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Synthesis of a New Rigid Bicyclic AMPP Ligand (TIAMPP) and Application in Asymmetric Hydrogenation

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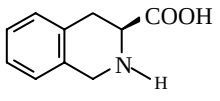
Abstract: The new rigid bicyclic AMPP((*S*)-TIAMPP) has been synthesized from the corresponding Ticol and Ph_2PCl. The application of *(S)*-TIAMPP in Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acids derivatives has been examined. Up to 93% ee was obtained.

Kewords: (*S*)-TIAMPP, synthesis, asymmetric hydrogenation.

During the past decade, much attention has been attracted in developing chiral aminophosphine phosphinites (AMPP) ligands for asymmetric hydrogenation[1] owing to the following advantages: (1) optically active amino alcohol as chiral source of AMPP is available; (2) AMPP can be conveniently prepared by reaction of the corresponding amino alcohol with chlorodiphenylphosphine in the presence of Et_3N. From the technological and economic standpoint, it is promising to develop highly effective chiral AMPP for asymmetric hydrogenation. It is known that the derivatives of prolinol, ProNOP[2]and hydroxyprolinol, E-ProNOP[3] with the cyclic backbone were proved to be favorable ligands to afford high enantioselectivity. So we prepared (*S*)-3-hydroxymethyl-1, 2, 3, 4-tetrahedroisoquinoline **2** ((*S*)-Ticol), (*S*)-N, O-bis(diphenylphosphino)-3-methoxy-1, 2, 3, 4-tetrahedroisoquinoline **3** ((*S*)-TIAMPP) and [Rh(*S*)-TIAMPP (COD)]BF_4 **4** from the 1, 2, 3, 4-tetrahydroisoquinoline-3-carboxylic acid **1** (Tic) (**Scheme 1**). The cationic rhodium complex **4** of this new rigid bicyclic AMPP ligand was found to be highly effective catalyst for asymmetric hydrogenation of dehydroamino acid derivatives.

As shown in **Scheme 1**, pure chiral **1** was synthesized from DL-Phe by chemoenzymic method[4]. New amino alcohol **2** was given by the reduction of **1** using $NaBH_4/I_2$ system[5], then **3** was prepared in the yield of 60.1% by the reaction of compound **2** with



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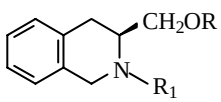

2 R=R_1=H **3** R=R_1=PPh

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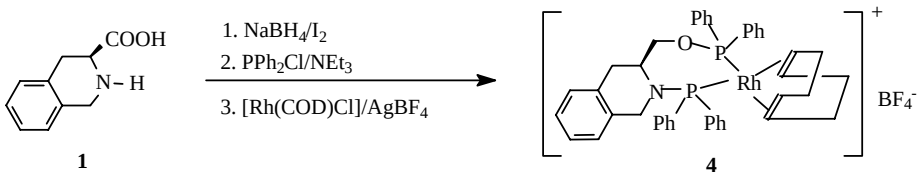
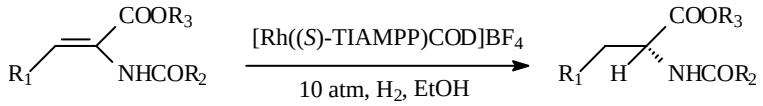
Schem 1 Synthesis of Rh((*S*)- TIAMPP) (COD)]BF_4



1 **4**

Table 1 Rh-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives



5 **6**

Entry	Substrate [a]	ee(%)
1	R_1=H, R_2=CH_3 , R_3= H	83[b]
2	R_1=H, R_2=CH_3, R_3=CH_3	86[b]
3	R_1=H, R_2= Ph , R_3=H	88[c]
4	R_1=H, R_2=Ph , R_3=CH_3	88
5	R_1=Ph, R_2=CH_3, R_3=H	92[c]
6	R_1=Ph, R_2=CH_3, R_3=CH_3	93
7	R_1=Ph, R_2=Ph , R_3= H	93[c]
8	R_1=Ph, R_2=Ph , R_3=CH_3	93

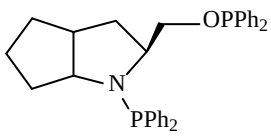
[a][substrate/[Rh((*S*)- TIAMPP) (COD)]BF_4=1:0.01; [b] The values of the optical yields were calculated with respect to the following value : N-acetyl-(R)-alanine[9] $[\alpha]_D^{25}$+66.5 (c=2, H_2O); [c]The ee values were determined by HPLC using Chiracel OD column after converting the products to the corresponding methyl ester. (eluent: *n*-hexane/2-propanol= 9:1, flow rate: 0.5 mL/min, retention times respectively: entry 3: t_R(min) = 13.1(minor), 17.5 (major); entry 5: t_R(min) = 10.5(minor) , 13.2 (major); entry 7: t_R(min)=13.5(minor), 17.2 (major)).

chlorodiphenylphosphine in the presence of triethylamine. It was purified by flash column chromatography over silica gel. **3** is viscous transparent oil, $[\alpha]_D^{25}$-27.3(c 1, benzene). Its structure has been identified by 500MHz ^{1}HNMR, ^{31}PNMR, ^{13}CNMR[6].

The Rh complex **4** was prepared according to the method of Shrock and Osborn[7]. All catalytic hydrogenations were carried out in EtOH at room temperature under 10 atm for 24 h, the working up procedure was followed the literature method[8].

To our knowledge, the 93% ee obtained with (*S*)-TIAMPP (**Table 1**) is the best result among those bicyclic AMPP ligands reported to date. Kreuzfeld had investigated asymmetric hydrogenation of compound **5** by Rh-catalysts generated *in situ* from $[Rh(COD)Cl]_2$ and the ligands of bicyclic AMPP **7**[10]and **8**[11]. The ee values were 72%, 90% respectively. Mortreux found the cationic rhodium complex bearing cyclic AMPP **9**[3] can afford 90% ee in asymmetric hydrogenation. The enantioselectivity of asymmetric hydrogenation of our experiment was increased. The high enantionselectivity of (S)-TIAMPP is rationalized by the phenyl that may increase the rigidity of the chiral ligand **3**. It is beneficial to stabilizing the spatial conformation of the active transition state of complex formed from the catalyst and substrate.

Moreover, (*S*)-TIAMPP can almost have the same enantioselectivity on the substrates both of dehydroamino acids and esters. The obtained products are all R-configuration. According to the view of Mortreux, (*S*)-TIAMPP formed δ-type with Rh(I), which determined R-configuration of the products. (*S*)-TIAMPP is stable enough to be purified by flash column chromatograph under air atmosphere.



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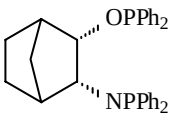

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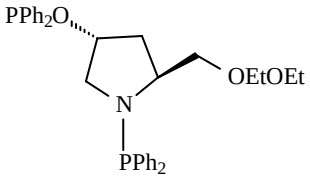

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In summary, we have synthesized the new rigid bicyclic AMPP ligand of (*S*)-TIAMPP for hydrogenation of dehydroamino acid precursors with good results. We are currently investigating the optimal conditions, such as the effects of solvent, hydrogen pressure, reaction temperature and substrate concentration on the asymmetric hydrogenation. At the same time, the application of **2** in asymmetrical addition of dialkylzincs to carbonyl compounds is in progress.

Acknowledgments

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References and Notes

1. For reviews on asymmetric hydrongenation using AMPP see: (a) F. Agbossou, J. F. Carpentier, F. Hapiot, I. Sussie, A. Mortreux, *Coord. Chem. Rev.*, **1998**, *178*, 1615. (b) R. L. Lou, A. Q. Mi, Y. Z. Jiang, Z. Li, F. M. Fu, A. S. C. Chan, *Tetrahedron*, **2000,** *56*(32), 5857. (c) H. J. Kreuzfeld, U. Schmidt, C. Dobler, W. Krause, *Tetrahedron:Asymmetry*, **1996**, *7*(4), 1011.
2. (a) E. Cesarotti, A. Chiesa, G. D. Alfonso, *Tetrahedron Lett.*, **1982,** *23*(29), 2995. (b) F. Agbossou, F. C. Carpentier, C. Hatat, *Organomet.*, **1995,** *14*, 2480.
3. A. Karim, A. Mortreux, *J. of Organomet. Chem.*, **1986,** *312*, 375.
4. D. C. Gong, H. Zhou, M. Z. Gong, P. Wei, P. K, Ouyang, *Xiandai Huagong(Modern Chemical Industry*, in Chinese), **2003,** *23*(12), 23.
5. General procedure: a 250 mL three neck round-bottom flask equipped with a magnetic stir bar, reflux condensaer, thermometer, and addition funnel was flushed with argon and charged with THF(125 mL), Tic(7.08 g, 40 mmol), $NaBH_4$(4.0 g, 108 mmol) whereupon a vigorous gas evolution was observed. Then a solution of I_2(10.2 g, 38.8 mmol)/THF(40 mL) was added dropwise at 25-30℃. After the addition was finished, the reaction mixture was refluxed over night. Excess reducing agent was cautiously destroyed by dropwise addition of MeOH(30 mL) at room temperature. The solvents were removed *in vacuo* and the residue was taken up in NaOH(200 mL, 20%). The product was extracted three times with CH_2Cl_2(100 mL). After drying over Na_2SO_4, the extract was evaporated to dryness. The residue was crystallized from toluene(20 mL). The colorless crystal **2** was obtained. The yield was 77%. m.p.114-117℃, $[\alpha]_D^{25}$ -104.2 (c 0.6, EtOH), purity>98%. (determined by

HPLC using Chiracel OD column). ^{1}HNMR($CDCl_3$, δ ppm) 6.88-7.29(m, 4H, Ph), 4.06(s, 2H, -CH_2NH-), 3.92 (d, 2H, J=3.2, -CH_2O-), 3.67(m, 1H, -NCHCH_2-), 3.05(d, 2H, J=11.7, PhCH_2CH-). Calcd. for $C_{10}H_{13}NO$: C 73.59, H 8.08, N 8.58. Found: C 73.28, H 8.11, N 8.27.

6. (*S*)-TIAMPP spectroscopic data: ^{1}HNMR($CDCl_3$, δ ppm) 6.62-7.39(m, 24H, 5Ph), 3.84(s, 2H, PhCH_2-), 3.73(d, 2H, J=3.4, -CH_2O-), 3.53 (m, 1H, -NCHCH_2-), 2.53(d, 2H, J=11.6, PhCH_2CH-); ^{13}CNMR($CDCl_3$, δ ppm) 30.2, 46.2, 53.9, 77.76, 128.2-142.3; ^{31}PNMR($CDCl_3$, δ ppm) 117.9(P(O)), 62.5(P(N)); Calcd. for $C_{34}H_{31}NOP_2$: C 76.85, H 5.84, N 2.63, P 11.67. Found: C 76.71, H 5.70, N 2.42, P 11.54.
7. R. R. Schrock, A. Osborn, *J. Am. Chem. Soc*., **1971,** *93*, 3089.
8. M. D. Fryzuk, B. Bosnich, *J. Am. Chem. Soc*., **1977,** *99*, 6262.
9. H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.*, **1972,** *94*, 6429.
10. C. Dobler, U. Schmidt, H. W. Krause, *et al.*, *Tetronhedron: Asymmetry*, **1995**, *6*(2), 358.
11. C. Dobler, H. J. Kreuzfeld, H. Pracejus, *J. Organomat. Chem.*, **1988,** *344*, 89.

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