*, 419–422.
[27] The P/Rh ratio of purified rhodium complexes of polymer-supported phosphoramidite ligands can be as high as 7:1. See ref.[9d] for details.
[28] a) H. M. Davies, A. M. Walji, T. Negashima, *J. Am. Chem. Soc.* **2004**, *126*, 4271–4280; b) H. Nakano, K. Takahashi, Y. Suzuki, R. Fujita, *Tetrahedron: Asymmetry* **2005**, *16*, 609–614; c) A. Leyva, H. Garcia, A. Corma, *Tetrahedron* **2007**, *63*, 7097–7111.
[29] a) R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Angew. Chem. Int. Ed.* **2005**, *44*, 4209–4212; b) M. Reetz, G. Mehler, *Tetrahedron Lett.* **2003**, *44*, 4593–4596.
[30] a) A. Duursma, R. Hoen, J. Schuppan, R. Hulst, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 3111–3113; b) C. Monti, C. Gennari, U. Piarulli, *Chem. Commun.* **2005**, 5281–5283; c) M. T. Reetz, Y. Fu, A. Meiswinkel, *Angew. Chem. Int. Ed.* **2006**, *45*, 1412–1415.
[31] a) T. Ikeda, H. Shimizu, H. Yamaoka, S. Okamura, *Macromolecules* **1977**, *10*, 1418–1419; b) J. M. Brown, H. Molinari, *Tetrahedron Lett.* **1979**, *20*, 2933–2936.
[32] The synthesis and the catalytic properties of **F15** will be described elsewhere.
[33] T. J. Colacot, E. S. Gore, A. Kuber, *Organometallics* **2002**, *21*, 3301–3304.
[34] Gel-phase ^{31}P NMR experiments did not allow identification and quantification of the rhodium species present in the polymeric and solution phases.
[35] For several heteroligand combinations, recycling experiments confirmed that a part of the activty originates from nonsupported species (for details, see Tables S4, S5, and S6 in the Supporting Information).
[36] Bidentate coordination modes of the supported ligands could hinder the selective formation of the heteroleptic complexes. Bidentate formation has been observed for (highly crosslinked) polystyrene-supported monodentate ligands. See ref.[31a] for details.
[37] Initial results with heteroligand combinations in the palladium-catalysed allylic alkylation, indicate that the anticipated supported heteroligand species are not formed selectively under catalytic conditions.
[38] D. Vinci, N. Mateus, X. Wu, F. Hancock, A. Steiner, Xiao, *J. Org. Lett.* **2006**, *8*, 215–218.

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As a result of a technical error, the Early View version of this paper contained the wrong Scheme 2; it has since been corrected.

