Chinese Chemical Letters Vol. 16, No. 10, pp 1321-1323, 2005 1321
http://www.imm.ac.cn/journal/ccl.html

Synthesis of Novel Monophosphoramidite Ligands Derived from L-Proline for Rh-catalyzed Asymmetric Hydrogenation of α-Dehydroamino Acid Esters

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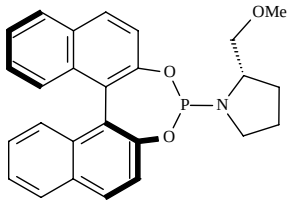
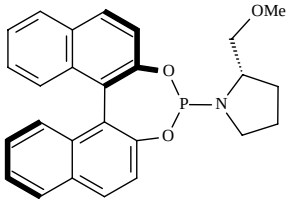
Abstract: Two novel monophosphoramidites were synthesized through a five-step transformation from commercially available L-proline. In the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives, ligand (S_c,R_a)-**1b** showed good enantioselectivity and up to 91% e.e. was obtained.

Keywords: Monophosphoramidite, L-proline, Rh-catalyzed asymmetric hydrogenation, α-dehydroamino acid.

Despite many bidentate P-chelate ligands have been achieved with encouraging performances[1,2], a renewed interest in the development of the chiral monodentate phosphorus-containing ligands for rhodium-catalyzed asymmetric hydrogenation has been paid attention in recent years[3-5]. Many monodentate phosphorus ligands have been reported, still there is a need for preparing readily available monodentate ligands, which have a broad application range in asymmetric hydrogenation. Recently, we have reported a series of new carbohydrates-based monophosphites, which gave exceptionally high enantioselectivities for asymmetric hydrogenation[6,7]. As a persistent effort in the development of novel efficient monodentate ligands, herein we report two new monophosphoramidite ligands (S_c,S_a)-**1a** and (S_c,R_a)-**1b** derived from L-proline and their application in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters.



(S_c,S_a)-**1a**



(S_c,R_a)-**1b**

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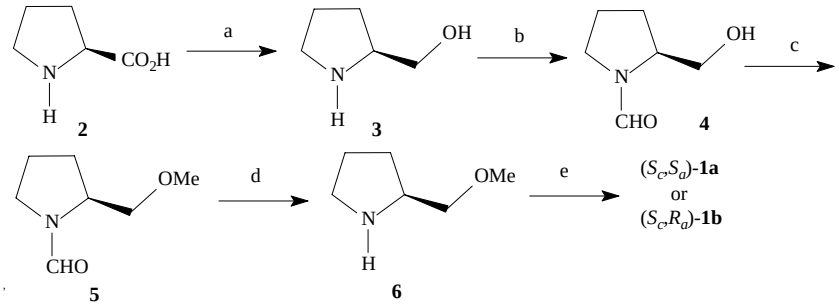
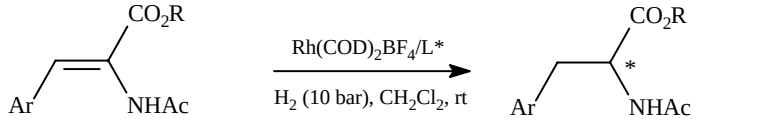
Scheme 1 Synthesis of monophosphoramidite (S_c,S_a)-**1a** and (S_c,R_a)-**1b**



Reagent and conditions: (a) $LiAlH_4$, THF, 0°C; (b) HCO_2Et, 50°C; (c) NaH, CH_3I, THF, rt to reflux; (d) KOH, 70°C; (e) (*R*)- or (*S*)-4-chloro-3,5-dioxa-4-phosphacyclohepta[2,1-α;3,4-α']-dinaphthalene, toluene, 0°C to rt

Scheme 2



7a R = Et, Ar = Ph;
7b R = Et, Ar = 4-ClPh;
7c R = Me, Ar = 4-ClPh;
7d R = Me, Ar = 4-MeOPh

8a R = Et, Ar = Ph;
8b R = Et, Ar = 4-ClPh;
8c R = Me, Ar = 4-ClPh;
8d R = Me, Ar = 4-MeOPh

Starting from commercially available L-proline, the target ligands were synthesized through a five-step transformation as outlined in **Scheme 1**. The initial step involved the synthesis of the key intermediate **6** according to a modified procedure reported by Wilson *et al*[8]. By the reduction, formylation, methylation and hydrolysis sequence, L-proline **2** was converted into the corresponding prolinol methyl ether **6**. Subsequent treatment of **6** with BINOL-derived (*S*)- or (*R*)-chlorophosphite[9] in toluene at 0°C gave the target ligands (S_c,S_a)-**1a** and (S_c,R_a)-**1b**[10] in nearly quantitative yields.

These new monophosphoramidites were then applied in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters (**Scheme 2**). The reaction was performed in CH_2Cl_2 at room temperature under H_2 pressure of 10 bar in the presence of 1 mol% catalysts prepared *in situ* from $Rh(COD)_2BF_4$ and 2.2 equiv. of chiral ligand, and the results are summarized in **Table 1**. Ligand (S_c,S_a)-**1a** surprisingly showed no catalytic activity and selectivity in the Rh-catalyzed asymmetric hydrogenation of ethyl (*Z*)-acetamidocinnamate **7a** while ligand (S_c,R_a)-**1b** gave a hydrogenation product in 90% e.e. (entry 2 *vs.* entry 1). This result suggested that (*S*)-central chirality and (*R*)-axial chirality was matched configurations in this kind of monophosphoramidites. We then selected the ligand (S_c,R_a)-**1b** for further study of this reaction. A variety of α-dehydroamino acid derivatives were undertaken to examine the efficiency of this catalyst system. All substrates were hydrogenated in good enantioselectivity, and the highest enantioselectivity of 91% e.e. was obtained in the hydrogenation of substrate **7b** with a chloro substitutent in phenyl ring (entry 5).

Table 1 Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives **7**[a]

Entry	Ligand	Substrate	Conv. (%)	Ee (%)[b]	Config.[c]
1	(S_c,S_a)-**1a**	**7a**	-	-	-
2	(S_c,R_a)-**1b**	**7a**	100	90	*S*
3	(S_c,R_a)-**1b**	**7b**	100	91	*S*
4	(S_c,R_a)-**1b**	**7c**	100	84	*S*
5	(S_c,R_a)-**1b**	**7d**	100	90	*S*

[a] Substrate/Rh/L* = 1/0.01/0.022, H_2 (10 bar), solvent = CH_2Cl_2, room temperature.
[b] Conversion and enantiomeric excesses were determined by GC using CP-Chiralsil-L-Val capillary (0.25 mm x 30 m) column.
[c] The absolute configuration was determined by comparing the GC retention times with GC data in the literature.

In conclusion, we have prepared two new monophosphoramidite ligands and good enantioselectivity of **1b** (91% e.e.) was obtained in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters. Further modification and application of these ligands are still in progress.

Acknowledgments

The authors would like to thank the National Natural Science Foundation of China (20472083) for financial support .

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10. Selected data for compound (S_c,S_a)-**1a**: $[\alpha]_D^{25}$ +161 (c 0.3, $CHCl_3$); ^{1}H NMR (DMSO-d_6, δ ppm) 1.43-1.52 (m, 3 H), 1.79-1.82 (m, 1 H), 2.38-2.39 (m, 1 H), 2.65-2.68 (m, 1 H), 3.04-3.12 (m, 2 H), 3.13 (s, 3 H), 3.80-3.81 (m, 1 H), 7.03-7.48 (m, 8 H), 7.89-8.03 (m, 4 H); ^{31}P NMR (DMSO-d_6, δ ppm) 149.1; HRMS Calcd. for $C_{26}H_{24}NO_3P$ + H: 430.1566, Found 430.1537. Selected data. for compound (S_c,R_a)-**1b**: $[\alpha]_D^{25}$ -434 (c 0.3, $CHCl_3$); ^{1}H NMR (DMSO-d_6, δ ppm) 1.41-1.46 (m, 3 H), 1.62-1.72 (m, 1 H), 2.11-2.19 (m, 1 H), 2.84-2.91 (m, 1 H), 3.17-3.23 (m, 2 H), 3.24 (s, 3 H), 3.62-3.70 (m, 1 H), 7.06-7.48 (m, 8 H), 7.92-8.02 (m, 4 H); ^{31}P NMR (DMSO-d_6, δ ppm) 149.9; HRMS Calcd. for $C_{26}H_{24}NO_3P$ + H: 430.1566, Found 430.1558.

Received 14 January, 2005