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The synthesis of a new nitrogen joined N-PEG-TsDPEN ligand and its application in asymmetric transfer hydrogenation of ketones in neat water

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ABSTRACT

A new polyethylene glycol (PEG) supported ligand, with the PEG chain attached to the nitrogen of TsDPEN, was synthesized using a very simple procedure. The Ru-catalyzed asymmetric transfer hydrogenation of various aromatic ketones in water was investigated with this chiral ligand. High chemical yields and enantioselectivities were obtained under very mild conditions. In addition, the chiral ligand was easily recycled several times and this catalyst was especially suitable for the preparation of chiral tetrahydronaphthalen-1-ol and 2,3-dihydro-1H-inden-1-ol (up to 98% conversion with 99% ee). The latter product can be used as the key intermediate for the synthesis of neuroprotective and anti-AChE agents Rasagiline and Ladostigil.

1. Introduction

Since the important breakthrough made by Noyori et al. in 1995, asymmetric transfer hydrogenation (ATH) has become one of the best reduction systems for both academia and industry [1–4]. As both the chiral ligands and metal in ATH are usually expensive and cannot be easily separated from the products, some immobilized ATH catalysts have been developed in recent years to match the economic and environmental requirements (Fig. 1).

Tu et al. developed a highly efficient heterogeneous catalyst through the immobilization of TsDPEN onto silica gel (**2**, Fig. 1), which demonstrated excellent enantioselectivities and high reactivities [5–7]. Xiao et al. prepared the polyethylene glycol (PEG) supported ligand (PTsDPEN) (**3**, Fig. 1) and the related ruthenium catalyst which represents one of the most efficient ligands for ATH in water [8,9]. Ohta et al. presented a novel task-specific chiral ionic ligand (**4**, Fig. 1) with an attached imidazolium salt, and demonstrated its use in the recyclable catalytic ATH of ketones by an HCO_2H–Et_3N azeotrope in Ils [10]. Deng designed and synthesized tunable dendritic N-mono-sulfonyl ligands (**2**, Fig. 1) via direct N-mono-sulfonylization of the chiral dendritic vicinal diamines [11,12]. Itsuno developed polymer-supported chiral sulfonamides containing a sulfonated pendant group (**5**, Fig. 1), in which the quaternary ammonium salt acting as a pendant increased both the reactivity and the enantioselectivity in asymmetric transfer hydrogenation in water [13]. Ying et al. anchored TsDPEN onto siliceous mesocellular foam and obtained excellent reactivity, enantioselectivity and reusability in ATH of an imine and ketones [14]. Liu et al. reported a facile preparation of a mesoporous silica-supported chiral catalyst by anchoring the Ru-DPEN-$PPh_2CH_2CH_2Si(OEt)_3$ complex onto mesoporous materials (SBA-15) through refluxing in toluene for 24 h [15]. This material showed high catalytic activity and excellent enantioselectivities for the ATH of various aromatic ketones [15]. In this paper, we present the preparation of a new PEG supported chiral ligand, N-PEG-TsDPEN and its application in ATH of ketones (**6**, Fig. 1). Currently, this approach is the simplest method for the preparation of immobilized ATH catalysts.

2. Results and discussion

We first selected a medium sized molecular weight polyethylene glycol (PEG750) and TsDPEN as starting materials for the synthesis of the chiral ligand N-PEG-TsDPEN (Scheme 1). The procedure was very simple. First, the reaction of MeO-PEG-OH, oxalyl chloride and dimethyl sulfoxide in dichloromethane gave the responding aldehyde in high yield. The aldehyde was then reacted with TsDPEN and hydrogen in the presence of platinum/carbon to give the N-PEG-TsDPEN in nearly quantitative yield. Other ligands with different PEG chains (e.g., TsDPEN-PEG-200, TsDPEN-PEG-300, TsDPEN-PEG-400, TsDPEN-PEG-1000, TsDPEN-PEG-2000) (Scheme 1), ligands with N-methoxyethyl (**9**) and simple alkyl

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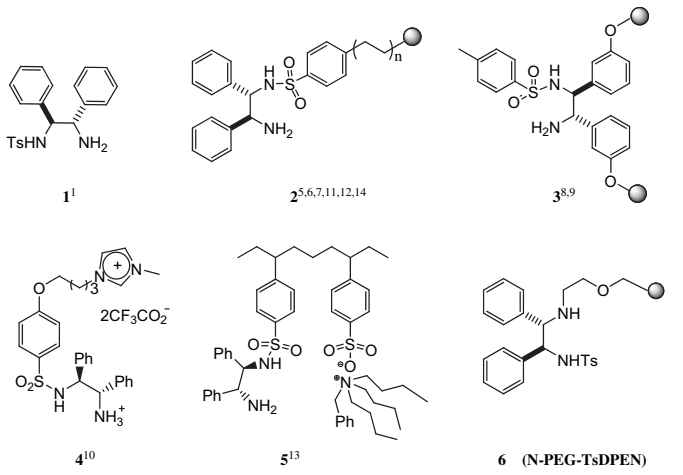


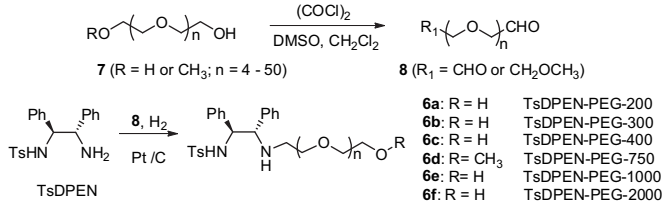
Fig. 1. Some immobilized TsDPEN chiral ligands for ATH.

chains (**10** and **11**) instead of PEG were also prepared using the same procedure to compare the effect of amino group modification.

Acetophenone was chosen as the model substrate, HCOONa as the hydrogen donor, and PEG2000 as the additive for study of the Ru-catalyzed asymmetric transfer hydrogenation using TsDPEN-PEG as the chiral ligand. Full conversion with 94–95% ee was obtained when the reaction was carried out at room temperature overnight (Table 1). The results indicate the reactivity of the nitrogen joined N-PEG-TsDPEN ligand was sufficiently active to facilitate ATH. In comparison with the reaction rate of the Ru-PEG-BsDPEN catalyst in water which we reported previously, the N-PEG-TsDPEN ligand displayed a slightly slower rate; however, similar or better enantioselectivities were observed. On the other hand, ligands with N-methoxyethyl and simple N-alkyl chains seem not favorable for the reaction rate of ATH although nearly the same enantioselectivities were obtained (Table 1, entries 8–10).

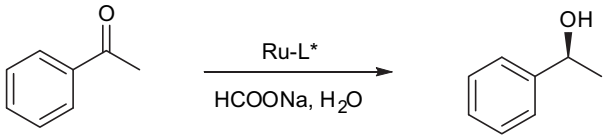
Various other aromatic ketones were also examined with N-PEG750-TsDPEN (**6d**) as chiral ligand under the optimized conditions and the results are listed in Table 2. The electronic effect of the substrates was important for the enantioselectivity of the reaction. The electron-donating substituents appear to be favorable for the enantioselectivities, for example, *p*-methylacetophenone provided 99% ee with a quantitative conversion, whereas *p*-fluoro, *p*-chloro and *p*-bromoacetophenone gave products with 95, 89 and 90% ee, respectively. Furthermore, *p*-nitroacetophenone only gave 84% ee using the same reaction conditions.

It is interesting that 1-tetralone, 1-indanone and 2-acetylnaphthalene all gave 99% ee with the N-PEG750-TsDPEN (**6d**) as the chiral ligand (Scheme 2 and Table 2, entry 10), which was higher than that found using other ligands such as PTsDPEN [8] or TsDPEN with HCOONa as the hydrogen donor. The results indicated that the N-PEG-TsDPEN ligand was favorable for particular steric substrates. The excellent ee values for these substrates, for example, 2,3-dihydro-1H-inden-1-ol or its derivatives, provide an alternative method for the preparation of key intermediates of several important drugs,



Scheme 1. The synthesis of chiral ligand N-PEGTsDPEN.

Table 1
Influence of chiral ligands on asymmetric transfer hydrogenation of acetophenone in water.[a]



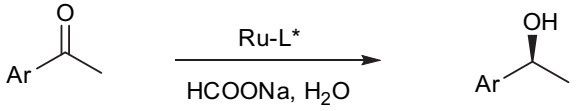
Entry	Ligands	Conversion (%)[b]	E.e (%)[c]
1	TsDPEN	>99	94.8
2	N-PEG200-TsDPEN (**6a**)	>99	94.6
3	N-PEG300-TsDPEN (**6b**)	>99	94.5
4	N-PEG400-TsDPEN (**6c**)	>99	94.8
5	N-PEG750-TsDPEN (**6d**)	>99	94.0
6	N-PEG1000-TsDPEN (**6e**)	>99	94.0
7	N-PEG2000-TsDPEN (**6f**)	>99	94.0
8	N-methoxyethyl-TsDPEN (**9**)	65	95.2
9	N-propyl-TsDPEN (**10**)	63	93.6
10	N-heptyl-TsDPEN (**11**)	32	93.0

[a] Reactions were carried out in 1 mmol scale at 40 °C with an S/*C* = 100 within 15 h.
[b] The conversions were determined by ^{1}H NMR.
[c] The ees were determined by HPLC on chiral OD-H column.

including the neuroprotective and anti-AChE agents, Rasagiline [16] and Ladostigil [17] (Fig. 2).

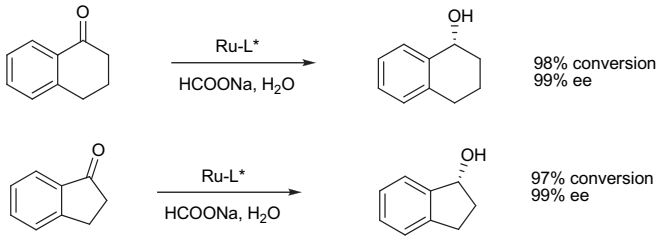
The recycling of the Ru-catalyst with different length of PEG moiety ligands (N-PEG200-TsDPEN (**6a**), N-PEG750-TsDPEN (**6d**) and N-PEG2000-TsDPEN (**6f**)) were investigated with acetophenone as the substrate and HCOONa as the hydrogen donor in water. The procedure was simple. After each catalytic cycle, hexane was added to extract the product and the residue containing the catalyst was reused by adding 1.0 equivalent of formic acid to regenerate sodium formate for the next cycle. The results in Table 3 indicated that the length of PEG moiety has an effect on the activity of the catalyst. For example, the conversion of ATH remained 99% at the eighth run with N-PEG2000-TsDPEN as the chiral ligand, whereas N-PEG750-TsDPEN and N-PEG200-TsDPEN kept the same conversion at the fifth and the third run at the same reaction conditions, respectively. Some Ru complex may be extracted to n-hexanes phase when short

Table 2
Asymmetric transfer hydrogenation of various ketones in water.[a]



Entry	Substrates	Conversion (%)[b]	E.e (%)[c]
1	Phenyl	>99	94
2	4-fluorophenyl	>99	95
3	4-chlorophenyl	>99	89
4	4-bromophenyl	>99	90
5	4-methylphenyl	>99	99
6	4-methoxyphenyl	86	94
7	4-nitrophenyl	>99	84
8	Furan-2-yl	>99	93
9	Propiophenone	>99	92
10	Naphthalen-2-yl	90	>99
11	Ferrocenyl	90[d]	98

[a] Reactions were carried out in 1 mmol scale at room temperature with an S/*C* = 100.
[b] The conversions were determined by ^{1}H NMR.
[c] The ees were determined by HPLC on chiral OD-H column.
[d] Isolated yield.



Scheme 2. Asymmetric transfer hydrogenation of tetralone and indanone.

N-PEG chain DPEN were used as the ligand. Therefore, longer chain might be more suitable for the catalyst recycle.

Extraction and separation of the products from particular polar substrates in the recycling process of the catalyst with TsDPEN as the chiral ligand was challenging in either non-polar solvents such as hexane or polar solvents such as ether (e.g., acetyl ferrocene). However, when Ru-N-PEG-TsDPEN was used as the chiral ligand of the ATH of acetyl ferrocene, the recycling of the catalyst proceeded smoothly. Table 3 summarized the results of the recycling of the catalyst. The results indicated good chemical yields were obtained following four cycles, and the enantioselectivity was consistent in all five cycles.

3. Experimental

3.1. General methods

NMR spectra were recorded with TMS as the internal standard on a Bruker 400 MHz spectrometer. Coupling constants were given in Hz. Enantiomeric excess was determined by HPLC on Chiralcel OD-H columns (4.6 mm × 250 mm). MS spectra were recorded on an Agilent LC-MS 6120 with APCI. Purification of the products was performed by column chromatography on silica gel (200–300 mesh).

3.2. Experimental procedures

3.2.1. The preparation of ligand **6d** (general procedure)

A solution of dimethyl sulfoxide (1.4 ml, 20 mmol) in CH_2Cl_2 (10 ml) was added dropwise over 3 min to a stirred solution of oxalyl chloride (1 ml, 22.6 mmol) in CH_2Cl_2 (50 ml) at −78 °C. After 5 min of stirring, a solution of MeO-PEG-OH (7.50g, 10 mmol) in CH_2Cl_2 (25 ml) was added dropwise over 30 min. After a further 30 min stirring, triethylamine (5.6 ml, 40 mmol) was added. The mixture was stirred at −78 °C for 1 h and then 2 h at room temperature. Water (40 ml) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to yield PEG-aldehyde (6.15g, 91%). The structure of the PEG-aldehyde was proved by the ^{1}H NMR analysis and 9.5 ppm indicated the presence of the hydrogen of aldehyde.

To a solution of (S,S)-TsDPEN (2 mmol) in CH_3OH (15 ml), PEG-aldehyde, 0.215g Pt/C and Na_2SO_4 (6 mmol) were added successively. The system was charged with hydrogen and stirred at room temperature for 24h. After the reaction was finished, the mixture was filtered to remove Pt/C and the filtrate was evaporated in vacuo to afford the crude product, which was purified by flash chromatography (silica gel, methanol/ethyl acetate 1:10). ^{1}H NMR ($CDCl_3$) δ: 7.59 (d, J = 7.6 Hz, 1H), 7.15–7.30 (m, 12H), 6.95 (d, J = 6.8 Hz, 2H), 5.03 (s, 1H), 4.51 (d, J = 5.2 Hz, 1H), 4.30 (d, J = 5.2 Hz, 1H), 2.40 (s, 3H) ppm. The mass spectrum of N-PEG-TsDPEN was measured by APCI-MS, and compared with starting material PEG750.

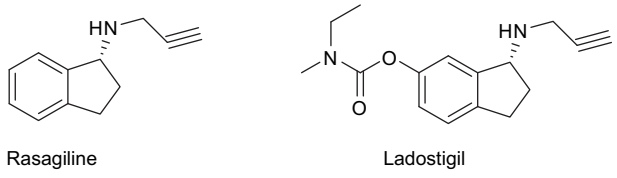


Fig. 2. Anti-AChE and neuropotective agents derived from indanone.

Table 3
Results of Catalyst Recycling in the Asymmetric Transfer Hydrogenation in Water[a].

Run	Ligands	Substrates	Time (h)	Conversion (%)[b]	E.e (%)[d]
1–8	**6f**	Acetophenone	6	>99	94
9	**6f**	Acetophenone	6	97	93.8
10	**6f**	Acetophenone	6	85	94
1–5	**6d**	Acetophenone	6	>99	93.7
6	**6d**	Acetophenone	6	98	93
7	**6d**	Acetophenone	12	80	92.5
1–3	**6a**	Acetophenone	6	99	94
4	**6a**	Acetophenone	6	87	93
1	**6d**	acetyl ferrocene	24	90[c]	97.5
2	**6d**	acetyl ferrocene	24	90[c]	97.7
3	**6d**	acetyl ferrocene	24	86[c]	97.5
4	**6d**	acetyl ferrocene	48	78[c]	97.0
5	**6d**	acetyl ferrocene	48	65[c]	96.5

[a] Reaction conditions were the same as used in Table 1, 1.0 equiv of HCOOH was added to regenerate HCOONa after each run.
[b] The conversions were determined by ^{1}H NMR.
[c] Isolated yuield.
[d] The ees were determined by HPLC on chiral OD-H column.

3.2.2. General procedure of catalyst recycling in asymmetric transfer hydrogenation of acetophenone in water

A suspension of $[RuCl_2(p\text{-cymene})]_2$ (3.1 mg, 0.005 mmol), PEG2000 (1.0 g) and N-PEG-TsDPEN ligand **6d** (13.5 mg, 0.012 mmol) in H_2O (1 ml) was purged with argon and stirred at 40 °C for 1 h. HCOONa (340 mg, 5.0 mmol) and acetophenone (120 mg, 1.0 mmol) were then introduced to the catalyst solution. The mixture was degassed three times, and stirred at 45 °C under an argon atmosphere. After 6 h, the product was extracted with n-hexane (2 ml) three times. The conversion was determined by ^{1}H NMR and the enantioselectivity was determined by chiral HPLC analysis.

The aqueous solution containing the catalyst was used for the subsequent transfer hydrogenation run: HCOOH (0.039 ml, 1 equiv.) was added to regenerate sodium formate and then acetophenone (120 mg, 1.0 mmol) was added into the aqueous solution for a new reaction cycle.

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Appendix. Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.jorganchem.2011.02.004.

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