SYNTHESIS OF NEW CHIRAL CATALYSTS, ISOQUINUCLIDINYLMETHANOLS, FOR THE ENANTIOSELECTIVE ADDITION OF DIETHYLZINC TO ARYL ALDEHYDES

Hiroto Nakano, Kazuto Iwasa, and Hiroshi Hongo*

Tohoku College of Pharmacy, Komatsushima, Aoba-ku, Sendai 981, Japan

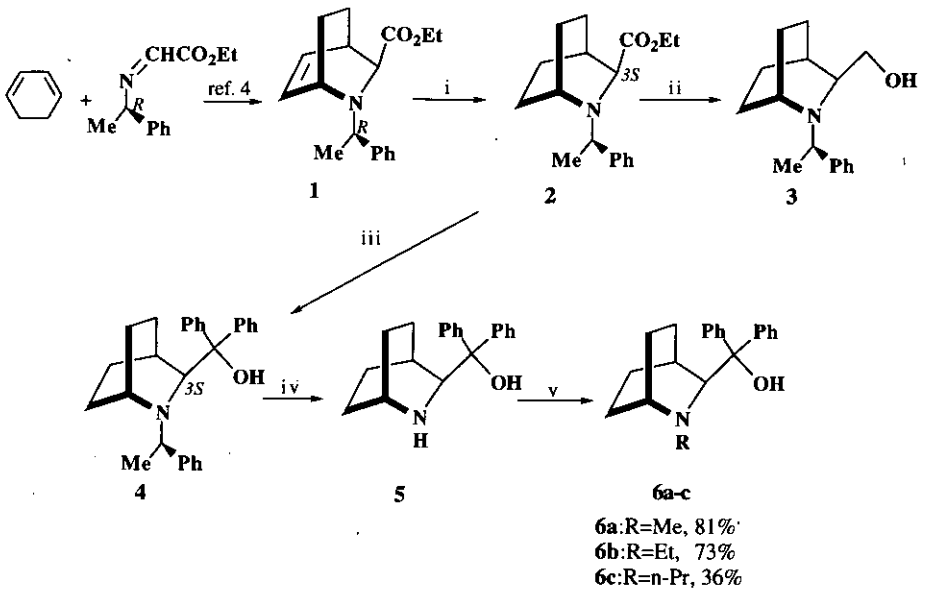
Abstract - New chiral ligands, isoquinuclidinylmethanols, were prepared and their catalytic abilities of asymmetric induction were examined in the addition of diethylzinc to aldehydes to furnish secondary alcohols in up to 76% e.e.

Catalytic asymmetric synthesis has been a challenging subject in organic synthesis. The development of efficient enantioselective catalysts applying to a wide range of carbon-carbon bond forming reactions[1] represents a pivotal challenge to the synthetic community. Among the catalysts, β-amino alcohols have proved to be extremely efficient catalysts in asymmetric reaction.[1,2] Recently, we have also reported that 2-azanorbornylmethanols[2k] were effective chiral catalysts for the enantioselective addition of diethylzinc to aldehydes. However, no report using isoquinuclidines, 2-azabicyclo[2.2.2]octanes, as chiral ligands has appeared in literature, although isoquinuclidines have potential as synthetic intermediates for syntheses of biologically active compounds.[3] In this paper, we wish to report a synthesis of new chiral ligands, isoquinuclidinylmethanol (**5**) and its derivatives (**3, 4, 6a-c**), which are sterically constrained β-amino alcohols similar to 2-azanorbornylmethanols, 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 was obtained from bicyclic amino acid ethyl ester (**1**), derived from the reaction of 1,3-cyclohexadiene with an optically active imine,[4] followed by catalytic hydrogenation and subsequent reduction with lithium aluminum hydride. The optical purities of bicyclic amino acid ethyl esters (100% e.e.) [(3*S*)-**1** and (3*S*)-**2**] were determined by hplc analysis using chiral column. Furthermore, chiral

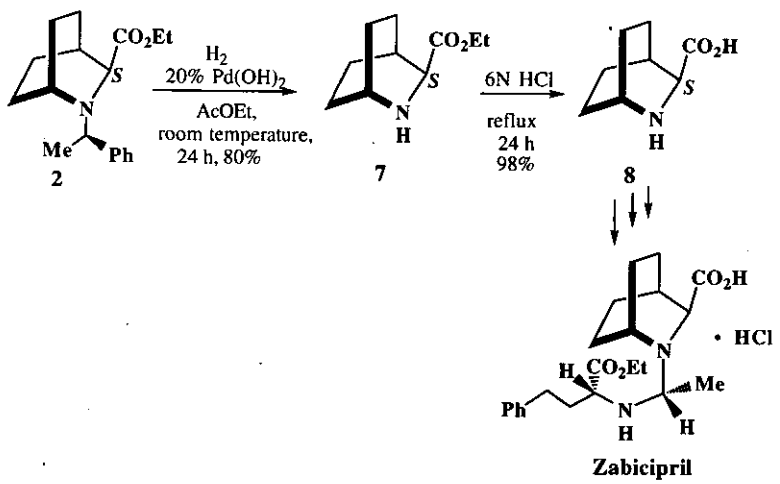
Dedicated to Dr. Shigeru Oae on the occasion of his 77th birthday.

Scheme 1



Reagents: i: H_2, Pd-C(10%), AcOEt, room temperature, 12 h, 92%; ii: $LiAlH_4$, THF, room temperature, 3 h, 86%; iii: PhMgBr,1,4-dioxane, reflux, 24 h, 70%; iv: H_2, 20% $Pd(OH)_2$, AcOEt, 74%; v: **6a** : R=Me (MeI, MeCN, reflux, 8 h), **6b** : R=Et or **6c** : n-Pr (EtI or n-PrI, K_2CO_3, MeCN, reflux, 24 h)

Scheme 2

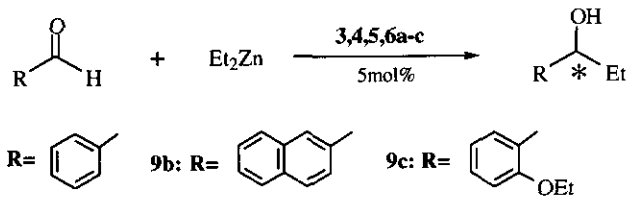


ligand (**4**) bearing a diphenylhydroxymethyl group was synthesized by the reaction of **2** with phenylmagnesium bromide. Chiral *N*-unsubstituted ligand (**5**) was obtained from **4** by hydrogenolysis and the reactions of **5** with various alkyl halides gave the corresponding chiral *N*-alkylated ligands (**6a-c**). These structures of **3,4,5,6a-c** were characterized by ir, ^{1}H-nmr spectroscopy, mass and high resolution mass spectrometries.

The absolute configuration at the 3-position within optical pure bicyclic amino acid ethyl ester [(3*S*)-**2**] was confirmed by chemical correlation, as shown in Scheme 2. *N*-Unsubstituted amino acid ethyl ester (**7**) obtained by hydrogenolysis of **2** was treated with hydrochloric acid to give amino acid (**8**)[3] which is the synthetic intermediate of zabicipril (S 9650-3) (a potent inhibitor of angiotensin converting enzyme). Considering this result, the absolute configuration at the 3-position within the all chiral ligands (**3,4,5,6a-c**) was assigned as 3*S*, respectively. In addition, the above chemical correlation also presented a new methodology for the synthesis of zabicipril (S 9650-3).

Having prepared these bicyclic amines, we examined their ability to catalyze the addition of diethylzinc to aromatic aldehydes (Table 1). First, the enantioselective addition of diethylzinc to benzaldehyde (**9a**) was

Table 1. Enantioselective addition of aldehydes with Et_2Zn.



Entry[a]	Ligand	Substrate: R	Yield(%)	E.e.(%)[b]	Config.
1	**3**	**9a**	10	0	--
2	**4**	**9a**	7	4	*R*[c]
3	**5**	**9a**	25	0	--
4	**6a**	**9a**	98	49	*S*
5	**6b**	**9a**	85	76	*R*
6	**6c**	**9a**	81	76	*R*
7	**6a**	**9b**	85	44	*S*[c]
8	**6b**	**9b**	62	72	*R*[d]
9	**6c**	**9b**	80	74	*R*
10	**6b**	**9c**	98	60	*R*[e]

a) All reactions were carried out in toluene-hexane(1:1) at room temperature for 7 h.
b) Determined by hplc analysis using DAICEL chiral cel OB or OD. c) Ref. 2i. d) Ref. 2f.
e) Ref. 2d

examined in the presence of a catalytic amount of chiral ligands (**3, 4, 5, 6a-c**) to afford chiral 1-phenyl-1-propanol, and *N*-ethylated ligand [**6b** (Entry 5)] proved to be the best catalyst (85%, 76% e.e.) compared to the other chiral ligands (Entries 1-4,6). Next, the reaction of β-naphthyl aldehyde (**9b**) with diethylzinc using chiral ligands [**6a,b,c** (Entries 7-9)] under the above reaction conditions was performed

to give chiral 1-(2-naphthyl)-1-propanol, and the best result (80%, 74% e.e.) was obtained by using *N*-propylated chiral ligand [**6c** (Entry 9)]. Furthermore, the enantioselective addition of diethylzinc to 2-ethoxybenzaldehyde (**9c**) in the presence of ligand (**6b**) gave enantioselectively chiral 1-(2-ethoxyphenyl)-1-propanol in high chemical yield and moderate enantiomeric excess (Entry 10, 98%, 60% e.e.). From these results, chiral ligands (**6b,c**) were found to be superior to chiral ligands (**3, 4, 5, 6a**) in terms of enantioselectivity. Interestingly, a stereochemical difference between **6b,c,** which gave (*R*)-alcohols (Entries 5, 6, 8, 9), and **6a,** which afforded (*S*)-alcohols (Entries 4, 7), as ligands was observed.

In conclusion, the first example of the enantioselective addition of diethylzinc to aryl aldehydes using isoquinuclidinylmethanols as catalysts has been reported and the new chral ligands catalyzed effectively the reaction.

EXPERIMENTAL

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Ir spectra were measured with a PERKIN ELMER 1725X spectrophotometer. ^{1}H-Nmr spectra were recorded on a JEOL JNM-PMX 60 and a JEOL JNM-GSX 400 spectrometers with TMS as an internal standard. The coupling patterns are indicated as follows: singlet=s, doublet=d, triplet=t, multiplet=m, and broad=br. Ms were taken on a Hitachi RMG-6MG and a JEOL-JNM-DX 303 spectrometers. Optical rotations were measured with a JASCO-DIP-370 digital polarimater.

General procedure for the enantioselective addition of Et_2Zn to aldehydes (9a-c): To a solution of chiral ligands [**3,4,5,6a-c** (0.0175 mmol)] in toluene (0.7 ml), diethylzinc (0.7 mmol, 0.7 ml of 1M solution in hexane) was added at room temperature. After the mixture had been stirred at room temperature for 30 min, aldehyde [**9a-c** (0.35 mmol)] was introduced. The homogeneous solution was stirred for 7 h at room temperature and quenched with 10% HCl. The organic layer was separated, and the aqueous layer was extracted with 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 with $CHCl_3$ to afford chiral aryl alcohols.

Ethyl (3*S*)-2-[(*R*)-1-phenylethyl]-2-azabicyclo[2.2.2]octane-3-carboxylate (2): A mixture of **1** (2.0 g, 7.02 mmol) and 10% Pd-C (80 mg) in ethyl acetate (50 ml) was stirred under a hydrodgen atmosphere at room temperature for 12 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to afford the residue. The residue was chromatographed on a silica gel column eluted

with hexane-ether (10:1) to give **2**. Optical yield of **2** was determined by hplc analysis using chiral column (Chiralcel OD).

2: 1.85 g, 92%, viscous oil, $[\alpha]_D^{24}$ -20.40° (c=2.5, $CHCl_3$). High resolution ms m/z : Calcd for $C_{18}H_{25}NO_2$ (M^+) : 287.1885. Found : 287.1858. Ir (film) cm^{-1} : 1746. ^{1}H-Nmr ($CDCl_3$) δ : 1.04 (3H, t, J=7.2 Hz), 1.35 (3H, d, J=6.6 Hz), 1.20-1.45 (2H, m), 1.52-1.68 (4H, m), 1.83-1.85 (1H, m), 1.90-2.03 (2H, m), 3.03 (1H, br s), 3.25 (1H, br s). 3.71 (1H, q, J=6.6 Hz), 3.85 (2H, q, J=7.2 Hz), 7.14-7.41 (5H, m).

(3*S*)-3-Hydroxymethyl-2-[(*R*)-1-phenylethyl]-2-azabicyclo[2.2.2]octane (3): To a stirred suspension of lithium aluminum hydride (75 mg, 1.98 mmol) in dry tetrahydrofuran (THF) (20 ml) was added **2** (500 mg, 1.74 mmol) at 0°C. The mixture was stirred at room temperature for 3 h, quenched by addition to water, and filterated through celite 545. The filtrate was concentrated *in vacuo* to afford the residue. The residue was chromatographed on a silica gel column eluted with $CHCl_3$-MeOH (20:1) to give **3**. Optical yield of **3** was determined by hplc analysis using chiral column (Chiralcel OD).

3: 218 mg, 86%, viscous oil, $[\alpha]_D^{20}$+28.50° (c=4.0, $CHCl_3$). High resolution ms m/z : Calcd for $C_{16}H_{23}NO$ (M^+) : 245.1780. Found : 245.1816. Ir (film) cm^{-1} : 3392. ^{1}H-Nmr ($CDCl_3$) δ : 1.27-1.48 (2H, m), 1.36 (3H, d, J=6.6 Hz), 1.55-1.91 (6H, m), 1.99-2.09 (1H, m), 2.62-2.69 (2H, m), 2.91-2.98 (3H, m), 3.71 (1H, q, J=6.6 Hz), 7.20-7.37 (5H, m),

(3*S*)-3-Diphenylhydroxymethyl-2-[(*R*)-1-phenylethyl]-2-azabicyclo[2.2.2]octane (4): Phenylmagnesium bromide (19.3 ml, 38.68 mmol) in 1,4-dioxane (40 ml) was added to a 1,4-dioxane (5 ml) solution of **2** (1.85 mg, 6.45 mmol) at room temperature, and the mixture was refluxed for 24 h. Saturated aqueous ammonium chloride was added to quench the reaction, and the organic layer was separated. The precipitate in the aqueous layer was filtered off, and the filtrate was extracted with chloroform. The combined organic layer was dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was chromatographed on a silica gel column eluted with ether-hexane (1:4) to give **4.**

4: 1.79 g, 70%, colorless prisms (ether - hexane), $[\alpha]_D^{23}$ -33.68° (c=1.9, $CHCl_3$), mp 202-203 °C. Ir (KBr) cm^{-1} : 3160. ^{1}H-Nmr ($CDCl_3$) δ : 0.92-1.00 (1H, m), 1.20-1.96 (8H, m), 1.32 (3H, d, J=6.9 Hz), 2.70 (1H, br s), 3.53 (1H, q, J=6.9 Hz), 4.20 (1H, br s), 6.54 (1H, br s), 7.05-7.89 (15H, m), *Anal.* Calcd for $C_{28}H_{31}NO$: C, 84.59; H, 7.86; N, 3.52. Found: C, 84.56; H, 7.96; N, 3.49. Ms m/z: 397.2406 (M^+).

(3*S*)-3-Diphenylhydroxymethyl-2-azabicyclo[2.2.2]octane (5): A mixture of **4** (1.79 g, 4.51 mmol) and 20% $Pd(OH)_2$ (930 mg) in ethyl acetate (60 ml) was stirred under a hydrodgen atmosphere at 45 °C for 72 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give the residue, which was chromatographed on a silica gel column eluted with $CHCl_3$-MeOH (7:1) to afford **5**.

5: 0.98 g, 74%, colorless prisms ($CHCl_3$ - hexane), $[\alpha]_D^{25}$ -67.14° (c=0.7, MeOH), mp 148-150 °C. Ir (KBr) cm^{-1} : 3327. ^{1}H-Nmr ($CDCl_3$) δ : 1.14-1.84 (8H, m), 2.25-2.33 (1H, m), 2.79 (1H, br s), 4.01-4.11 (1H, m), 7.11-7.62 (10H, m). *Anal.* Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.57; H, 7.77; N, 4.47. Ms m/z: 293 (M^+).

(3*S*)-3-Diphenylhydroxymethyl-2-methyl-2-azabicyclo[2.2.2]octane (6a) : A mixture of **5** (200 mg, 0.68 mmol) and methyl iodide (0.06 ml, 1.02 mmol) in acetnitrile (15 ml) was refluxed for 18 h. The solvent was removed, and the residue was chromatographed on a silica gel column eluted with $CHCl_3$ to give **6a.**

6a: 170 mg, 81%, colorless prisms (ether - hexane), $[\alpha]_D^{24}$ -24.25° (c=1.0, $CHCl_3$), mp 139-141 °C. Ir (KBr) cm^{-1} : 3139, 1730. ^{1}H-Nmr ($CDCl_3$) δ : 0.93-1.01 (1H, m), 1.25-1.67 (5H, m), 1.83-2.06 (3H, m), 1.92 (3H, s), 2.54 (1H, br s), 3.45 (1H, br s), 6.08 (1H, br s), 7.07-7.83 (10H, m). *Anal.* Calcd for $C_{21}H_{25}NO_3S$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.75; H, 8.39; N, 4.50. Ms m/z: 307 (M^+).

General procedure for the synthesis of *N*-ethylated or *N*-propylated (3*S*)-3-diphenylhydroxymethyl-2-azabicyclo[2.2.2]octanes (6b or 6c): A mixture of **5** (200 mg, 1.02 mmol), ethyl iodide (0.08 ml, 1.02 mmol) or n-propyl iodide (0.10 mg, 1.02 mmol), and anhydrous potassium carbonate (141 mg, 1.02 mmol) in acetonitrile (15 ml) was refluxed for 24 h. The solvent was removed, and the residue was chromatographed on a silica gel column eluted with $CHCl_3$ to give **6b** or **6c.**

6b: 160 mg, 73%, colorless prisms (ether - hexane), $[\alpha]_D^{23}$ -31.57° (c=1.9, $CHCl_3$), mp 144-146 °C. Ir (KBr) cm^{-1} : 3159. ^{1}H-Nmr ($CDCl_3$) δ : 0.70 (3H, t, J=7.2 Hz), 0.94-1.01 (1H, m), 1.25-2.00 (9H, m), 2.32-2.44 (1H, m), 2.77-2.78 (1H, m), 3.56 (1H, br s), 6.36 (1H, br s), 7.08-7.78 (10H, m). *Anal.* Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 81.91; H, 8.60; N, 4.10. Ms m/z: 321 (M^+).

6c: 82 mg, 36%, colorless prisms (ether - hexane), $[\alpha]_D^{21}$ -43.33° (c=0.6, $CHCl_3$), mp 127-129 °C. Ir (KBr) cm^{-1} : 3158. ^{1}H-Nmr ($CDCl_3$) δ : 0.50 (3H, t, J=7.4 Hz), 0.98-1.94 (12H, m), 2.33-2.42 (1H,

m), 2.72 (1H, br s), 3.57 (1H, br s), 6.33 (1H, br s), 7.07-7.78 (10H, m). *Anal.* Calcd for $C_{23}H_{29}NO$: C, 82.30; H, 8.71; N, 4.17. Found: C, 82.05; H, 8.89; N, 4.22. Ms m/z: 335 (M^+).

Ethyl 2-azabicyclo[2.2.2]octane-3-carboxylate (7): A mixture of **2** (1.0 g, 3.48 mmol) and 20% $Pd(OH)_2$ (540 mg) in ethyl acetate (40 ml) was stirred under a hydrodgen atmosphere at room temperature for 24 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give the residue. The residue was chromatographed on a silica gel column eluted with $CHCl_3$-MeOH (40:1) to afford **7**.

7: 510 mg, 80%, viscous oil, $[\alpha]_D^{22}$ +13.52° (c=1.35, $CHCl_3$), High resolution ms m/z : Calcd for $C_{10}H_{17}NO_2$ (M^+) : 183.1259. Found : 183.1282. Ir (film) cm^{-1} : 1730. ^{1}H-Nmr ($CDCl_3$) δ : 1.28 (3H, t, J=7.1 Hz), 1.46-1.92 (8H, m), 1.98-2.00 (1H, br s), 2.32 (1H, s), 2.90 (1H, br s), 3.70 (1H, br s), 4.11-4.30 (2H, m).

2-Azabicyclo[2.2.2]octane-3-carboxylic acid (8): A solution of **7** (40 mg, 0.22 mmol) in 6N hydrochloric acid (14 ml) was refluxed on the oil bath for 24 h. The mixture was concentrated to dryness under reduced pressure. The last trace of water was azeotroped with toluene. The residue was triturated with acetone to give **8**.

8: 33 mg, 98%, $[\alpha]_D^{23}$-15° (c=0.7, H_2O) [lit.,[3] $[\alpha]_D^{25}$-17° (c=1.0, H_2O)].

REFERENCES

1. Reviews: a) R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.,* 1991, **30**, 49. b) K. Soai and S. Niwa, *Chem. Rev.,* 1992, **92**, 833. c) R. Noyori, *Asymmetric Catalysis in Organic Synthesis,* J. Wiley & Sons Inc, New York, 1994, Chapter 5.
2. a) A. A. Smaardijk and H. Wynberg, *J. Org. Chem.*, 1987, **52**, 135. b) K. Soai, A. Ookawa, T. Kubo, and U. Ogawa, *J. Am. Chem. Soc.,* 1987, **109**, 7111. c) K. Tanaka, H. Ushio, and H. Suzuki, *J. Chem. Soc., Chem. Commun.*, **1989**, 1700. d) S. Itsuno, Y. Sakurai, K. Ito, T. Maruyama, S. Nakahama, and J. M. J. Frechet, *J. Org.Chem.*, 1990, **55**, 304. e) M. Watanabe, S. Araki, Y. Butsugan, and M. Uemura, *J. Org.Chem.*, 1991, **56**, 2218. f) M. Hayashi, T. Kaneko, and N. Oguni, *J. Chem. Soc., Perkin Trans. I*, **1991**, 25. g) K. Kimura, E. Sugiyama, T. Ishizuka, and T. Kunieda, *Tetrahedron Lett.,* 1992, **33**, 3147. h) T. Mehler and J. Martinens, *Tetrahedron : Asymmetry*, 1994, **5**, 207. i) M. Ishizaki, K. Fujita, M. Shimamoto, and O. Hoshino, *Tetrahedron :*

Asymmetry, 1994, **5**, 411. j) K. Soai, T. Hayase, K. Takai, and C. Shimada, *J. Org. Chem.*, 1994, **59**, 7908. k) H. Nakano, N. Kumagai, T. Kabuto, H. Matsuzaki, and H. Hongo, *Tetrahedron : Asymmetry*, 1995, **6**, 1233. l) M. Shi, Y. Satoh, T. Makihara, and Y. Masaki, *Tetrahedron : Asymmetry*, 1995, **6**, 2109.

3. M. Vincent, C. Pascard, M. Cesario, G. Remond, J. Bouchet, Y. Charton, and M. Laubie, *Tetrahedron Lett.*, 1992, **33**, 7369.
4. H. Abraham and L. Sterlla, *Tetrahedron,* 1992, **48**, 9707.

Received, 15th April, 1996