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Six-membered bis(azaphosphorinane), readily available ligand for highly enantioselective asymmetric hydrogenations

Yongjun Yan and Xumu Zhang*

104 Chemistry Building, Department of Chemistry, The Pennsylvania State University, University Park, PA 16802, USA

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Abstract—A new six-membered bis(azaphosphorinane) ligand has been readily prepared starting from an inexpensive chiral epoxide; excellent enantioselectivities (up to over 99% ee) have been achieved in the Rh-catalyzed asymmetric hydrogenations of β-dehydroamino acid derivatives and α-arylenamides.

Transition-metal catalyzed asymmetric hydrogenation is one of the most efficient methods for preparing chiral compounds. Most of the efforts in this area have been focused on the search for new highly enantioselective chiral ligands[1] because enantioselectivities are often substrate dependent. Subtle changes of ligand structure either electronically or sterically often have dramatic impacts on enantioselectivities. Among numerous ligands reported, DuPhos and BPE developed by Burk et al. in early 1990s have been shown highly efficient for asymmetric hydrogenations of functionalized prochiral olefins and ketones.[2] During the past decade, many bis(phospholane) ligands derived from DuPhos and BPE have been reported.[3] The typical phospholane synthesis involves the use of a chiral 1,4-diol. The expensive chiral 1,4-diols used for the preparation of DuPhos and BPE were originally synthesized through electrochemical Kolbe coupling. Biocatalysis route was introduced later.[3] Other chiral 1,4-diols prepared from inexpensive chiral pool such as D-mannitol were prepared by multistep synthesis.[4] Though many five-membered bis(phospholane) ligands have been developed, there is only one known six-membered bis(oxaphosphorinane) ligand reported for asymmetric hydrogenations.[5] A seven-step synthetic route to this ligand has been developed and up to 97.5% ee and 94.2% ee were obtained in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives and itaconic acid, respectively.

Previously, we have successfully prepared several DuPhos type ligands such as PennPhos,[6] Binaphane[7] and Ketalphos.[4d,f] Our goal is to develop new chiral ligands which are highly efficient, yet easily obtainable from inexpensive and readily available starting materials. As the result of our continued efforts, herein we would like to report the facile synthesis of a novel six-membered bis(azaphosphorinane) ligand, 4,4′-(1,2-ethanediyl)bis[(3*R*,5*R*)-1,3,5-trimethyl-1,4-azaphosphophorinane] **1** and its applications in highly enantioselective Rh-catalyzed asymmetric hydrogenations of β-dehydroamino acid derivatives and α-arylenamides.

The ligand design was based on the following considerations: (1) conformation rigidity is often required to achieve high enantioselectivities in asymmetric hydrogenation. We reason a six-membered phosphorinane is conformationally more rigid than a five-membered phospholane thus may provide a rigid chiral environment around the metal center; (2) a chiral 1,5-diol, the precursor to the six-membered phosphorinane ring, can be readily prepared by reacting a primary amine with a chiral epoxide in a single step. The synthetic route for ligand **1** is depicted in Scheme 1. Thus, aqueous methyl amine reacted with 2.2 equiv of (*S*)-propylene oxide **2** in methanol at 60 °C to afford the chiral 1,5-diol **3** in 95% yield. After removing the solvent, the ring-opening product was pure enough and was directly used for the next step without further purification. Cyclization with thionyl chloride in dry dichloromethane at 0 °C in the presence of triethylamine proceeded smoothly. The initial attempts to oxidize the cyclic sulfite intermediate using the $RuCl_3/NaIO_4$ catalytic

* Corresponding author. Tel.: +1 814 865 4221; fax: +1 814 865 3292; e-mail: xumu@chem.psu.edu

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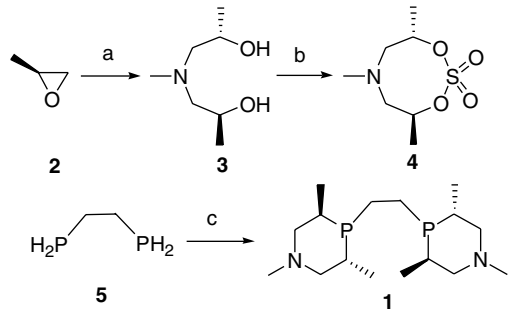
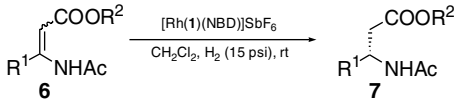


Scheme 1. Synthesis of ligand **1**. Reagents and conditions: (a) methylamine, 60 °C, MeOH, 95%; (b) (i) $SOCl_2$, NEt_3, CH_2Cl_2, (ii) $RuCl_3$, $NaIO_4$, CH_3CN/H_2O, pH < 1, 61%; (c) (i) *n*-BuLi (2 equiv), THF; (ii) **4** (2 equiv), (iii) *n*-BuLi (2.2 equiv), THF, 36%.

system developed by Sharpless[8] under the standard reaction condition were unsuccessful. The oxidation reaction did not occur because the cyclic sulfite intermediate contains a tertiary amine moiety, which poisoned the ruthenium catalyst in the oxidation process. To facilitate the Ru-catalyzed reaction, the nitrogen atom of the tertiary amine has to be masked. Although the standard oxidation condition requires the removing of acidic species, we found that adjusting the pH to <1 by simply adding concd HCl to the reaction mixture can efficiently mask the amine moiety and promote the oxidation reaction. Since the acidified cyclic sulfite is a salt and soluble in water, a 1:1 CH_3CN/H_2O mixture was used as a solvent instead of $CCl_4/CH_3CN/H_2O$. The overall yield of cyclic sulfate **4** from the chiral 1,5-diol **3** was 61%. Metalation of 1, 2-bis(phosphino)ethane **5** with 2 equiv of *n*-BuLi at room temperature followed by addition of 2 equiv of cyclic sulfate **4** and another 2.2 equiv of *n*-BuLi finally provided the desired ligand **1**[9] in 36% yield as a viscous oil.

The ligand **1** has been employed in the asymmetric hydrogenations of β-dehydroamino acid derivatives. The hydrogenation reactions were carried out at room temperature under 15 psi of H_2 in the presence of 1 mol % [Rh(**1**)(NBD)]SbF_6 prepared by mixing ligand **1** with 1.0 equiv of $[Rh(NBD)_2]SbF_6$. As shown in Table 1, a variety of β-alkyl β-(acylamino) acrylates **6** have been hydrogenated with excellent enantioselectivities. Both (*E*)- and (*Z*)-isomeric substrates gave the hydrogenation products **7** with the same configuration using Rh-**1** catalyst. For hydrogenations of (*E*)-isomers **6a**–**g**, high enantioselectivities (99 to >99% ee) have been obtained (Table 1, entries 1–7). Changing the ester groups and alkyl substituents showed no significant variations in enantioselectivities. Ligand **1** also gave excellent enantioselectivities for the hydrogenations of (*Z*)-isomers **6h**–**i** (Table 1, entries 8 and 9) though the ee values were slightly less than those of the corresponding (*E*)-isomers **6a** and **6e** (Table 1, entries 1 and 5). Compared with the Rh–Me–DuPhos catalyst (which gave 98.2% ee and 87.8% ee for the asymmetric hydrogenations of (*E*)-**6a** and (*Z*)-**6h**, respectively),[10] Rh–**1** catalyst provided much higher ee value for the (*Z*)-isomer (Table 1, entries 1 and 8). There are only few catalytic systems which can achieve over 95% ee for the asymmetric hydrogenations

Table 1. Asymmetric hydrogenation of β-alkyl β-(acylamino) acrylates with Rh–**1** catalyst[a]



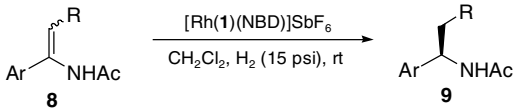
Entry	Substrate	R^1	R^2	ee (%)
1	(*E*)-**6a**	Me	Me	>99
2	(*E*)-**6b**	Et	Me	>99
3	(*E*)-**6c**	*i*-Pr	Me	>99
4	(*E*)-**6d**	*i*-Bu	Me	99
5	(*E*)-**6e**	Me	Et	99
6	(*E*)-**6f**	*n*-Pr	Et	99
7	(*E*)-**6g**	Me	*i*-Pr	99
8	(*Z*)-**6h**	Me	Me	96
9	(*Z*)-**6i**	Me	Et	96

[a] Reactions were carried out under 15 psi of H_2 in CH_2Cl_2 at room temperature for 24 h with full conversion. Substrate/[Rh(**1**)(NBD)]SbF_6 = 100:1. For absolute configuration and ee (%) value determinations, see Ref. 12 for detail.

of (*Z*)-isomers of β-alkyl β-(acylamino) acrylates.[11] These results are among the highest enantioselectivities achieved to date for the hydrogenations of β-alkyl β-(acylamino) acrylates.

With Rh–**1** catalyst, a variety of α-arylenamides **8** were also hydrogenated to afford chiral amides **9** with excellent enantioselectivities (Table 2). For terminal α-arylenamides **8a**–**f** (Table 2, entries 1–6), *para*-substituted phenylenamides **8c**–**e** (Table 2, entries 3–5) generally led to better enantioselectivities than nonsubstituted α-phenylenamide **8a** (Table 2, entry 1), while enantioselectivity decreased for a *meta*-substituted phenylenamide **8b** (Table 2, entry 2). It should be noted that for the hydrogenations of β-substituted arylenamides **8g**–**8l** (Table 2, entries 7–12), *E*/*Z* isomeric mixtures were employed and the hydrogenation reactions can tolerate

Table 2. Asymmetric hydrogenation of α-arylenamides with Rh–**1** catalyst[a]



Entry	Substrate	Ar	*R*	ee (%)
1	**8a**	Ph	H	96
2	**8b**	*m*-MePh	H	95
3	**8c**	*p*-CF_3Ph	H	98
4	**8d**	*p*-CyPh	H	>99
5	**8e**	*p*-PhPh	H	98
6	**8f**	2-Np	H	>99
7	**8g**	Ph	Me	99
8	**8h**	*p*-CF_3Ph	Me	98
9	**8i**	*p*-MeOPh	Me	97
10	**8j**	2-Np	Me	>99
11	**8k**	Ph	*i*-Pr	98
12	**8l**	Ph	Bn	97

[a] Reactions were carried out under 15 psi of H_2 in CH_2Cl_2 at room temperature for 24 h with full conversion. Substrate/[Rh(**1**)(NBD)]SbF_6 = 100:1. For the *E*/*Z* ratio of **8g**–**l**, absolute configuration and ee (%) value determinations, see Ref. 13 for detail.

the geometry of the substrates. A series of β-substituted phenylenamides **8g**,**k** and **8l** (Table 2, entries 7, 11 and 12), as *E*/*Z* isomeric mixtures, were hydrogenated with excellent enantioselectivities regardless of different β-substituents. No significant electronic effect of the substitution at the aryl group of the enamides was observed on the enantioselectivities (Table 2, entries 8 and 9). Enantiomeric excesses of over 99% were obtained in the hydrogenations of more bulky 2-naphthyl enamides **8f** and **8j** (Table 2, entries 6 and 10). The enantioselectivities achieved with ligand **1** for the hydrogenation of *E*/*Z* isomeric mixtures of β-substituted α-arylenamides are comparable to or better than those reported with Me–DuPhos and BPE ligands.[13]

In conclusion, new bis(azaphosphorinane) ligand **1** has been easily prepared from inexpensive, readily available starting materials. To the best of our knowledge, this ligand provides the first example of six-membered bis(phosphorinane) ligands for the highly enantioselective asymmetric hydrogenations of β-dehydroamino acid derivatives and α-arylenamides. To make the ligand useful for large-scale industrial applications, further ligand modification is needed because the substrate-to-catalyst ratio and the reaction rate are lower compared with other bisphosphine ligand such as DuPhos due to the presence of basic nitrogen in the ligand itself.

Acknowledgements

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