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

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Abstract - New chiral ligands, isoquinuclidinylmethanethiols, 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 94% ee.

β-Amino alcohols have proved to be extremely efficient catalysts in catalytic asymmetric synthesis.[1-3] Recently, ephedrine- and pyrrolidine-based β-amino thiols have been shown to be effective ligands similar to β-amino alcohols for the enantioselective addition.[4] Herein, we wish to report the synthesis of diastereomeric new β-amino thiol ligands (**4a**) and (**4b**) having isoquinuclidine skeleton, and a attempt as these ligands for high enantioselective addition of diethylzinc to aldehydes.

New chiral ligands (**4a**) and (**4b**) were synthesized easily from the corresponding β-amino esters (**1a**) and (**1b**)[5] (Scheme 1). The amino esters (**1a**) and (**1b**) were easily obtained from the imino-Diels-Alder reaction of cyclohexadiene with imine as a diastereomeric mixture [the ratio of 9 (**1a**) : 2 (**1b**)] and were converted to the amino alcohols (**2a**)[3b] and (**2b**) in two steps. The compounds (**2a**) and (**2b**) were mesylated with methanesulfonyl chloride and triethylamine to give the corresponding mesylates (not isolated), and subsequent displacement with potassium thioacetate[6] in ethanol gave the corresponging thioacetates (**3a**) and (**3b**), respectively. Finally, treatments of **3a** and **3b** with lithium aluminum hydride gave the chiral ligands (**4a**) and (**4b**) in good yields. These structures of **3a**, **4a**, **2b**, **3b**, **4b**, and **6** were characterized by IR, ^{1}H-NMR spectroscopy, high-resolution mass spectrometry, and elemental analysis.

The absolute configuration at the 3-position within optical pure bicyclic amino acid ethyl ester (3*R*)-**1b** was confirmed by chemical correlation, as shown in Scheme 1. Previously, we determined the absolute configuration of **1a** by conversion from **1a** to amino acid ethyl ester (3*S*)-**5**[3b]. Similarly, the diastereomer

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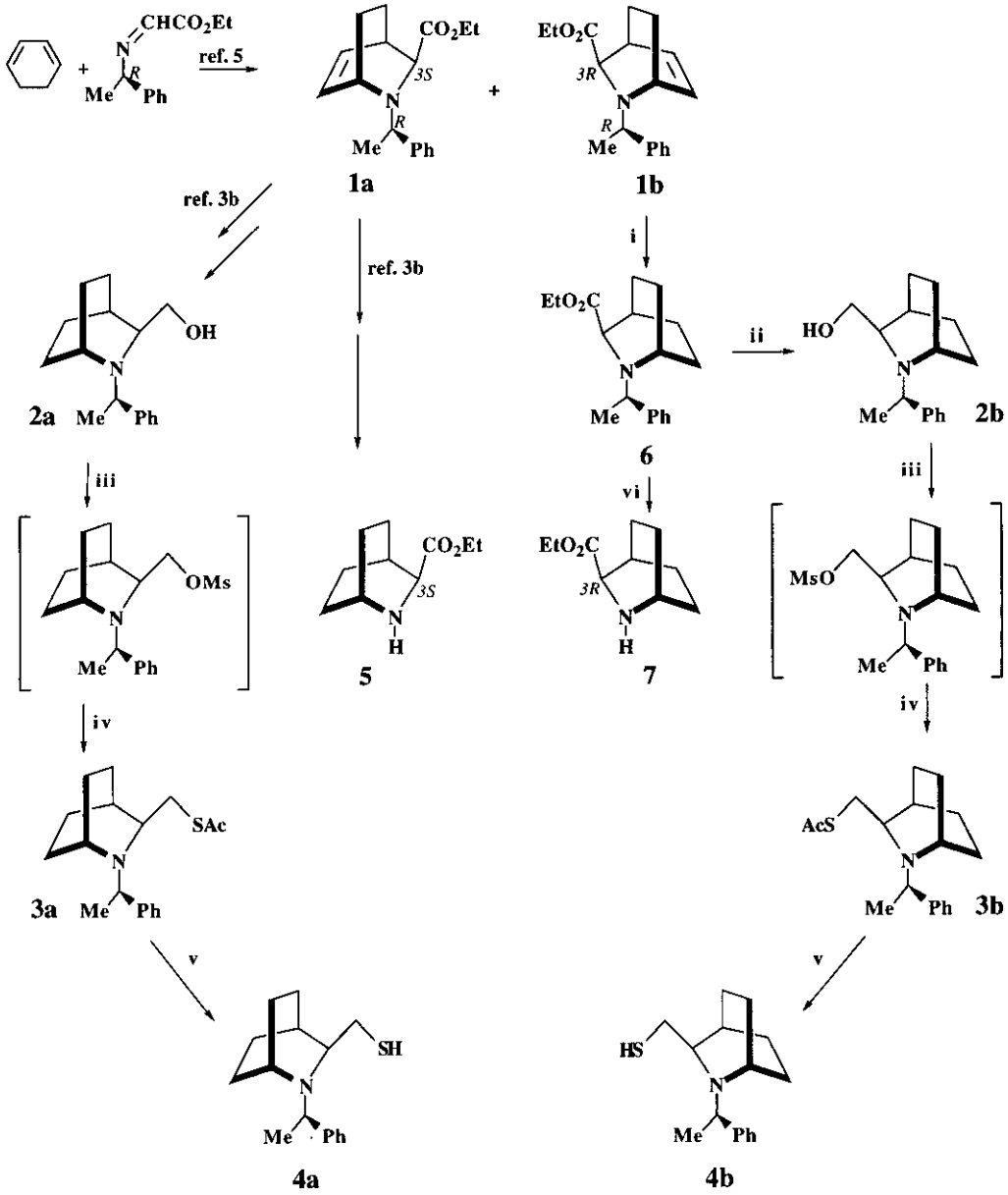
Dedicated to the memory of Dr. Shunichi Yamada.

Scheme 1

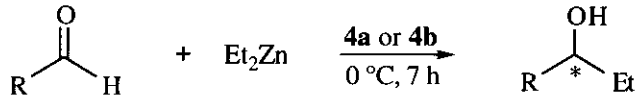


Reagents. i. H_2, Pd-C(10%), AcOEt, rt, 12 h, 90%, ii. $LiAlH_4$, THF, rt, 3 h, 83%; iii: MsCl, Et_3N, CH_2Cl_2, 0 ℃, 3 h, iv AcSK, EtOH, reflux, 20 h, **3a** 75%, **3b**, 73%; v: $LiAlH_4$, THF, rt, 6 h, **4a**: 80%, **4b** 76%, vi. H_2, $Pd(OH)_2$(20%), AcOEt, rt, 24 h, 78%

(**1b**) also was converted to **7**, $[\alpha]_D^{23}$-13.22° (c=1.0, $CHCl_3$) ; **5**[3b] : $[\alpha]_D^{22}$+13.52° (c=1.7, $CHCl_3$). From this result, the absolute configuration at the 3-position within **1b** was assigned as *R*.

Next, the asymmetric catalytic capabilities of isoquinuclidinylmethanethiols (**4a**) and (**4b**) were investigated in the application for the zinc-catalyzed asymmetric addition to aldehydes. The reaction of benzaldehyde with diethylzinc was examined in the presence of a catalytic amount (5 mol%) of the chiral

Table 1. Enantioselective Addition of Diethylzinc to Aldehydes Using **4a** and **4b** as a Catalyst.



Entry[a]	Aldehyde	Catalyst	Yield, %	ee, %	Config
1	benzaldehyde	**4a**	38	71[b]	*R*[c]
2	benzaldehyde	**4b**	68	94	*S*[c]
3	2-naphthylaldehyde	**4b**	49	94[b]	*S*[d]
4	2-bromobenzaldehyde	**4b**	98	94[b]	*S*[e]
5	2-ethoxybenzaldehyde	**4b**	79	79[f]	*S*[g]
6	(*E*)-cinnamaldehyde	**4b**	75	45[b]	*S*[d]
7	cyclohexanealdehyde	**4b**	34	94[h]	*S*[i]
8	*n*-octylaldehyde	**4b**	62	58[h]	*S*[i]

a) All reactions were carried out in toluene-hexane(1:1) at 0 ℃ for 7 h.
b) Determined by HPLC analysis using DAICEL chiralcel OD c) Ref. 2e. d) Ref. 2f.
e) Ref 4f f) Determined by HPLC analysis using DAICEL chiralcel OB.
g) Ref. 2d. h) Determined by optical rotation value. i) Ref. 2j.

ligand (**4a**) or (**4b**). Interestingly, although the catalyst (**4a**) gave the optically active 1-phenylpropanol (**8**) in only moderate ee (71% ee) (Entry 1), the diastereomeric catalyst (**4b**) afforded **8** in high ee (94% ee) (Entry 2) as shown in Table 1. Thus, it may be deduced that **4b** blocks the approach of the attacking species to one of the enantiotopic faces of benzaldehyde better than **4a**. Under the same reaction conditions, β-naphthylaldehyde and 2-bromobenzaldehyde were examined by using the better ligand (**4b**), and afforded the corresponding secondary alcohols in high ee (94% ee) (Entries 3 and 4). Similarly,

cyclohexanealdehyde was also ethylated in 94% ee (Entry 7). Furthermore, 2-ethoxybenzaldehyde was ethylated in moderate ee (79% ee) (Entry 5). However, (*E*)-cinnamaldehyde and *n*-octylaldehyde were ethylated only in 45% ee and 58% ee, respectively (Entries 6 and 8).

In conclusion, we have synthesized diastereomeric new β-amino thiol ligands (**4a**) and (**4b**) having isoquinuclidine skeleton, and **4b** proved to be efficient as a catalyst in asymmetric addition of diethylzinc to aldehydes.

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-EX 270 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 diethylzinc to aldehydes : To a solution of chiral ligand (**4a**) or (**4b**) (0.0175 mmol) in toluene (0.7 mL), diethylzinc (0.7 mmol, 0.7 mL of 1M solution in hexane) was added at 0 °C. After the mixture had been stirred at 0 °C for 30 min, aldehydes (0.35 mmol) were introduced. The homogeneous solution was stirred for 7 h at 0 °C 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 to afford chiral alcohols.

Ethyl (3*R*)-2-[(*R*)-1-Phenylethyl]-2-azabicyclo[2.2.2]octane-3-carboxylate (6) : A mixture of **1b** (2.0 g, 7.02 mmol), 10% Pd-C (80 mg), and ethyl acetate (50 mL) was stirred under a hydrodgen atmosphere at rt 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 **6**. Optical yield of **6** was determined by HPLC analysis using chiral column (Chiralcel OD).

6 : 1.81 g, 90%, viscous oil, $[\alpha]_D^{23}$ -14.54° (c=1.1, $CHCl_3$), HRMS m/z : Calcd for $C_{18}H_{25}NO_2$ (M^+) : 287.1885. Found : 287.1880. IR (film) cm^{-1} : 1742. ^{1}H-NMR ($CDCl_3$) δ : 1.16-1.39 (2H, m), 1.19 (3H, d, J=6.6 Hz), 1.30 (3H, t, J=7.2 Hz), 1.51-1.97 (7H, m), 2.44 (1H, br s), 3.42 (1H, br s), 3.66 (1H, q, J=6.6 Hz), 4.21 (2H, q, J=7.2 Hz), 7.17-7.45 (5H, m).

(3*R*)-3-Hydroxymethyl-2-[(*R*)-1-phenylethyl]-2-azabicyclo[2.2.2]octane (2b) : To a stirred suspension of lithium aluminum hydride (75 mg, 1.98 mmol) in dry THF (20 mL) was added **6** (500 mg, 1.74 mmol) at 0 °C. The mixture was stirred at rt for 3 h, quenched by addition to water, and filterated 1.74 mmol) at 0 °C. The mixture was stirred at rt 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 **2b**. Optical yield of **2b** was determined by HPLC analysis using chiral column (Chiralcel OD).

2b : 354 mg, 83%, colorless prisms (ether), $[\alpha]_D^{21}$-24.99° (c=0.6, $CHCl_3$), mp 105-107 °C. IR (film) cm^{-1} : 3271. ^{1}H-NMR ($CDCl_3$) δ : 1.15-1.48 (4H, m), 1.36 (3H, d, J=6.6 Hz), 1.57-1.65 (4H, m), 1.86-2.03 (2H, m), 2.49 (1H, br s), 2.92 (1H, d, J=6.6 Hz), 3.49 (1H, d, J=9.7 Hz), 3.64 (1H, dd, J=7.1, 9.7 Hz), 3.76 (1H, q, J=6.6 Hz), 7.20-7.32 (5H, m). *Anal.* Calcd for $C_{16}H_{23}NO$: C, 78.32 ; H, 9.45 ; N, 5.71. Found : C, 78.24 ; H, 9.48 ; N, 5.57. MS m/z : 245 (M^+).

(3*S*)-3-Acetylthiomethyl-2-[(*R*)-1-phenylethyl]-2-azabicyclo[2.2.2]octane (3a) : To a solution of **2a** (1.0 g, 4.08 mmol) in CH_2Cl_2 (15 mL) were added Et_3N (1.1 mL, 8.16 mmol) and MsCl (0.5 mL, 6.12 mmol) at 0 °C under Ar. The reaction mixture was stirred for 3 h at 0 °C. The mixture was concentrated *in vacuo*. Ethanol (25 mL) and KSAc (1.4 g, 12.24 mmol) were added to the crude product and the mixture was refluxed for 20 h under Ar. Solvent was removed under reduced pressure. The residue was dissolved in ether and the ether solution was washed with water. The organic layer was dried over $MgSO_4$. The crude product was chromatographed on a silica gel column eluted with hexane-ether (10 : 1) to give **3a**. Optical yield of **3a** was determined by HPLC analysis using chiral column (Chiralcel OD).

3a : 930 mg, 75%, viscous oil, $[\alpha]_D^{20}$-27.77° (c=0.9, $CHCl_3$), HRMS m/z : Calcd for $C_{18}H_{25}NOS$ (M^+) : 303.1657. Found : 303.1664. IR (film) cm^{-1} : 1693. ^{1}H-NMR ($CDCl_3$) δ : 1.26-1.98 (9H, m), 1.36 (3H, d, J=6.6 Hz), 2.26 (3H, s), 2.64-2.75 (3H, m), 2.83 (1H, br s), 3.86 (1H, q, J=6.6 Hz), 7.21-7.45(5H, m).

(3*R*)-3-Acetylthiomethyl-2-[(*R*)-1-phenylethyl]-2-azabicyclo[2.2.2]octane (3b) : To a solution of **2b** (1.0 g, 4.08 mmol) in CH_2Cl_2 (15 mL) were added Et_3N (1.1 mL, 8.16 mmol) and MsCl (0.5 mL, 6.12 mmol) at 0 °C under Ar. The reaction mixture was stirred for 3 h at 0 °C. The mixture was concentrated *in vacuo*. Ethanol (25 mL) and KSAc (1.4 g, 12.24 mmol) were added to the crude product and the mixture was refluxed for 20 h under Ar. Solvent was removed under reduced pressure. The residue was dissolved in ether and the ether solution was washed with water. The organic layer was dried over

$MgSO_4$. The crude product was chromatographed on a silica gel column eluted with hexane-ether (10 : 1) to give **3b**. Optical yield of **3b** was determined by HPLC analysis using chiral column (Chiralcel OD).

3b : 905 mg, 73%, viscous oil, $[\alpha]_D^{23}$+46.66° (c=0.9, $CHCl_3$), HRMS m/z : Calcd for $C_{18}H_{25}NOS$ (M^+) : 303.1657. Found : 303.1633. IR (film) cm^{-1} : 1693. ^{1}H-NMR ($CDCl_3$) δ : 1.04-1.16 (1H, m), 1.25-1.82(8H, m), 1.43 (3H, d, J=6.6 Hz), 2.34 (3H, s), 2.39-2.40 (1H, m), 2.75-2.93 (2H, m), 3.30 (1H, dd, J=3.3, 13,3 Hz), 3.72 (1H, q, J=6.6 Hz), 7.16-7.35 (5H, m).

(3*S*)-3-Mercaptomethyl-2-[(*R*)-1-phenylethyl]-2-azabicyclo[2.2.2]octane (4a) : To a stirred suspension of lithium aluminum hydride (125 mg, 3.30 mmol) in dry THF (10 mL) was added a solution of **3a** (500 mg, 1.65 mmol) in dry THF (10 mL) at 0 °C. The mixture was stirred at rt for 6 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 (10 : 1) to give **4a**.

4a : 345 mg, 80%, viscous oil, $[\alpha]_D^{22}$+13.33° (c=1.2, CH_3OH), HRMS m/z : Calcd for $C_{16}H_{23}NS$ (M^+) : 261.1551. Found : 261.1588. IR (film) cm^{-1} : 1601. ^{1}H-NMR ($CDCl_3$) δ : 0.88 (1H, br s), 1.27-1.44 (2H, m), 1.33 (3H, d, J=6.6 Hz), 1.52-1.79 (5H, m), 1.92-2.02 (3H, m), 2.23 (1H, dd, J=7.7, 10.8 Hz), 2.54 (1H, td, J=2.5, 2.6, 10.8 Hz), 2.92-2.93 (1H, m), 3.68 (1H, q, J=6.6 Hz), 7.22-7.40 (5H, m).

(3*R*)-3-Mercaptomethyl-2-[(*R*)-1-phenylethyl]-2-azabicyclo[2.2.2]octane (4b) : To a stirred suspension of lithium aluminum hydride (125 mg, 3.30 mmol) in dry THF (10 mL) was added a solution of **3b** (500 mg, 1.65 mmol) in dry THF (10 mL) at 0 °C. The mixture was stirred at rt for 6 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 (10 : 1) to give **4b**.

4b : 328 mg, 76%, colorless prisms (hexane), $[\alpha]_D^{24}$+10.00° (c=0.5, $CHCl_3$), mp 55-57 °C, IR (film) cm^{-1} : 1603. ^{1}H-NMR ($CDCl_3$) δ : 0.88 (1H, br s), 1.06-1.22 (1H, m), 1.26-1.91 (7H, m), 1.31 (3H, d, J=6.6 Hz), 2.02 (1H, br s), 2.34-2.38 (1H, m), 2.63-2.67 (3H, m), 3.69 (1H, q, J=6.6 Hz), 7.16-7.33 (5H, m). *Anal.* Calcd for $C_{16}H_{23}NS$: C, 73.51 ; H, 8.87 ; N, 5.36. Found : C, 73.49 ; H, 9.02 ; N, 5.28. MS m/z : 261 (M^+).

Ethyl (3*R*)-2-Azabicyclo[2.2.2]octane-3-carboxylate (7) : A mixture of **6** (1.0 g, 3.48 mmol), 20% $Pd(OH)_2$ (540 mg), and ethyl acetate (40 mL) was stirred under a hydrodgen atmosphere at rt 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 : 498 mg, 78%, viscous oil, $[\alpha]_D^{23}$ -13.22° (c=1.0, $CHCl_3$) [lit.,[3b] : $[\alpha]_D^{22}$+13.52° (c=1.7, $CHCl_3$)].

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