Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 6, pp. 1233-1236, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00151-4

Synthesis of New Chiral Catalysts, *N*-Alkyl-2-azanorbornylmethanols, for the Enantioselective Addition of Diethylzinc to Arylaldehydes

Hiroto Nakano,[a] Noriyuki Kumagai,[a] Chizuko Kabuto,[b] Hisao Matsuzaki,[a] and Hiroshi Hongo[a]*

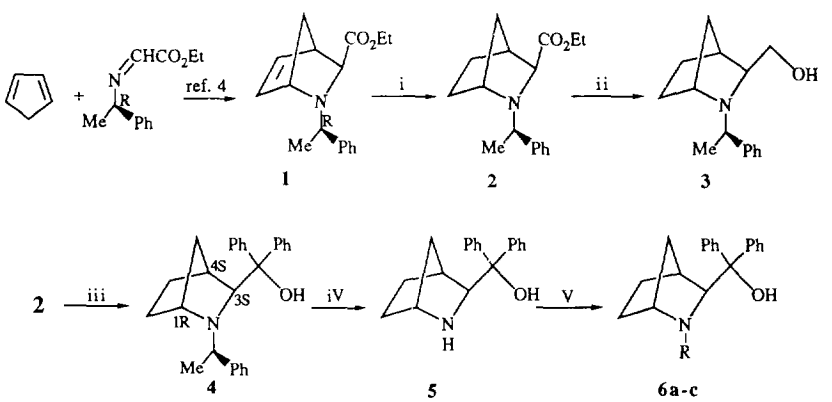
a Tohoku College of Pharmacy, Aoba-ku, Sendai 981, Japan
b Department of Chemistry, Faculty of Science, Tohoku University, Aobayama, Sendai 980, Japan

Abstract: New chiral ligands, 2-azanorbornylmethanols, were prepared and catalyzed the addition of diethylzinc to aldehydes to furnish secondary alcohols in up to 92%ee.

Recently, catalytic asymmetric synthesis has been a challenging subject in organic synthesis. For example, the asymmetric addition of dialkylzinc to aldehydes in the presence of catalytic amounts of chiral ligands is a potentially important method for the preparation of enantiomerically pure secondary alcohols.[1] Particularly, β-amino alcohols have proved to be extremely efficient catalysts in this reaction.[2] 2-Azanorbornenes, 2-azabicyclo[2.2.1]heptenes, have great potential as synthetic intermediates for the synthesis of biologically active compounds.[3] In this communication, we wish to report the synthesis of new chiral ligands, 2-azanorbornylmethanol **5** and its *N*-alkyl derivatives **3, 4, 6a-c** which are sterically constrained β-amino alcohols, and the first use of them as catalysts in the enantioselective addition of diethylzinc to aldehydes.

Preparations of chiral ligands, **3,4,5, 6a-c** are described in scheme 1. Chiral ligand **3** having a hydroxymethyl substituent in the side chain, was obtained as a viscous oil, $[\alpha]_D^{23}$+60.62 (c1.6, $CHCl_3$), in

Scheme 1



Reagents.
i: H_2, Pd-C(10%), CH_3CO_2Et, 20°C, 24h, 96%;
ii: $LiAlH_4$, THF, 15h, 70%;
iii: PhMgBr, THF, 20°C, 24h, 80%;
iv: H_2, 20%$Pd(OH)_2$, CH_3CO_2Et, 98%;
v: RX, CH_3CN, reflux, over night

6a : R=Me, 85%
6b : R=Et, 89%
6c : R=iso-Propyl, 30%

77% yield from bicyclic amino acid ethylester **1**, derived from the reaction of cyclopentadiene with an imine[4], followed by catalytic hydrogenation and reduction with lithium aluminum hydride. Furthermore, chiral ligand **4** bearing a diphenylmethanol group in side chain, mp 143-144°C, $[\alpha]_D^{23}$-22.6 (c0.9, $CHCl_3$), was synthesized by the reaction of **2**, viscous oil, $[\alpha]_D^{23}$+2.08 (c4.8, $CHCl_3$), with phenylmagnesium bromide in 80% yield. Chiral *N*-unsubstituted ligand **5**, mp 133-134°C, $[\alpha]_D^{19}$-78.75 (c0.1, $CHCl_3$) was obtained from **4** by hydrogenolysis with palladium hydroxide in a quantitative yield, and the reactions of **5** with various alkyl halides gave the corresponding chiral *N*-alkylated ligands **6a-c** [**6a**: mp 102-103°C, $[\alpha]_D^{18}$+19.0 (c1.0, $CHCl_3$), 85%; **6b**: mp 102-103°C, $[\alpha]_D^{20}$-27.50 (c0.4, $CHCl_3$), 89%; **6c**: mp 97-98°C, $[\alpha]_D^{21}$-230.0 (c0.1, $CHCl_3$), 30%]. These structures of **3,4,5, 6a-c** were characterized by IR, ^{1}H-NMR spectroscopy, mass and high-resolution mass spectrometry. The absolute configuration within chiral ligand [1R, 3S, 4S]-**4** was determined by single crystal X-ray analysis[5] (Fig. 1.). Considering this result, the absolute configurations of the other chiral ligands **3, 5, 6a-c** also were assigned as [1R,3S,4S]-**3** , [1R,3S,4S]-**5**, and [1R,3S,4S]-**6a-c**, respectively. Chiral ligand **4** showed usual bond lengths and angles. The phenyl substituents, A and B, in **4** were almost diagonal with the dihedral angle of 99.0°, and B and C were almost parallel with the dihedral angle of 9.0°. One interesting feature to be noted was the formation of intramolecular hydrogen bonding between hydroxyl group (O1-H) and nitrogen atom (N1) (the distance = 1.769Å, the angle = 130.4°).

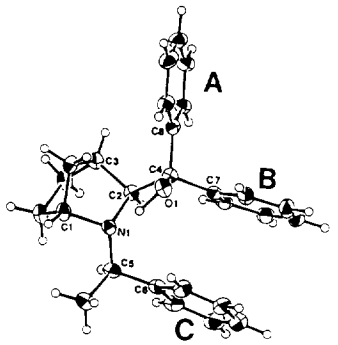
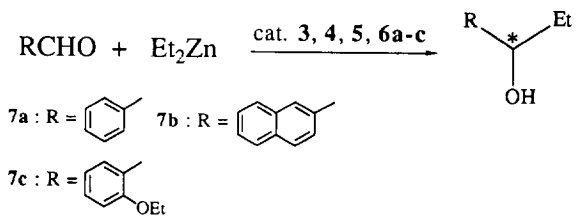


Fig. 1. ORTEP drawing of **4**

Selected bond lengths (Å) and angles (°): N(1)-C(1) 1.507(4), N(1)-C(5) 1.491(4), C(2)-C(3) 1.508(4), N(1)-C(2) 1.541(4), C(2)-C(4) 1.576(4), C(4)-C(7) 1.545(4), C(4)-C(8) 1.556(4), C(5)-C(6) 1.502(4),C(4)-O(1) 1.416(4), N(1)-C(2)-C(4) 110.3(2), N(1)-C(5)-C(6) 112.7(2),C(2)-N(1)-C(5) 116.1(2), C(2)-C(4)-C(7) 114.8(2), C(2)-C(4)-C(8) 111.5(2), C(2)-C(4)-O(1) 108.1(2), C(7)-C(4)-O(8) 106.1(2), C(1)-N(1)-C(5) 113.3(2), C(3)-C(2)-C(4) 116.5(2),

Having prepared these bicyclic amines, we examined their ability to catalyze the addition of diethylzinc to aromatic aldehyde (Scheme 2 and Table 1). First, the enantioselective addition of benzaldehyde with diethylzinc was examined in the presence of catalyitic amounts of chiral ligands **3, 4, 5, 6a-c** to afford chiral

Scheme 2



1-phenyl-1-propanol, and *N*-methylated ligand **6a** (entry 4) was proved to be better catalyst (84%, 76%ee) than the other chiral ligands (entry 1-3). Next, the reaction of β-naphthylaldehyde with diethylzinc using chiral

ligands **4**, **6a,b** (entry 7-9) under the above reaction conditions was performed to give chiral 1-(2-naphthyl)-1-propanol, and the best result (81%, 92%ee) was obtained by using *N*-methylated chiral ligand **6a** (entry 8) similar to the case of benzaldehyde (entry 4). Furthermore, the enantioselective addition of 2-ethoxybenzaldehyde with diethylzinc in the presence of ligand **6a** gave also enantioselectively 1-(2-ethoxyphenyl)-1-propanol in high chemical and enantiomeric excess (entry 10, 97%, 82%ee). From these results, the *N*-methylated chiral ligand **6a** was found to be superior to chiral ligands **3, 4, 5, 6b,c** in terms of enantioselectivity.

A typical procedure is as follows: To a solution of chiral ligand **6a** (5.1mg, 0.0175mmol) in toluene (0.7ml), diethylzinc (0.7mmol, 0.7ml of 1M solution in hexane) was added at 0°C. After the mixture had been stirred at 0°C for 30min, benzaldehyde (37.1mg, 0.35mmol) was introduced. The homogeneous solution was stirred for 7h at 0°C and quenched with 10%HCl. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was dried ($MgSO_4$) and then evaporated under reduced pressure. The residue was purified by preparative TLC over silica gel to afford (*S*)-1-phenyl-1-propanol (40mg, 84%, 76%ee).

Table 1 : Enantioselective addition of Et_2Zn to aldehydes

Entry[a]	Ligand	Substrate: R	Concentration(mol%)	Yield(%)	E.e.(%)[b]	Config.
1	**3**	**7a**	20	53	22	*S* [c]
2	**4**	**7a**	10	21	28	*S*
3	**5**	**7a**	20	42	36	*R* [c]
4	**6a**	**7a**	10	84	76	*S*
5	**6b**	**7a**	10	95	54	*S*
6	**6c**	**7a**	10	86	68	*S*
7	**4**	**7b**	10	25	42	*S* [c]
8	**6a**	**7b**	5	81	92	*S*
9	**6b**	**7b**	10	95	67	*S*
10	**6a**	**7c**	5	97	82	*S* [d]

a) All reactions were carried out in toluene-hexane(1:1) at 0°C for 7h; b) Determined by HPLC analysis using DAICEL chiral cel OB or OD; c) Ref. 3g; d) Ref. 3d

Further investigation for the mechanistic pathway of the reaction, modification, and application of new chiral ligands, 2-azanorbornylmethanols, is in progress.

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4. The imine derived from (*R*)- or (*S*)-phenylethylamine and ethyl glyoxylate reacts with cyclopentadiene to give the bicyclic amino acid ethylesters with high diastereoselectivity, respectively. The relative configuration within the bicyclic product **1** was determined by NOE difference spectrum between the benzylic proton and 1-H and 3-H in ^{1}H-NMR spectroscopy: (a) Waldmann, H.; Braun, M. *Liebigs Ann. Chem.*, **1991**, 1045; (b) Bailey, P, D.; Brown, G, R.; Korber, F.; Reed, A.; Wilson, R, D. *Tetrahedron: Asymmetry*, **1991**, 2, 1263.
5. Crystal data of **4**: Crystal size=0.25x0.25x0.3mm, Rigaku AFC5PR diffractometer(45kV, 200mA), temperature=283K, Cu-Kα radiation(λ=1.5418Å), a=15.406(2), b=22.827(4), c=5.977(2)Å, V=2102.0(7)Å^3, the space group= $P2_12_12_1$, Z=4, Dcalcd=1.212g/cm^3, μ(CuKα)=5.23cm^{-1}, 2θ–ω scan mode, scan speed of 8°min^{-1}, measured reflections=1979 reflections used for refinement= 1726 [Io>3σ(Io)]. The final R values are 0.041(Rw=0.056). The structure was solved by the direct method and refined by the fullmatrix least-squares method. All non-hydrogen atoms were refined anisotropically and hydrogen atoms found in the successive D-fourire map were refined isotropically.

(*Received in Japan* 10 *April* 1995)