Immobilized Catalysts

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Parallel Synthesis and Screening of Polymer-Supported Phosphorus-Stereogenic Aminophosphane–Phosphite and –Phosphinite Ligands**

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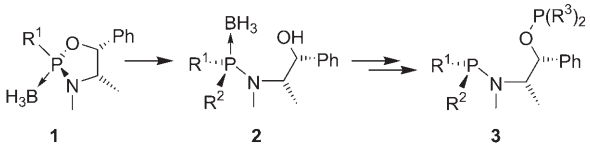
In the past there has been a renewed interest in developing polymer-bound ligands and the corresponding catalysts. The primary advantages of polymer-supported ligands are the ease of purification during the synthesis and the ability to recover and reuse both the transition metal and the ligand.[1] Resin-bound chiral ligands have proven their efficiency in asymmetric catalysis.[2] The combinatorial synthesis and screening of chiral ligand libraries is an efficient method for finding enantioselective catalysts[3] and a number of successful approaches have been reported.[4,5] Although solid-phase organic synthesis (SPOS) has proven its efficiency in high-speed routes towards chemical libraries, surprisingly, examples in which SPOS is applied in the combinatorial synthesis and screening of phosphorus ligands are rare.[6] Recently, we reported the solid-phase parallel synthesis of a variety of phosphites and phosphoramidites.[7] Herein, we report an efficient route for the parallel synthesis of polymer-supported phosphorus-stereogenic aminophosphane–phosphite and aminophosphane–phosphinite bidentate ligands, as well as their application in rhodium-catalyzed asymmetric hydrogenation.

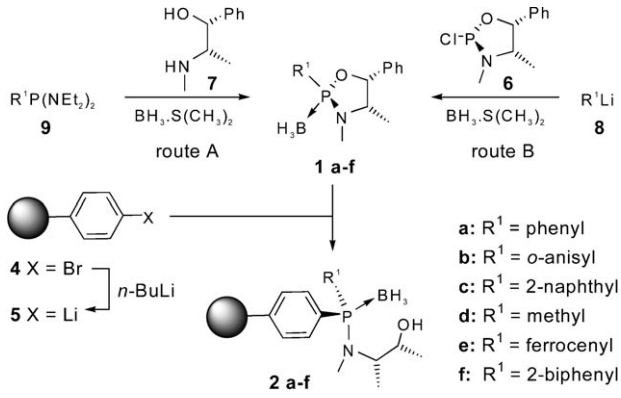
P-stereogenic aminophosphane–phosphite and aminophosphane–phosphinite ligands (**3**, Scheme 1) have successfully been applied in asymmetric hydrogenation[8] and hydroformylation.[9] As a result of the modular structure of this class of ligands, there is an enormous potential for ligand fine-tuning (R^1, R^2, and R^3), which makes them ideal candidates for the parallel synthesis of (supported) ligand libraries.



Scheme 1. Modular synthesis of aminophosphane ligands.

However, these types of ligands have all been developed in the traditional synthetic way requiring troublesome and laborious ligand optimization. A generally applicable combinatorial approach has not been developed yet because the synthetic methodology is still lacking. To assemble libraries of these chiral ligands the development of an efficient solid-phase methodology is pivotal, not only to allow automated synthesis but also to circumvent work-up and purification problems, inherent to solution-phase synthesis.

Following the general synthetic route developed by Jugé and co-workers (Scheme 1),[8] we developed the following route towards supported analogues.[10] The reaction of oxazaphospholidine borane **1a** (R^1 = phenyl) with the lithiated analogue **5** (Scheme 2)[11] of 4-bromo functionalized polystyrene **4** yielded a white resin that, based on the chemical shift of the relatively sharp resonance signal observed in its gel-phase ^{31}P NMR[12] spectrum (δ = 71.4 ppm), was identified as **2a** (Scheme 2). To create structural diversity, we synthesized oxazaphospholidine boranes **1a–f** and the subsequent reaction with **5** yielded aminophosphane boranes **2a–f**. Oxazaphospholidine boranes **1b**, **1c**, and **1d** were obtained using a method described by Jugé et al. for the synthesis of **1a** (route A, Scheme 2).[13] Based on a procedure developed by Ziao et al., **1f** was synthesized analogously to **1e** (route B).[14]



Scheme 2. Synthesis of resin-bound aminophosphane boranes **2a–f**.

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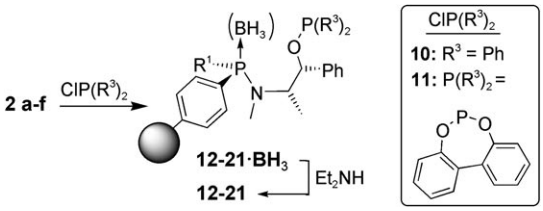
Since purification of the resins is accomplished by a simple washing procedure, the oxazaphospholidine boranes **1** can be applied in excess (>1.5 equiv) without compromising the purity of the resulting immobilized aminophosphanes **2**. Elemental analysis and ^{31}P gel-phase NMR spectroscopy indicated that the polymer-supported aminophosphane boranes **2a–f** were formed in excellent yield and purity with high diastereoselectivity (diastereomeric ratio >96:4).[15] The hydroxy-functionalized resins **2a–f** proved suitable starting materials for resin-bound aminophosphane-based bidentate ligands. For instance, reaction of **2d** with an excess (>1.3 equiv) chlorodiphenylphosphane (**10**; Scheme 3) in the presence of a base, gave the corresponding aminophosphane–borane–phosphinite **15·BH$_3$** cleanly, as shown by the ^{31}P NMR spectrum which displayed typical resonance signals for the phosphinite ($\delta = 113$ ppm) and aminophosphane–borane ($\delta = 69$ ppm) moieties. The borane was straightforwardly removed using neat Et_2NH, yielding chelating ligand **15** (Scheme 3) as was confirmed by an upfield shift of $\Delta\delta =$ 12 ppm of the phosphorus amide signal in the ^{31}P NMR spectrum. The (stereo)chemical purity of more than 92% is sufficient for parallel screening of a library of catalysts.[3f,g]



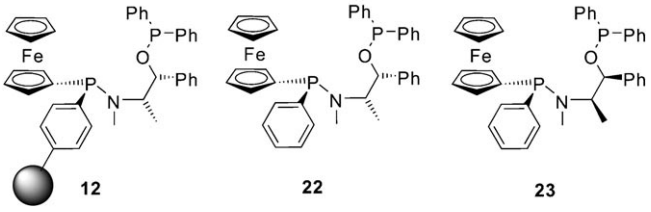
Scheme 3. Solid-phase synthesis of ligands **12–21**.

Following this facile synthetic route, we synthesized ten resin-bound bidentate ligands in good purity by reaction of resins **2a–f**, with **10** or **11** (2,2′-biphenol phosphorochloridite). The structures of the resins are summarized in Table 1.[16] The synthesis of a larger library by application of other chlorophosphorus reagents is currently underway.

Table 1: Parallel-synthesized supported ligands.

Ligand	R^1	R^3	Ligand	R^1	R^3
12	ferrocenyl	diphenyl	**17**	*o*-anisyl	biphenol
13	*o*-anisyl	diphenyl	**18**	2-biphenyl	biphenol
14	phenyl	diphenyl	**19**	methyl	biphenol
15	methyl	diphenyl	**20**	2-naphthyl	biphenol
16	ferrocenyl	biphenol	**21**	phenyl	biphenol

Waldmann et al. demonstrated that ligand optimization on solid support mirrored the results obtained with the analogues ligands in homogeneous solution.[17] To investigate the catalytic behavior of the homogeneous counterparts of our resin-bound ligands, we synthesized aminophosphane phosphinite **22** (Scheme 4). The reaction of oxazaphospholidine borane **1f** with phenyllithium, followed by the addition

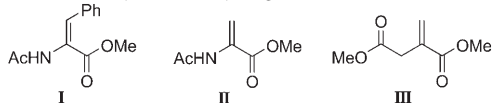


Scheme 4. Structure of supported ligand **12**, and of non-supported **22** and **23**.

of $ClPPh_2$ and subsequent treatment with Et_2NH gave, after purification by column chromatography, **22** in 38% yield.

The resin-bound ligands were used in the rhodium-catalyzed asymmetric hydrogenation of methyl α-acetamidocinnamate (**I**), methyl α-acetamidoacrylate (**II**), and dimethyl itaconate (**III**). For this purpose the ligands were dispersed in methylene chloride in the presence of 1 equivalent of [Rh(cod)$_2$]BF$_4$ (cod = cyclooctadiene). After stirring for 2 h the resins were separated from the solution phase by filtration and subsequently washed. The resulting yellow solids (orange for the ferrocenyl containing resins), were applied as catalysts (Table 2). Both activity and enantioselectivity depended strongly on the structure of substituents R^1 and R^3. Con-

Table 2: Results of asymmetric hydrogenation.



Entry[a]	Ligand	Substrate	Solvent	Conv.[%][b]	*ee* [%][c]
1	**12**	**I**	CH_2Cl_2	31	49 (*R*)
2	**12**	**I**	C_6H_6	17	59 (*R*)
3	**13**	**I**	C_6H_6	4	17 (*R*)
4	**14**	**I**	C_6H_6	18	32 (*R*)
5	**16**	**I**	CH_2Cl_2	>99	42 (*S*)
6	**16**	**I**	C_6H_6	53	69 (*S*)
7	**17**	**I**	CH_2Cl_2	51	65 (*S*)
8	**17**	**I**	C_6H_6	13	73 (*S*)
9	**18**	**I**	C_6H_6	14	<2 (*S*)
10	**20**	**I**	C_6H_6	98	55 (*S*)
11	**22**	**I**	C_6H_6	62	79 (*R*)
12[d]	**23**	**I**	C_6H_6	98	87 (*S*)
13	**12**	**II**	CH_2Cl_2	>99	10 (*R*)
14	**13**	**II**	CH_2Cl_2	39	6 (*R*)
15	**14**	**II**	CH_2Cl_2	58	7 (*S*)
16	**16**	**II**	CH_2Cl_2	79	19 (*S*)
17	**16**	**II**	C_6H_6	64	44 (*S*)
18	**17**	**II**	CH_2Cl_2	>99	74 (*S*)
19	**17**	**II**	C_6H_6	52	89 (*S*)
21[e]	**17**	**II**	C_6H_6	46	85 (*S*)
22[e]	**17**	**II**	C_6H_6	39	81 (*S*)
23	**18**	**II**	C_6H_6	44	35 (*S*)
24	**16**	**III**	C_6H_6	70	79 (*R*)
25	**17**	**III**	C_6H_6	<1	n.d.
26	**20**	**III**	C_6H_6	17	47 (*R*)

[a] Conditions: [Rh] = 2.5 mM, Rh/substrate = 1:30, $p(H_2) = 15$ bar, $T =$ 25 °C, $t = 20$ h, 0.5 mL solvent. [b] Percentage conversion of substrate, determined by GC. [c] Enantiomeric excess of product, determined by chiral GC (absolute configuration drawn in parenthesis). [d] Data taken from Ref. [8b], $t = 47$ h. [e] The reaction was carried out with Rh-loaded **17** recovered from the previous run. n.d. = not determined.

versions varied between <1 and $>99\,\%$, while the enantiomeric excess (*ee*) ranged from <2 up to 89 %. In general, the activity of the resin-bound catalysts was higher in CH_2Cl_2 than in benzene, although in the latter solvent higher enantioselectivities were observed.

Resin-bound **12** and its non-supported analogue **22** gave comparable reaction rates in the rhodium-catalyzed hydrogenation of cinnamate **I** and both formed predominately the *R*-enantiomer. The enantioselectivity observed for the polymer-bound ligand **12** was however lower than that for the corresponding non-supported ligand **22**, 59 % versus 79 % *ee*, respectively (Table 2, entries 2 and 11).

The related non-supported ligand **23** (Scheme 4) is derived from (+)-ephedrine and has been applied by Jugé and co-workers in the asymmetric hydrogenation of α-acetamidocinnamate **I** under identical reaction conditions, allowing a comparison with (the performance of) **22**.[8b] The inversed order of introduction of the substituents at the aminophosphane P-atom in the synthesis of **22** compared to the reported analogue **23** will provide the same configuration of the P-stereogenic phosphorus for both **22** and **23**, and thus the ligands differ merely in the configuration of the carbon backbone. Interestingly, by altering the configuration of the ephedrine moiety, the enantiomeric excess of the hydrogenation product switched from 87 % (*S*) with ligand **23** to 79 % (*R*) for ligand **22**. This result clearly demonstrates the importance of the configuration of the chiral ephedrine backbone on the enantiomeric outcome of the hydrogenation reaction. The small difference in *ee* value between **22** and **23** can be attributed to matched/mismatched configurations of the phosphorus and the ephedrine moieties.[18] Combined with the decisive influence of substituent R^2 and the configuration of the P-atom, as established by the group of Jugé,[8] this information allows the rational design of highly efficient ligands.

In the rhodium-catalyzed hydrogenation of cinnamate **I** with supported **12**–**14** predominately the *R*-enantiomer was formed (Table 2, entries 1–4). Interestingly, in the cases of ligands **16**–**20**, each bearing a biphenol moiety as the R^3 substituent, the hydrogenation provided the phenylalanine derivative with the (*S*) absolute configuration (Table 2, entries 5–10). The presented parallel solid-phase synthesis and screening of bidentate ligands shows its value and efficiency, because small variations in ligand structure have a tremendous influence on both the activity and the enantioselectivity of the catalyst.

Finally, we tested the recycling of the resin-bound catalyst in the asymmetric hydrogenation of acrylate **II**, for which we recovered catalyst **17** after the reaction and subjected it to a subsequent catalytic hydrogenation (Table 2, entries 19–21). The recovered catalysts could be recycled with a slight loss in activity (52–39 %) and enantioselectivity (89–81 % *ee*). These results demonstrate that in addition to the easy parallel solid-phase preparation, the supported ligands offer the advantage of recovery and reutilization in consecutive asymmetric hydrogenation reactions.

In summary, we have shown the efficient parallel solid-phase synthesis of a series of resin-bound P-stereogenic aminophosphane–phosphinite and aminophosphane–phosphite ligands. The solid-phase procedures allow the rapid synthesis and screening of the new resin-bound ligands. The ligands form active hydrogenation catalysts, displaying moderate to good enantioselectivities. Studies to expand the structurally diversity of our resin-bound chelating ligands are currently in progress. Furthermore we have demonstrated the importance of the configuration of the chiral ephedrine backbone on the product chirality.

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