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Polymer-supported monodentate phosphite ligands for asymmetric hydrogenation

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Abstract—Several new polymer-supported monophosphite ligands have been developed and the rhodium complexes were shown to be highly efficient, highly enantioselective and easily separable catalysts for asymmetric hydrogenation of itaconates, enamides, α-dehydroamino acid derivatives and β-dehydroamino acid derivatives.

The rhodium-catalyzed asymmetric hydrogenation of prochiral olefins is a well established methodology for the production of enantiomerically enriched molecules.[1] Chiral bisphosphorus-ligands have played a major role in this reaction since the pioneering work of Knowles and Kagan.[1] After 30 years of neglect, the monodentate phosphorus ligands[2] gained importance in asymmetric catalysis at the beginning of this millennium through the work of Feringa, de Vries, Reetz, Pringle and others.[3] Since then the development of monodentate phosphorus ligands for asymmetric catalysis has proceeded rapidly due to their easy preparation, good stability and excellent performance in catalysis.[3–5] Limitations in the practical use of monodentate phosphorus ligands are the difficult separations and problematic recycling. To overcome these issues, some immobilized chiral monodentate phosphoramidite ligands have been developed recently.[6] Indeed, polymer-supported transition metal complexes are continuing to gain interest because of their ease of use and recyclability;[7] recovery of such catalysts by simple filtration can provide a process improvement over homogeneous catalysis not only because of the reuse of the expensive chiral ligands and metals but also, more importantly, because the potentially toxic transition metal species can be cleanly removed from the reaction mixture. Continuing our interest in chiral monodentate phosphorus ligands[3d,e] and polymer-supported chiral ligands,[8] we have developed some polymer-supported chiral monodentate phosphite ligands for asymmetric hydrogenation. Very recently, polyethylene glycol (PEG) supported monodentate phosphite ligands and phosphoramidite ligands for asymmetric hydrogenation were reported by Zheng[9] and van Maarseveen.[10] Their work encouraged us to disclose our results on polymer-supported chiral monodentate phosphite ligands for asymmetric hydrogenation, which were produced contemporaneously.

The synthesis of polymer-supported chiral monodentate phosphite ligands **1**, **2** and **3** is very simple and straightforward, as shown in Scheme 1. Thus, the insoluble polymer-supported monodentate phosphites **1d** and **1e** can be prepared quantitatively by simple treatment of commercially available polystyrene-supported PEGs, TentaGel-OH (~0.26 mmol OH/g) and PS-PEG$_{600}$-OH (~0.35 mmol OH/g), with the BINOL-based chlorophosphite **4** in CH_2Cl_2 at room temperature in the presence of triethylamine, followed by filtration. Reaction of commercially available or easily prepared polymer-supported alcohols with the BINOL-based chlorophosphite **4** in CH_2Cl_2 at room temperature in the presence of trioctylamine, precipitation with diethyl ether and filtration gave the soluble PEG-supported monophosphites **1a**–**c**,[11] **2** and **3** in almost quantitative yields. The use of trioctylamine is essential for the easy separation of polymer-supported monophosphites as trioctylamine hydrochloride is soluble in diethyl ether.[12] The structures and high purities of PEG-supported monophosphites **1a**–**c**, **2** and **3** were confirmed by ^{1}H and ^{31}P NMR spectra. Noticeably, these PEG-supported monophosphites show

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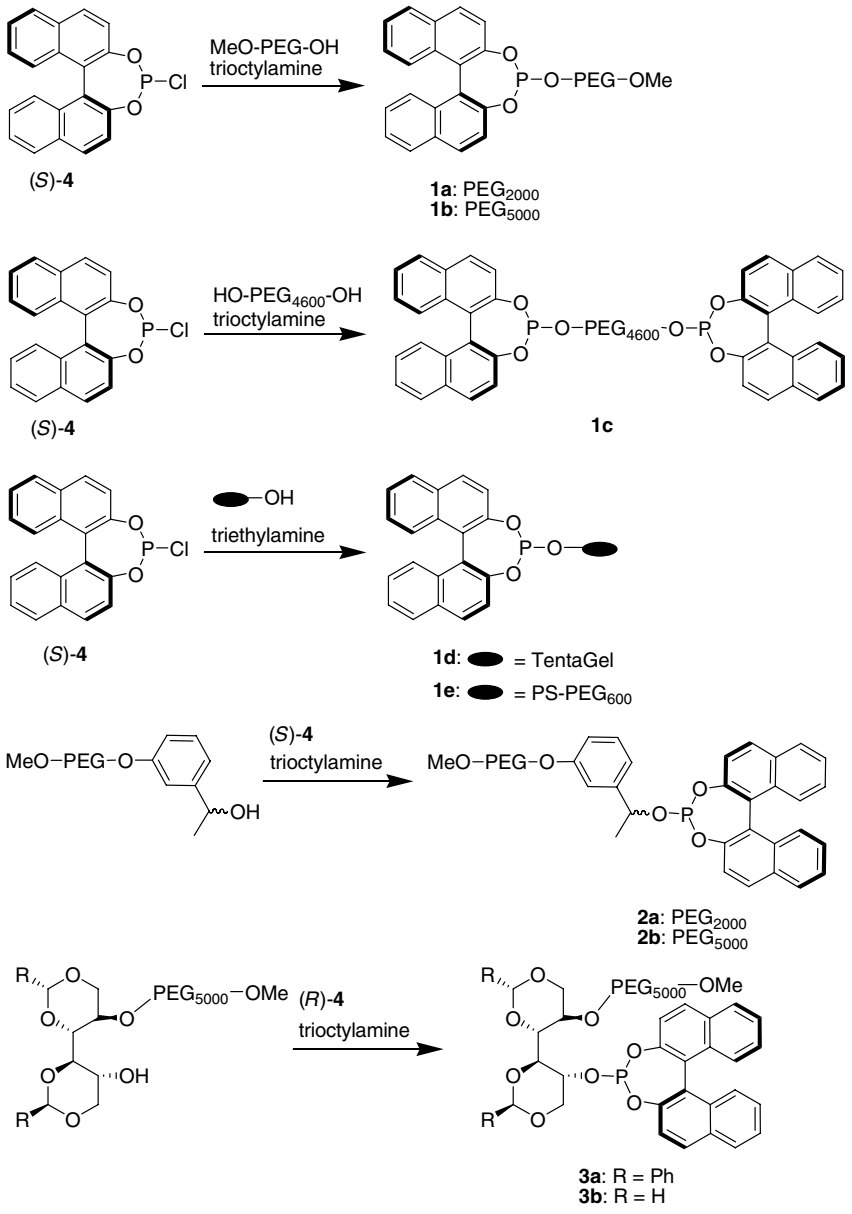
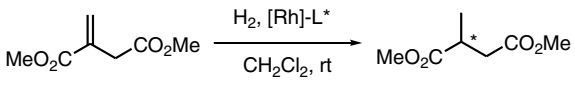


Scheme 1.

good air stability. Thus, the ligands did not show any changes in their ^{1}H or ^{31}P NMR spectra even after being stored under air in a refrigerator for more than two years.

The results of asymmetric hydrogenation reactions catalyzed by Rh-complexes showed that all the soluble PEG-supported monophosphites, except **1c**, were highly effective and enatioselective for a wide range of substrates, such as itaconates, enamides, α-dehydroamino acid derivatives and β-dehydroamino acid derivatives. First, we compared all the polymer-supported monophosphites in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate. Thus, hydrogenation of dimethyl itaconate at room temperature under a H_2 pressure of 20 bar in the presence of a Rh catalyst, generated in situ from $Rh(COD)_2OTf$ (0.05 mol %) and polymer-supported monodentate phosphite (2.2 equiv with respect to Rh) in CH_2Cl_2, gave optically active dimethyl 2-methylsuccinate (Table 1). MeO-PEG-supported ligands displayed high enantioselectivities and activities. Ligand **1a** gave dimethyl (*S*)-2-methylsuccinate in 91.5% ee (entry 1). The enantioselectivity is similar with **1b** having a higher molecular weight PEG chain (entry 2). Moreover, ligands **2** and **3** having 1-phenylethyl and protected D-mannitol moieties gave much higher enantioselectivities (entries 6–9), which are comparable or better than those obtained with the corresponding monomeric ligands.[3a,5a] Notably, ligands **3**, in which the (*S*)-BINOL moiety of ligands **1** and **2** was replaced with (*R*)-BINOL, gave enantiomeric products compared with those using ligands **1** and **2**. Interestingly, the soluble ligand **1c**, prepared from HO-PEG-OH, showed much lower activity and enantioselectivity (entry 3), probably due to the formation of macromolecular Rh-complexes, which are structurally similar to the 'self-supported catalysts' developed by Ding.[6d] Insoluble polymer-immobilized catalysts

Table 1. Asymmetric hydrogenation of dimethyl itaconate[a]



Entry	L*	S/C[b]	Time (h)	Conv. (%)	ee (%)[c]
1	**1a**	2000	16	100	91.5 (*S*)
2	**1b**	2000	16	100	92.7 (*S*)
3	**1c**	2000	16	88	74.0 (*S*)
4	**1d**	2000	16	69	64.2 (*S*)
5	**1e**	2000	16	74	59.3 (*S*)
6	**2a**	2000	16	100	**97.8** (*S*)
7	**2b**	2000	16	100	**97.9** (*S*)
8	**3a**	2000	16	100	**98.3** (*R*)
9	**3b**	2000	16	100	**97.9** (*R*)
10	**2a**	**10,000**	16	100	**97.6** (*S*)
11	**2a**	**10,000**	**0.5**	100	**97.4** (*S*)[d]

[a] Reaction conditions: 10 mmol of substrate, 0.005 mmol of [Rh-(COD)$_2$]OTf, 0.011 mmol of ligand, 2 mL of CH_2Cl_2, room temperature and H_2 pressure of 20 bar.
[b] Ratio of substrate to catalyst.
[c] Determined by GC using a Chiraldex G-TA (40 m × 0.25 mm) column.
[d] Reaction conditions: 200 mmol of substrate, 0.02 mmol of [Rh-(COD)$_2$]OTf, 0.044 mmol of ligand, 10 mL of CH_2Cl_2, room temperature and a H_2 pressure of 30 bar.

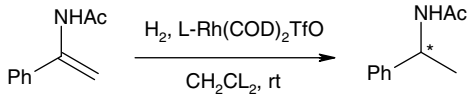
often display lower enantioselectivities and activities in catalysis in comparison with their corresponding monomeric counterparts. This was found to be the case with the insoluble immobilized monodentate phosphites **1d** and **1e** (entries 4–5). The soluble PEG-supported catalysts were extremely active. For example, hydrogenation of dimethyl itaconate (200 mmol) was carried out for 30 min at room temperature under a H_2 pressure of 30 bar in the presence of a Rh catalyst [generated in situ from Rh(COD)$_2$OTf (0.02 mmol) and **2a** (0.044 mmol) in CH_2Cl_2 (10 mL)] to give dimethyl (*S*)-2-methylsuccinate in quantitative yield and 97.4% ee and with a TOF of >20,000 h^{-1} (entry 11). To the best of our knowledge, this is one of the most active catalysts for asymmetric hydrogenation of dimethyl itaconate. More importantly, the activity of the catalyst increases with substrate concentration and H_2 pressure, while the enantioselectivity is independent of substrate concentration and H_2 pressure.

Similarly, the Rh-catalyzed hydrogenation of enamides to optically active amides proceeded with excellent enantioselectivity (up to 96.4% ee) in the presence of soluble polymer-supported monodentate phosphites. Again, ligands **2** and **3** gave superior results compared to ligands **1** (Table 2).

For the Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives, ligands **2** and **3** again gave excellent enantioselectivities (up to 96.5% ee), which are comparable or better than those obtained with the corresponding monomeric ligands (Table 3).[3a,5a]

Finally, we examined the Rh-catalyzed hydrogenation of β-dehydroamino acid derivatives. Ligands **2** and **3** also turned out to be the most active in this reaction and provided excellent enantioselectivities of up to 96.5% ee (Table 4).

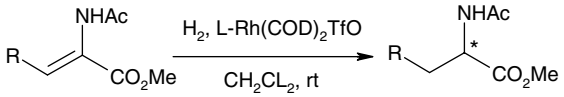
Table 2. Asymmetric hydrogenation of an enamide[a]



L	S/C[b]	H_2 (psi)	Time (h)	Conv. (%)	ee (%)[c]
1b	200	200	14	100	92.3 (*R*)
2a	200	200	14	100	95.7 (*R*)
2b	200	200	14	100	95.0 (*R*)
3a	200	200	14	100	96.4 (*S*)
3b	200	200	14	100	95.6 (*S*)

[a] Reaction conditions: 1 mmol of substrate, 0.005 mmol of [Rh-(COD)$_2$]OTf, 0.011 mmol of ligand, 2 mL of CH_2Cl_2, room temperature.
[b] Ratio of substrate to catalyst.
[c] Determined by GC using a Chrompack Chirasil-Dex CB (25 m × 0.25 mm) column.

Table 3. Asymmetric hydrogenation of α-dehydroamino acid derivatives[a]



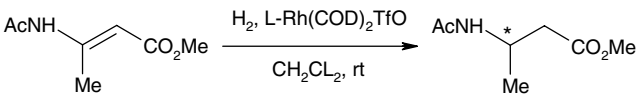
L	R	S/C[b]	H_2 (psi)	Time (h)	Conv. (%)	ee (%)[c]
1b	H	200	100	2	100	88.2 (*R*)
2a	H	200	100	2	100	96.2 (*R*)
2b	H	200	100	2	100	95.5 (*R*)
3a	H	200	100	2	100	94.7 (*S*)
3b	H	200	100	2	100	94.6 (*S*)
1b	H	200	50	1	100	90.2 (*R*)
2a	H	200	50	1	100	96.5 (*R*)
2b	H	200	50	1	100	94.7 (*R*)
3a	H	200	50	1	100	95.8 (*S*)
3b	H	200	50	1	100	96.3 (*S*)
1b	Ph	200	50	1	95.4	83.4 (*R*)
2a	Ph	200	50	1	95.4	90.6 (*R*)
2b	Ph	200	50	1	94.6	91.1 (*R*)
3a	Ph	200	50	1	95.1	92.4 (*S*)
3b	Ph	200	50	1	95.7	92.5 (*S*)

[a] Reaction conditions: 1 mmol of substrate, 0.005 mmol of [Rh-(COD)$_2$]OTf, 0.011 mmol of ligand, 2 mL of CH_2Cl_2, room temperature.
[b] Ratio of substrate to catalyst.
[c] Determined by GC using a Chrompack Chirasil-Dex CB (25 m × 0.25 mm) column.

An attractive feature of the present catalytic system lies in the fact that the catalyst can be readily removed from the product by addition of a low polarity solvent or simply by washing with water. Thus, when hydrogenation is complete, the Rh-complex can be easily removed by precipitation with the addition of diethyl ether or by washing with water to give a colourless organic layer containing the product.

In summary, we have developed several new polymer-supported monophosphite ligands, with PEG, PS-PEG and PEG-supported alcohols as the alkoxy moiety of the monophosphites and have shown them to be highly efficient, highly enantioselective and easily separable in Rh-catalyzed asymmetric hydrogenations of a wide range of substrates, such as itaconates, enamides, α-

Table 4. Asymmetric hydrogenation of β-dehydroamino acid derivatives[a]



L	S/C[b]	H_2 (psi)	Time (h)	Conv. (%)	ee (%)[c]
1b	100	300	15	78.2	85.1 (*R*)
2a	100	300	15	96.4	93.7 (*R*)
2b	100	300	15	84.8	96.5 (*R*)
3a	100	300	15	80.0	95.2 (*S*)
3b	100	300	15	82.3	95.1 (*S*)

[a] Reaction conditions: 1 mmol of substrate, 0.01 mmol of [Rh-(COD)$_2$]OTf, 0.022 mmol of ligand, 2 mL of CH_2Cl_2, room temperature.

[b] Ratio of substrate to catalyst.

[c] Determined by GC using Chrompack Chirasil-Dex CB (25 m × 0.25 mm) column.

dehydroamino acid derivatives and β-dehydroamino acid derivatives.[13]

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13. *Asymmetric hydrogenation—general procedure*: In a 10 mL vial, a solution of [Rh(COD)$_2$]OTf (2.3 mg, 0.005 mmol) and ligand (0.011 mmol) in anhydrous and degassed CH_2Cl_2 (2 mL) was stirred for 10 min at room temperature, then the substrate in the desired amount was added. The vial was placed in a stainless autoclave. The autoclave was purged three times with H_2, and the pressure was set to the desired value, and hydrogenation was performed at room temperature for the appropriate time. After carefully venting the H_2, the reaction mixture was concentrated, diluted with Et_2O and passed through a short silica gel plug. The resulting solution was used directly for analysis.