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Asymmetric Hydrogenation of Ketones with Polymer-Supported Chiral 1,2-Diphenylethylenediamine

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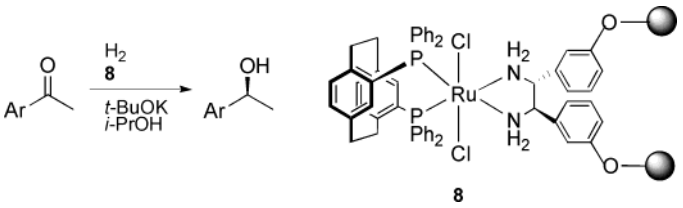
ABSTRACT



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A poly(ethylene glycol)-supported chiral diamine (PEG-2), in which the polymer is attached to the phenyl rings, has been synthesized and shown to be highly effective in asymmetric hydrogenation of unfunctionalized aromatic ketones with the possibility of reuse. PEG-2 can also serve as a chiral scaffold on which various immobilized chiral catalysts could be easily built.

Asymmetric catalysis with polymer-supported transition metal complexes has attracted a great deal of recent interest.[1] A prominent advantage of immobilized chiral catalysts lies in easy catalyst separation and recycle. This is important considering in particular that such catalysts are usually expensive and toxic. When the supporting polymer is soluble and can be separated by various chemical and physical means, an additional advantage is offered: the reaction is performed homogeneously, leading to higher rates and better enantioselectivities than catalysts immobilized on solids.[1a,b]

Optically active 1,2-diphenylethylenediamine [DPEN, (*R*,*R*)-**1**] is one of the most important chiral ligands. DPEN and its derivatives have been used as ligands for metals such as Ru(II), Co(II), Al(III), Mn(III), and Os(VIII) to generate highly enantioselective catalysts for many asymmetric organic transformations, such as asymmetric reduction of ketones,[2] Aldol reaction,[3] Diels−Alder reaction,[4] epoxidation,[5] and dihydroxylation.[6] Polymer-supported DPEN and derivatives have recently been reported and shown to be efficient in the asymmetric hydrogenation and transfer hydrogenation of ketones.[7,8] So far all of the immobilization methods hinge on the functionalization of the nitrogen atom and thus render further derivatization difficult and are limited to reactions where the coordinating amino group NH_2 can be modified. To the best of our knowledge, polymer-

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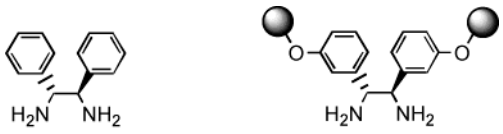
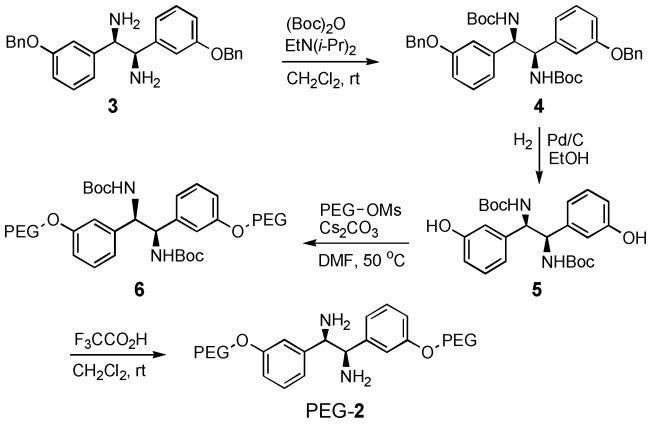
supported DPEN, in which the polymer is linked to the phenyl rings, had not been reported before this research was launched.[9] We report herein that the poly(ethylene glycol)-supported (*R*,*R*)-**2** (PEG-**2**) is an efficient ligand for the asymmetric hydrogenation of simple ketones, furnishing excellent enantioselectivities and enabling easy catalyst separation and recycle. We also demonstrate that PEG-**2** can provide a versatile chiral platform on which various immobilized chiral catalysts can be readily built.



1 PEG-**2**

PEG-**2** was synthesized from the functionalized, enantiomerically pure 1,2-diphenylethylenediamine (*R*,*R*)-**3**, which was prepared from 3-benzyloxylbenzaldehyde (Scheme 1).[10]

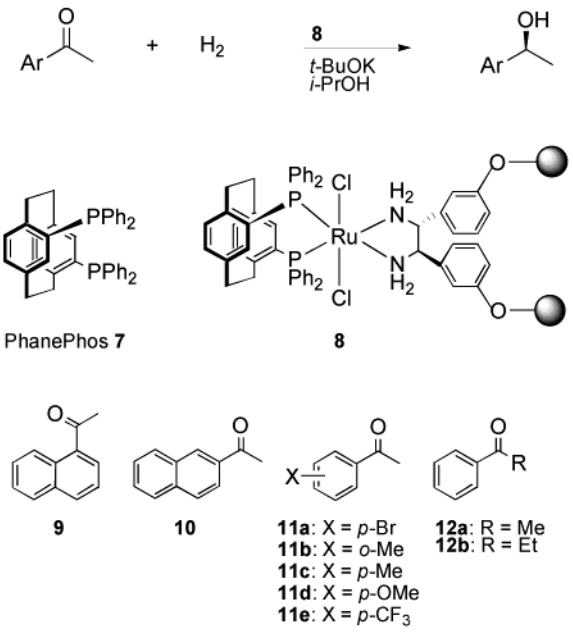
Scheme 1. Synthesis of Poly(ethylene glycol)-Supported PEG-**2**



Protection with Boc of (*R*,*R*)-**3**, followed by the reduction of **4** with hydrogen in the presence of Pd/C, afforded (*R*,*R*)-**5** in almost quantitative yield. The diphenol (*R*,*R*)-**5** was then converted into PEG-**2** by reaction with poly(ethylene glycol) 2000 monomethyl ether mesylate and removal of Boc at **6**. As with other PEG-supported ligands/catalysts,[1a,b] PEG-**2** is soluble in polar solvents such as lower alcohols, water and DMF, but insoluble in solvents of low polarity such as diethyl ether.

To investigate the efficiency of PEG-**2** in asymmetric catalysis, the ruthenium-catalyzed asymmetric hydrogenation of simple ketones developed by Noyori and co-workers was chosen as a model reaction (Scheme 2).[2] The Noyori catalyst

Scheme 2. Asymmetric Hydrogenation of Ketones with **8**



operates on a dual ligand system composed of a chiral primary diamine and a chiral bisphosphine, e.g., DPEN and BINAP, and successful attempts have been made in its immobilization through the BINAP naphthyl rings.[7] We first prepared the catalyst **8** by reacting the PhanePhos ligand (*S*)-**7** with $[(\text{benzene})RuCl_2]_2$ at 100 °C in DMF for 3 h, followed by treatment with 1 equiv of PEG-**2** at room temperature for 12 h.[11,12] Our initial effort was directed at probing the asymmetric induction of the catalyst using acetonaphthone **9** as substrate. In the presence of **8** under 10 bar H_2, the asymmetric hydrogenation of **9** in 2-propanol using *t*-BuOK as base provided (*S*)-1-naphthylethanol in 98% yield and 97% ee over 2 h at S/C = 2000 at room temperature. The ee is comparable to that obtained with the parent, molecular catalyst, $[((S)\text{-PhanePhos})RuCl_2((R,R)\text{-DPEN})]$.[11a]

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(9) While our work was in progress, which was first communicated at the 11th ICI Symposium in May 2002, two publications appeared where DPEN was immobilized through functionalization at the phenyl ring: (a) Itsuno, S.; Tsuji, A.; Takahashi, M. *Tetrahedron Lett.* **2003**, *44*, 3825. (b) Ma, Y.-P.; Liu, H.; Chen, L.; Cui, X.; Zhu, J.; Deng, J.-G. *Org. Lett.* **2003,** *5*, 2103.

(10) The details of the synthesis will be published elsewhere.

(11) PhanePhos: 4,12-bis(diphenylphospino)-[2,2]paracyclophane. See: (a) Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173. (b) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207. (c) Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 4441.

(12) The nitrogen content of PEG-**2** is 0.61% (or 92% of theoretical loading), which leads to a Ru/**7**/diamine ratio of 1/1/1.1 in **8**.

Table 1. Results of Asymmetric Hydrogenation of Ketones with **8**[a]

ketone	time (h)	conversion (%)[b]	ee (%)[b]
9	2	98	97 (*S*)
9[c]	10	100	97 (*S*)
10	2	100	96 (*S*)
11a	2	99	94 (*S*)
11b	4	100	93 (*S*)
11c	4	100	97 (*S*)
11d	4	100	90 (*S*)
11e	4	99	90 (*S*)
12a	2	100	94 (*S*)
12b	3	100	92 (*S*)

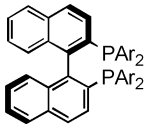
[a] Reactions were performed at room temperature under 10 bar H_2 with 1.0−2.0 M solution of ketone in *i*-PrOH at S/C = 2000 with *t*-BuOK as base (base/Ru = 12) unless otherwise noted. [b] Determined by chiral GC. The alcohol configuration was determined by comparison of GC retention time or sign of optical rotation with literature data. [c] S/C = 10000, initial H_2 pressure 50 bar.

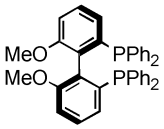
The asymmetric hydrogenation was then extended to other ketone substrates. As shown in Table 1, the immobilized **8** exhibited excellent enantioselectivities and activities for the hydrogenation of various aromatic ketones, including 2-acetonaphthone, substituted acetophenones, and propiophenone. The acetophenones **11a**−**e**, regardless of being activated or deactivated, all furnished high ee's. Of particular note is that the reaction can be run at a much higher S/C ratio without affecting the ee, as exemplified by the hydrogenation of **9** at S/C = 10 000.

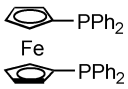
A most important feature of polymer-supported catalysts is their easy separation and reuse. This is the case with the catalyst **8**. A recycling experiment was carried out with ketone **9** at 9 bar H_2 and S/C = 1000 over 3 h. The catalyst was then precipitated by Et_2O, and the product was removed by syringe. In three consecutive reactions, the catalyst afforded conversions of 98%, >99%, and 96%, with the corresponding ee's being 96.1%, 96.1%, and 96.0%, showing only slightly decreased activity and no loss in enantioselectivity. The leached ruthenium in the Et_2O solution upon precipitation of the catalyst was shown, without any optimization, to be low at 2.7 ppm, a feature that is particularly appealing to the manufacture of pharmaceutical intermediates.

Unlike many other immobilized ligands, PEG-**2** can readily be used as a scaffold to build tailor-made chiral catalysts by combining with desired ligands or by derivatization. As the first step toward this direction, four ruthenium complexes of (*R*)-BINAP, (*R*)-tolBINAP, (*R*)-MeO-BIPEHP, and DPPF were individually complexed with PEG-**2** to give four catalysts, each containing an amino functionality necessary for the ketone hydrogenation. As shown in Table 2, the

Table 2. Asymmetric Hydrogenation of Ketones by Combining PEG-**2** with Different Bisphosphines[a]







13a: Ar = C_6H_5, (*R*)-BINAP **14**: (*R*) -MeO-BIPHEP **15**: DPPF
13b: Ar = *p*-$CH_3C_6H_4$, (*R*)-Tol-BINAP

phosphine	time (h)	conversion (%)	ee (%)
13a[b]	4	99	98 (*S*)
13b	12	100	91 (*S*)
14[b]	12	99	92 (*S*)
15[b]	4	99	61 (*S*)

[a] See Table 1 for conditions. [b] The catalysts were prepared in situ by reacting the ruthenium-phosphine complex with PEG-**2** in *i*-PrOH.

catalysts derived from the three chiral phosphines all resulted in excellent ee values, and with the (*R*)-BINAP ligand, an ee of 98% was observed. DPPF produced an active catalyst but did not yield a high enantioselectivity, although it could be asymmetrically activated by PEG-**2** upon coordination to ruthenium.[13]

In conclusion, a supported chiral diamine has been developed and shown to be highly effective in asymmetric hydrogenation of simple aromatic ketones. A further interesting aspect of this study is that ligands such as this could serve as a chiral platform on which to build catalysts of designer properties.

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Supporting Information Available: Experimental procedures for the synthesis of chiral PEG-**2**, procedures for the hydrogenation of aromatic ketones and catalyst recycle, and analytical data for chiral aromatic alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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