Readily available, recoverable and soluble polymer-monophosphite ligands for highly enantioselective Rh-catalyzed hydrogenation†

Xiang-Ping Hu,[a] Jia-Di Huang,[ab] Qing-Heng Zeng[ab] and Zhuo Zheng*[a]

Received (in Cambridge, UK) 9th August 2005, Accepted 31st October 2005
First published as an Advance Article on the web 25th November 2005
DOI: 10.1039/b511323g

A new family of readily available, recoverable and soluble polymer-monophosphite ligands were prepared and successfully used in the Rh-catalyzed asymmetric hydrogenation of enamides and β-dehydroamino acid esters, in which up to 99 and 99.9% ee were obtained, respectively.

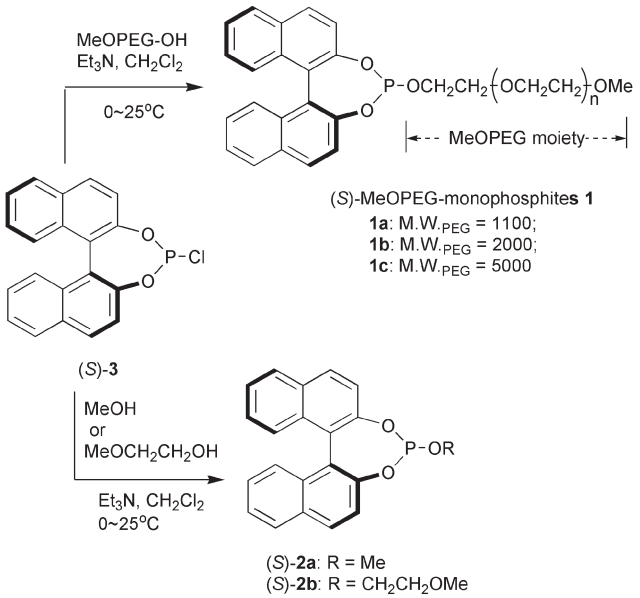
The homogeneous catalytic asymmetric hydrogenation of functionalized prochiral olefins is one of the most developed and useful transition metal-catalyzed reactions.[1] The use of chiral phosphorus ligands has been found to be extremely successful, and those that are bidentate have been the most effective.[2] However, the past few years have witnessed a renewed interest in the development of chiral monodentate phosphorous ligands. Pioneering studies from the groups of Pringle,[3a] Reetz[3b] and Feringa[3c] have shown that chiral monodentate phosphonite, phosphite or phosphoramidite ligands also yield highly active and selective Rh catalysts for the hydrogenation of a variety of alkenes, giving comparable or sometimes better results than those obtained with bidentate ligands.[4] The limitation in the practical use of monodentate phosphorous ligands are their difficult separation and recycling. To overcome this problem, some immobilized chiral monodentate phosphorous ligands have been developed very recently.[5] The immobilization of homogeneous chiral catalysts could solve some of the problems of homogeneous catalysts, such as difficult separation and recycling of expensive chiral catalysts.[6] However, the immobilized ligands or catalysts often display lower enantioselectivity and less efficiency in their catalysis in comparison with their parent counterparts. In many cases, the synthesis of the immobilized ligand or catalyst is much more difficult than its parent counterpart since an additional functional group or linker is usually required to be introduced into the parent ligand, primarily to allow its anchoring to supports, usually involving a multi-step procedure. Therefore, one of the remaining challenges in the immobilization of chiral ligands concerns the need to develop readily accessible and cheap polymer-supported ligands which have activities and selectivities comparable to those of their homogeneous parent counterparts, as well as being easily separated from the reaction mixture and recycled several times.

Recently, Reetz's[7] and our[8] group have independently reported carbohydrate-derived monophosphite ligands that exhibited excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of vinyl carboxylates, enamides and dimethyl itaconate. The excellent enantioselectivities and pronounced effect of the carbohydrate backbone in those ligands indicated that the additional oxygen-containing groups, orientated in a spatial configuration in the alkoxy moiety of monophosphites, could significantly improve the enantioselectivity. These carbohydrate-derived monophosphite ligands may act like hemilabile ligands in catalytic hydrogenation, and the additional oxygen-containing groups may form only weak metal–oxygen bonds that may be cleaved reversibly.[9] As a result of this secondary interaction between the oxygen donor and central metal, the rotation of the Rh–P bond is effectively restrained and empty coordination sites are made available, when needed, in the course of catalytic cycles, without separation of the oxygen donors from the complex fragment, leading to a selectivity-enhancing effect. With this in mind, we then surmised that the introduction of a polyethylene glycol (PEG) structure as the alkoxy moiety of the monophosphite ligand might result in a new class of highly effective "polymer-monophosphites" for Rh-catalyzed asymmetric hydrogenation, due to the potential for secondary interactions between the oxygen atoms abundant in the PEG structure and the central metal. Since BINOL is currently one of the cheapest chiral auxiliaries and a large number of PEGs with different molecular weights are commercially available, BINOL-derived MeOPEG-monophosphites are cheap and likely to be of great industrial interest. Interestingly, though they are one of the most important kinds of monodentate phosphorous ligand, there are still no reports on the immobilization of monophosphite ligands for use in Rh-catalyzed asymmetric hydrogenation to the best of our knowledge. Herein, we report our results on the development of this kind of readily available, recoverable and soluble PEG monomethyl ether-derived polymer-monophosphites (MeOPEG-monophosphites) **1** for the highly enantioselective hydrogenation of various enamides and β-alkyl-β-(acylamino)acrylates.

The synthetic pathway to these MeOPEG-monophosphites **1** is straightforward, as outlined in Scheme 1. Simple treatment of the BINOL-based chlorophosphite **3** with an equimolar amount of commercially available PEG monomethyl ether (MeOPEG–OH) in CH_2Cl_2 at 0–25 °C, in the presence of triethylamine, gave rise to the target MeOPEG-monophosphites **1**. The resulting polymer ligands **1** can be easily separated from the reaction mixture. After removal of the salt $Et_3N{\cdot}HCl$, which was formed in the reaction, by simple filtration, diethyl ether was added to the reaction mixture and a white precipitate of the crude MeOPEG-monophosphites **1** formed immediately. The crude product was collected by filtration, and then the minimum amount of CH_2Cl_2 added to it to

[a]*Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, 116023, China. E-mail: zhengz@dicp.ac.cn; Fax: (+86) 411-84684746; Tel: (+86) 411-84669077*
[b]*Graduate School of Chinese Academy of Sciences, Beijing, 100039, China*

† Electronic Supplementary Information (ESI) available: Experimental details and characterisation data for the compounds prepared, including ^1H and ^{31}P NMR spectra. See DOI: 10.1039/b511323g

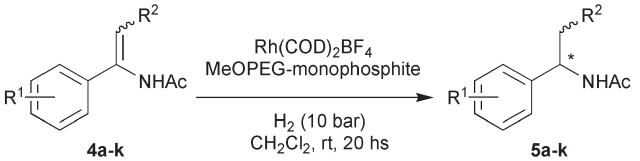


Scheme 1 Synthesis of monophosphites (*S*)-**1a–c** and (*S*)-**2a–b**.

ensure the complete dissolution of the residue. Diethyl ether was added again and MeOPEG-monophosphites **1** of high purity were precipitated. The ^{1}H NMR and ^{31}P NMR spectra were consistent with the expected structure and demonstrated the high purity of the polymer ligands. Noticeably, these MeOPEG-monophosphites show good air stability. Thus, ligand **1b** did not show any changes in its ^{1}H or ^{31}P NMR spectra, even after being stored unprotected for more than one month.

The asymmetric hydrogenation of *N*-(1-phenylethenyl)acetamide **4a** by the use of glycol monomethyl ether-derived monophosphite **2b** has been reported recently by Reetz *et al.*[10] Unfortunately, only moderate enantioselectivity was obtained, but significantly higher than that from **2a** with a methoxy group as the alkoxy moiety of monophosphite (Table 1, entries 1 and 2). Compared with the glycol monomethyl ether derived monophosphite **2b**, the MeOPEG-monophosphite ligands provided a greatly improved enantioselectivity in the asymmetric hydrogenation of *N*-(1-phenylethenyl)acetamide **4a** under identical conditions. Thus, hydrogenation of **4a** at room temperature under a H_2 pressure of 60 bar in the presence of a Rh catalyst, generated *in situ* from $Rh(COD)_2BF_4$ (0.2 mol%) and MeOPEG-monophosphite **1a** (2.0 equiv. with respect to Rh) in CH_2Cl_2, gave the hydrogenation product in quantitative yields and 96% ee (Table 1, entry 3). When hydrogenation was performed in the presence of 1.0 mol% Rh catalyst under a H_2 pressure of 10 bar, the enantioselectivity was further increased to 98% ee (Table 1, entry 4). The enantioselectivity was still high, but a little lower, with the Rh catalysts from MeOPEG-monophosphites **1b** and **1c**, which gave quantitative yields of *N*-(1-phenylethyl)acetamide **5a** in 97 and 93% ee, respectively (Table 1, entries 5 and 6). These results indicate that the PEG moiety in the monophosphite ligand had an important influence on the enantioselectivity, with the MeOPEG-monophosphite, having a lower molecular weight PEG chain, tending to afford higher enantioselectivities. When the catalyst derived from **1a** was used in the hydrogenation of various enamides, all of the reactions gave extremely high ee values with full conversions

Table 1 Asymmetric hydrogenation of enamides **4a–k** catalyzed by Rh-MeOPEG-monophosphites in CH_2Cl_2[a]



4a-k **5a-k**

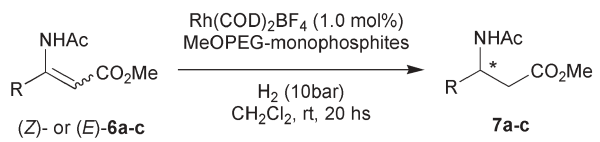
Entry	Ligand	Substrate (R^1, R^2)	*S*/*C*[e]	ee (%)[b]
1	(*S*)-**2a**	**4a** (H, H)	500	76 (*R*)[c]
2	(*S*)-**2b**	**4a** (H, H)	500	86 (*R*)[c]
3	(*S*)-**1a**	**4a** (H, H)	500	96 (*R*)[d]
4	(*S*)-**1a**	**4a** (H, H)	100	98 (*R*)
5	(*S*)-**1b**	**4a** (H, H)	100	97 (*R*)
6	(*S*)-**1c**	**4a** (H, H)	100	93 (*R*)
7	(*S*)-**1a**	**4b** (4-CF_3, H)	100	97 (*R*)
8	(*S*)-**1a**	**4c** (4-Cl, H)	100	98 (*R*)
9	(*S*)-**1a**	**4d** (4-Br, H)	100	98 (*R*)
10	(*S*)-**1a**	**4e** (4-Me, H)	100	98 (*R*)
11	(*S*)-**1a**	**4f** (4-OMe, H)	100	99 (*R*)
12	(*S*)-**1a**	**4g** (3-OMe, H)	100	98 (*R*)
13	(*S*)-**1a**	**4h** (H, Me)	100	97 (*R*)
14	(*S*)-**1a**	**4i** (4-Cl, Me)	100	97 (*R*)
15	(*S*)-**1a**	**4j** (4-OMe, Me)	100	96 (*R*)
16	(*S*)-**1a**	**4k** (H, Et)	100	97 (*R*)

[a] Reaction conditions: 0.5 mmol of substrate, 1 mol% of catalyst (L : Rh = 2.2 : 1), 3 mL of CH_2Cl_2, room temperature and a H_2 pressure of 10 bar. Full conversions were achieved in all reactions. [b] Determined by GC using a Chiral Select 1000 capillary (0.25 mm × 30 m) column. [c] The data was reported by Reetz *et al.*[10] [d] Reaction conditions: 0.2 mol% catalyst (L : Rh = 2.0 : 1) under a H_2 pressure of 60 bar in CH_2Cl_2 at 30 °C for 20 h. [e] S/C: molar ratio of substrate and catalyst.

(Table 1, entries 7–12). The results revealed that an electron-donating group on the phenyl ring of the substrate enhances the enantioselectivity, and the best ee value of 99% was obtained in the hydrogenation of *N*-(1-(4-methoxy)phenylethyl)acetamide **4f** (Table 1, entry 11). Notably, Rh/MeOPEG-monophosphite complex **1a** also exhibited high enantioselectivity for the hydrogenation of *E*/*Z* mixtures of β-substituted enamides **4h–k**, and gave the hydrogenation product with an ee of up to 97% (Table 1, entries 13–16), thereby demonstrating the wide scope of the present Rh/MeOPEG-monophosphite catalyst system in the hydrogenation of enamides.

We next tested the efficiency of these MeOPEG-monophosphites in the Rh-catalyzed asymmetric hydrogenation of β-alkyl-β-(acetylamino)acrylates **6**. The monophosphite ligands developed thus far are not very effective for this challenging asymmetric reaction. It is only very recently that some monophosphite ligands have been found to show excellent enantioselectivity. However, high catalyst loadings (*S*/*C* = 50/1) and high H_2 pressures were usually required to guarantee high enantioselectivity.[11] It was found that MeOPEG-monophosphites induced a remarkably enantioselective Rh-catalyzed hydrogenation of β-alkyl-β-(acetylamino)acrylates **6**, the results of which are summarized in Table 2. The results revealed that in the hydrogenation, (*E*)-β-alkyl-β-(acetylamino)acrylates showed higher activities than their corresponding *Z*-isomers, and substrates with bulkier alkyl substituents tended to give better results. Thus, the best results were obtained in the hydrogenation of (*E*)-**6c** under a H_2 pressure of 10 bar, which provided the hydrogenation product in 100% conversion and

Table 2 Asymmetric hydrogenation of β-alkyl-β-(acylamino)acrylates **6** catalyzed by Rh-MeOPEG-monophosphites **1** in CH_2Cl_2[a]



(*Z*)- or (*E*)-**6a-c** → **7a-c**

Entry	Ligand	Substrate (R)	Conversion (%)	ee (%)[b]
1	**1a**	(*Z*)-**6a** (Me)	73	97 (*S*)
2	**1a**	(*E*)-**6a** (Me)	94	96 (*S*)
3	**1a**	(*E*)-**6b** (Et)	100	98 (*S*)
4	**1a**	(*E*)-**6c** (^{i}Pr)	100	99.9 (*R*)
5	**1a**	(*E*)-**6c** (^{i}Pr)	100	99.9 (*R*)[c]
6	**1b**	(*E*)-**6c** (^{i}Pr)	100	99.9 (*R*)[c]
7	**1c**	(*E*)-**6c** (^{i}Pr)	100	99.9 (*R*)[c]

[a] Reactions were performed under 10 bar H_2 pressure in CH_2Cl_2 at room temperature for 20 h. Substrate : $Rh(COD)_2BF_4$: ligand = 50 : 1 : 2.2. [b] Enantiomeric excesses were determined by GC using a chiral Select 1000 capillary (0.25 mm × 30 m) column and a Varian Chirasil-L-Val capillary (0.25 mm × 30 m) column. [c] Substrate : $Rh(COD)_2BF_4$: ligand = 100 : 1 : 2.2.

99.9% ee, even at 1.0 mol% catalyst loadings (Table 2, entries 5–7). To the best of our knowledge, few monophosphite ligands have been reported as showing such high enantioselectivity and catalytic activity in this reaction.

As well as the high efficiency observed in the Rh-catalyzed asymmetric hydrogenation of enamides and β-alkyl-β-(acetylamino)acrylates, another salient and practical feature of these MeOPEG-monophosphite ligands is that they are easily separated and recovered from the reaction mixture. After completion of the hydrogenation, ether was added to the reaction mixture and a precipitate was formed immediately. Simple filtration under an Ar atmosphere afforded separation of the precipitated catalyst and products remaining in solution. An exception was **1a** with a low molecular weight PEG chain, which was separated as a brown oil. We then examined the reuseability of the recovered Rh complex of MeOPEG-monophosphite ligand **1b** in the hydrogenation of *N*-(1-phenylethenyl)acetamide **4a**, the results of which are summarized in Table 3. The recovered catalyst was submitted to the next catalytic reaction without any further addition of Rh. The recovered catalyst could be recycled with only a slight loss of enantioselectivity (from 97% ee in the first run to 91% ee in the fourth run) (Table 3, runs 1–4). After the completion of the hydrogenation in the third run, a brown oil was separated. This oil also showed good enantioselectivity, giving the hydrogenation product in 91% ee and 100% conversion accompanied by another dark brown oil, formed after the addition of ether (Table 3, run 4). These results demonstrate that the MeOPEG-monophosphite ligands have the advantage of easy recovery and reutilization in asymmetric hydrogenation, in addition to their facile preparation and high efficiency.

Table 3 The recycling of Rh/MeOPEG-monophosphite **1b** catalyst in the enantioselective hydrogenation of *N*-(1-phenylethenyl)acetamide **4a**[a]

Run	Conversion (%)	ee (%)[b]
1	100	97 (*R*)
2	100	97 (*R*)
3	100	96 (*R*)
4	100	91 (*R*)

[a] Reactions were performed in the presence of 5 mmol of substrate in 10 mL of CH_2Cl_2 at room temperature and a H_2 pressure of 10 bar for 24 h. The molar ratio of **4a** : Rh : L = 100 : 1 : 2.2 in the first run. [b] Enantiomeric excesses were determined by GC using a Chiral Select 1000 capillary (0.25 mm × 30 m) column.

In conclusion, we have reported the first examples of polymer-monophosphite ligands, using a PEG structure as the alkoxy moiety of monophosphites, for use in the highly effective Rh-catalyzed enantioselective hydrogenation of enamides and β-(acylamino)acrylates. As well as obtaining higher enantioselectivities than their parent ligands, these polymer-monophosphites have the advantages of being readily available, air stable, easily separated and recovered from the reaction mixture, and conveniently recyclable several times. Further investigations of other catalytic asymmetric reactions with these polymer-monophosphite ligands are under way.

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