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SYNTHESIS OF NEW CHIRAL CATALYSTS, 2-AZANORBORNYLOXAZOLIDINES, FOR ENANTIOSELECTIVE ADDITION OF DIETHYLZINC TO ALDEHYDES

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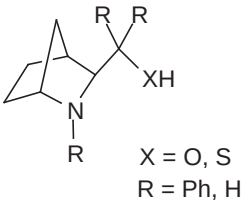
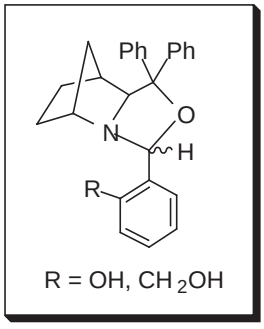
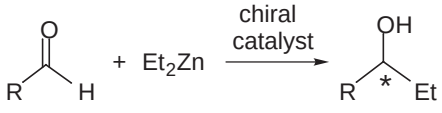
Abstract - Optically active 2-azanorbornyloxazolidines were prepared from 2-azanorbornylmethanols and catalyzed the enantioselective addition of diethylzinc to aldehydes to give optically active secondary alcohols.

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 represents a pivotal challenge to the synthetic community. Among the catalysts, β-amino alcohols have proved to be extremely efficient catalysts in catalytic reaction.[1] Recently, 2-azanorbornylmethanols (**A**) have been shown to be effective catalysts to some catalytic asymmetric reactions by our group[2] and others.[3] Chiral oxazolidines are very effective catalysts[4] as with β-amino alcohols in catalytic reactions. However, to the best of our knowledge, few examples have been reported for oxazolidine catalyst[5] in this area. In this Note, we wish to report the synthesis of a series of new chiral catalysts, 2-azanorbor-



Chiral Catalyst **A**



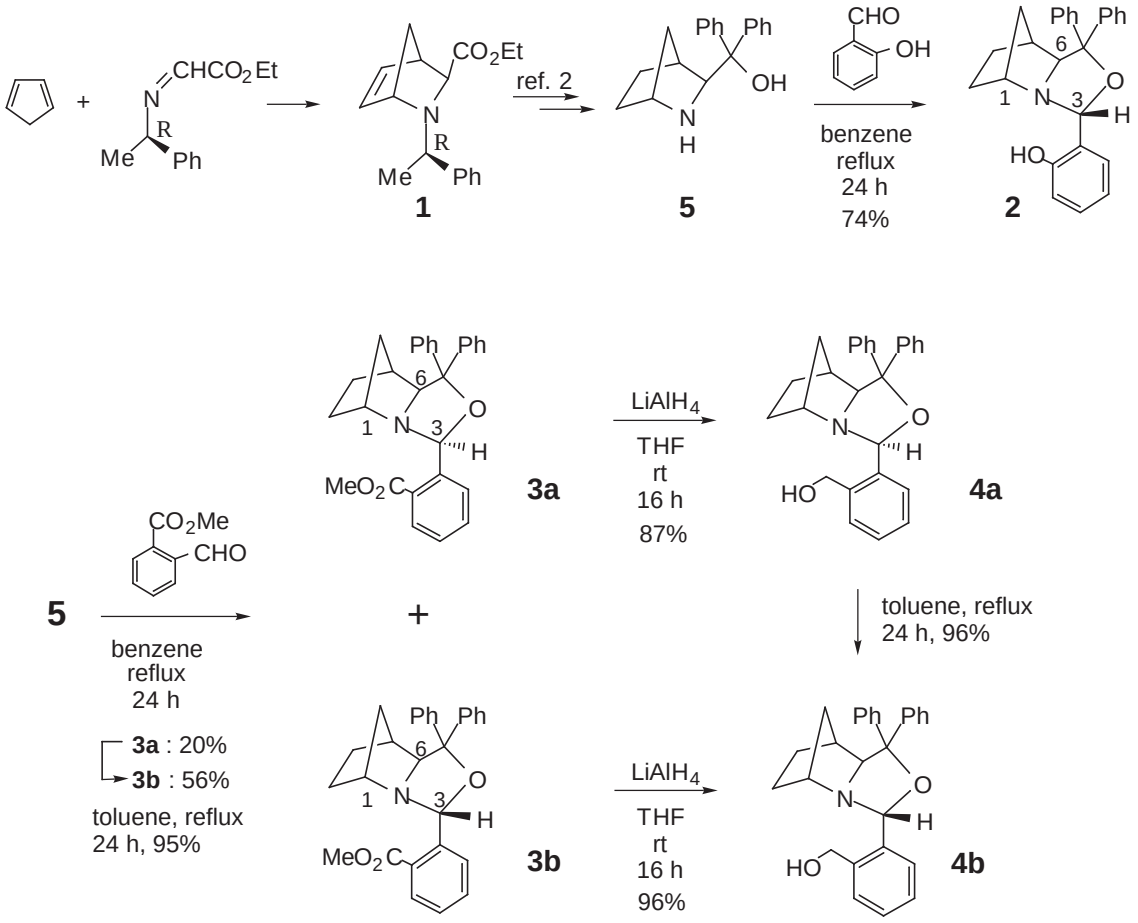


Dedicated to Professor Shô Itô on the occasion of his 77th birthday.

nyloxazolidines (**2, 4a,** and **4b**) fused 2-azanorbornane skeleton with oxazolidine skeleton, and their use as chiral catalysts in the asymmetric addition to aldehydes.[6] The asymmetric addition of diethylzinc to aldehydes in the presence of catalytic amounts of chiral catalysts is a convenient method for the preparation of enantiomerically pure secondary alcohols. 2-Azanorbornyloxazolidines (**2, 4a,** and **4b**) are sterically constrained catalysts and their bicyclo[2.2.1] ring system in these may block effectively the approach of the attacking species to one of the enantiotopic faces of aldehydes.

Preparations of the chiral catalysts (**2, 4a,** and **4b**) are described in Scheme 1. The chiral 2-aza-norbornyloxazolidine (**2**) was synthesized by the condensation of 2-azanorbornylmethanol (**5**)[2] with

Scheme 1

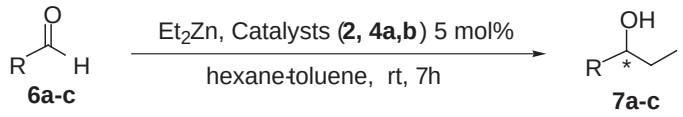


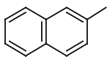
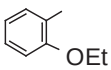
2-hydroxybenzaldehyde in 74% yield diastereoselectively. The treatment of **5** with 2-methoxycarbonyl-benzaldehyde gave the corresponding condensed products (**3a** and **3b**) as a mixture of two isomers (**3a** :

20%, **3b** : 56%). The obtained **3a** was converted to **3b** in refluxing toluene in excellent yield. Diastereomerically pure compounds (**3a** and **3b**) were isolated from the mixture by column chromatography. The stereochemistry of the newly created chiral center at the 3-position of the oxazolidine ring in **3a** and **3b** was determined by the NOE measurement of ^{1}H-NMR spectra. Thus, the NOE experiment for **3a** confirmed an interaction between hydrogen at the 3-position and it at the 6-position. However, **3b** did not have the interaction between the hydrogens at the same positions (3- and 6-position). The compounds (**3a** and **3b**) were converted to new type catalysts (**4a** and **4b**) by the reduction using $LiAlH_4$ in excellent yields (**4a** : 87%, **4b** : 96%). In addition, the obtained **3a** and **4a** were isomerized smoothly to the corresponding diastereomers (**3b** and **4b**) under heated conditions in 96 and 94% yields.

In order to examine the ability of the catalysts the enantioselective addition of diethylzinc to benzaldehyde (**6a**) was tried at 0 °C in the presence of a catalytic amount (5 mol%) of 2-azanorbornyl-oxazolidines (**2, 4a, and 4b**). All catalysts gave optically active 1-phenyl-1-propanol (**7a**) (Entries 1-3, Table 1). The relation between the enantiomeric excess of the obtained alcohol and the catalysts is

Table 1. Enantioselective Addition of Diethylzinc to Aromatic Aldehyde Using Chiral Catalysts (**2, 4a,b**)



6a :  **6b** :  **6c** : 

Entry[a)]	Substrate	Catalyst	Yield(%)	Ee(%)	Config.
1	**6a**	**2**	98	38[b)]	*S*
2	**6a**	**4a**	23	50[b)]	*S*
3	**6a**	**4b**	72	77[b)]	*S*
4	**6b**	**4b**	70	72[b)]	*S*
5	**6c**	**4b**	65	68[c)]	*S*

a) All reactions were carried out in toluene-hexane(1:1). *b*) Optical yields were determined by HPLC analysis [DAICEL chiralcel OD, *iso*-PrOH : Hexane (6a, 2:98; 6b, 1:99)]. *c*) Optical yields were determined by HPLC analysis [DAICEL chiralcel OB, *iso*-PrOH : Hexane (4:96)].

shown in Table 1. The catalyst (**2**) having phenolic hydroxy moiety afforded (*S*)-**7a** in low optical yield (38% ee) (Entry 1). The chiral catalyst (**4a**) having primary hydroxy moiety also did not work as good catalyst (50% ee) (Entry 2). However, the isomer (**4b**) of **4a** proved to be better catalyst (72%, 77% ee) (Entry 3) than the others. Next, the reaction of *β*-naphthylaldehyde (**6b**) with diethylzinc using the chiral catalyst (**4b**) (Entry 4) under the same reaction conditions was performed to give optically active (*S*)-1-(2-naphthyl)-1-propanol (**7b**), and this reaction gave the moderate result (70%, 72% ee). Furthermore, the enantioselective addition of 2-ethoxybenzaldehyde (**6c**) with diethylzinc in the presence of the catalyst (**4b**) gave also enantioselectively (*S*)-1-(2-ethoxyphenyl)-1-propanol (**7c**) in moderate chemical yield and enantiomeric excess (65%, 68% ee) (Entry 5).

In conclusion, we have prepared new chiral catalysts, 2-azanorbornyloxazolidines, for the zinc-catalyzed asymmetric addition of aromatic aldehydes.

EXPERIMENTAL

General. IR spectra were measured with a PERKIN ELMER 1725X spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-GSX 270 and a JNM-LA 600 spectrometers with TMS as an internal standard. 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 polarimeter. Diethylzinc in hexane was obtained from Kanto Chemical Co. Reactions with diethylzinc were performed under an argon atmosphere by using Schlenk-type glassware. Thin layer chromatography was performed with Merk F-254 silica gel plates. Preparative thin layer chromatography was carried out on Merk PSC-Fertirplatten Kieselgel 60 F-254 plates.

(1*R*,3*R*,6*S*,7*S*)-3-(2-Hydroxylphenyl)-5-diphenyl-4-oxa-2-azatricyclo[5.2.1.0^{2,6}]decane (2)

Compound (**5**) (140 mg, 0.50 mmol), 2-hydroxybenzaldehyde (122 mg, 1 mmol) and benzene (30 mL) were placed in a flask equipped with a Dean-Stark trap. The mixture was refluxed overnight. The solution was cooled and the solvent was recovered. The residue was purified by preparative TLC (ether : hexane = 1:3) to give the desired product (**2**) (140 mg, 74 %) as colorless prisms, mp 141-142 °C

(ether), $[\alpha]_D^{23}$= -127.9° (c 1.4, $CHCl_3$). IR (film) cm^{-1}: 3615. ^{1}H-NMR ($CDCl_3$) δ : 13.07 (br s, 1H), 7.46-7.00 (m, 12H), 6.71-6.61 (m, 2H), 5.67 (s, 1H), 4.14 (s, 1H), 3.42 (s, 1H), 2.42 (s, 1H), 1.66-1.43 (m, 4H), 1.35 (d, *J*=10.5 Hz, 1H), 0.94 (d, *J*=10.5 Hz, 1H), ^{13}C-NMR ($CDCl_3$) δ : 157.86, 145.14, 141.94, 129.73, 128.11, 127.95, 127.65, 127.03, 126.77, 126.52, 126.17, 125.85, 121.26, 118.31, 116.90, 97.15, 88.86, 75.77, 61.15, 39.91, 32.31, 29.44, 28.13. *Anal.* Calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.26; H, 6.70; N, 3.42. Ms m/z: 383 (M^+).

(1*R*, 3*S*, 6*S*, 7*S*)- and (1*R*, 3*R*, 6*S*, 7*S*)-3-(2-Methoxycarbonylphenyl)-5-diphenyl-4-oxa-2-azatricyclo-[5.2.1.0^{2,6}]decanes (3a and 3b)

Compound (**5**) (200 mg, 0.72 mmol), 2-methoxycarbonylbenzaldehyde (140 mg, 3.48 mmol) and benzene (30 mL) were placed in a flask equipped with a Dean-Stark trap. The mixture was refluxed overnight. The solution was cooled and the solvent was recovered. The residue was purified by preparative TLC (ether : hexane = 1:1) to give the desired products (**3a** and **3b**) (**3a**: 60 mg, 20%. **3b**: 305 mg, 56%), respectively, as colorless prisms [**3a** : mp 134-135 °C (ether). **3b** : mp 37-39 °C (ether)], **3a** : $[\alpha]_D^{23}$= -30.0° (c 1.3, $CHCl_3$), **3b** : $[\alpha]_D^{23}$= -96.0° (c 1.5, $CHCl_3$). **3a**: IR (film) cm^{-1}: 3625, 1728. ^{1}H-NMR ($CDCl_3$) δ : 7.61 (m, 1H), 7.52 (m, 1H), 7.42-7.39 (br s, 2H), 7.29-7.24 (m, 2H), 7.17-7.15 (m, 3H), 7.15-7.03 (m, 2H), 6.99-6.87 (m, 3H), 6.40 (s, 1H), 4.07 (s, 1H), 3.98 (s, 3H), 3.40 (s, 1H), 2.05 (s, 1H), 1.64-1.43 (m, 5H), 0.84 (d, *J*=9.9 Hz, 1H), ^{13}C-NMR ($CDCl_3$) δ: 169.53, 146.51, 143.66, 142.41, 130.67, 130.23, 128.81, 128.28, 127.67, 127.27, 126.94, 126.68, 126.22, 126.19, 95.30, 88.85, 76.38, 63.11, 52.08, 40.32, 32.87, 30.12, 28.18. *Anal.* Calcd for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40; N, 3.29. Found: C, 78.90; H, 6.60; N, 3.05. Ms m/z: 425 (M^+). **3b**: IR (film) cm^{-1}: 3610, 1725. ^{1}H-NMR ($CDCl_3$) δ: 8.17 (d, *J*=7.8 Hz, 1H), 7.82(d, *J*=7.8 Hz, 1H), 7.66-7.53 (m, 5H), 7.46-7.17 (m, 7H), 6.07 (s, 1H), 4.18 (s, 1H), 3.83 (s, 3H), 2.71 (s, 1H), 1.91 (s, 1H), 1.48 (d, *J*=9.6 Hz, 1H), 1.41-1.19 (m, 4H), 0.56 (d, *J*=9.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ: 167.60, 145.81, 143.28, 136.59, 131.39, 130.36, 129.82, 128.20, 127.93, 127.74, 127.45, 127.18, 127.11, 126.38, 126.33, 89.79, 87.03, 75.44, 57.70, 52.23, 39.79, 33.95, 30.89, 27.86. *Anal.* Calcd for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40; N, 3.29. Found: C, 78.89; H, 6.63; N, 3.10. Ms m/z: 425 (M^+).

Isomerization of 3a to 3b

The toluene (10 mL) solution of **3a** (100 mg) was refluxed overnight. After cooling, the mixture was concentrated and purified on PTLC (ether : hexane = 2:1) to yield **3b** as colorless prisms (95 mg, 95%).

(1*R*,3*S*,6*S*,7*S*)-3-(2-Hydroxymethylphenyl)-5-diphenyl-4-oxa-2-azatricyclo[5.2.1.$0^{2,6}$]decane (4a)

To a stirred suspension of lithium aluminum hydride (150 mg, 0.35 mmol) in dry THF (5 mL) was added a solution of **3a** (150 mg, 0.35 mmol) in dry THF (2 mL) at 0 °C. The mixture was stirred at rt for 15 h, quenched by addition to water, and filterated through celite 545. The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to afford the residue. The residue was chromatographed on a silica gel column (ether : hexane = 2:1) to give **4a** (120 mg, 87%) as colorless prisms, mp 62-64 °C (ether), $[\alpha]_D^{23}$= -77.6° (c 1.7, $CHCl_3$). IR (film) cm^{-1}: 3611. ^{1}H-NMR ($CDCl_3$) δ: 8.00 (d, *J*=7.2 Hz, 1H), 7.74-7.10 (m, 14H), 5.63 (s, 1H), 4.71 (d, *J*=12.9 Hz, 1H), 4.32 (d, *J*=12.9 Hz, 1H), 4.21 (s, 1H), 2.81 (s, 1H), 2.02 (s, 1H), 1.65 (d, *J*=9.9 Hz, 1H), 1.37-1.22 (m, 4H), 0.65 (d, *J*=9.9 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ :145.27, 142.49, 138.57, 134.04, 129.71, 128.67, 128.45, 128.22, 128.09, 127.90, 127.86, 127.45, 126.60, 126.18, 126.06, 125.69, 125.40, 89.31, 87.91, 74.55, 64.29, 57.84, 40.00, 33.53, 30.37, 27.38. *Anal.* Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52. Found: C, 81.30; H, 7.05; N, 3.23. Ms m/z: 397 (M^+).

(1*R*,3*R*,6*S*,7*S*)-3-(2-Hydroxymethylphenyl)-5-diphenyl-4-oxa-2-azatricyclo[5.2.1.$0^{2,6}$]decane (4b)

To a stirred suspension of lithium aluminum hydride (150 mg, 0.35 mmol) in dry THF (5 mL) was added a solution of **3b** (150 mg, 0.35 mmol) in dry THF (2 mL) at 0 °C. The mixture was stirred at rt for 15 h, quenched by addition to water, and filterated through celite 545. The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to afford the residue. The residue was chromatographed on a silica gel column (ether : hexane = 2:1) to give **4b** (134 mg, 96%) as colorless prisms, mp 130-132 °C (ether), $[\alpha]_D^{23}$= -54.0° (c 1.5, $CHCl_3$). IR (film) cm^{-1}: 3620, 1605. ^{1}H-NMR ($CDCl_3$) δ: 7.50-7.15 (m, 14H), 6.87 (br s, 1H), 5.36 (s, 1H), 5.10 (d, *J*=11.5 Hz, 1H), 4.12 (d, *J*=11.5 Hz, 1H), 4.10 (s, 1H), 3.18 (s, 1H), 2.81 (br s, 1H), 1.66-1.44 (m, 4H), 1.01 (d, *J*=10.7 Hz, 1H), 0.86 (d, *J*=10.7 Hz, 1H). ^{13}C-NMR

($CDCl_3$) δ : 146.16, 141.94, 141.92, 137.53, 131.42, 130.83, 129.85, 128.24, 128.15, 127.45, 127.06, 126.66, 126.03, 125.87, 98.66, 88.97, 63.63, 58.25, 40.32, 31.93. *Anal.* Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52. Found: C, 81.35; H, 7.10; N, 3.32. Ms m/z: 397 (M^+).

Isomerization of 4a to 4b

The toluene (10 mL) solution of **4a** (100 mg) was refluxed overnight. After cooling, the mixture was concentrated and purified on PTLC (ether : hexane = 2:1) to yield **4b** as colorless prisms (96 mg, 96%).

General Procedure for the Enantioselective Addition of Diethylzinc to Aldehydes:

To a solution of chiral catalysts [**2, 4a,b** (0.0175 mmol)] in toluene (0.7 mL), diethylzinc (0.7 mmol, 0.7 mL of 1 M solution in hexane) was added at rt. After the mixture had been stirred at rt for 30 min, aldehydes (**6a-c**) (0.35 mmol) were introduced. The homogeneous solution was stirred for 7 h at rt 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 the corresponding chiral alcohols (**7a-c**), respectively. The products were identified by comparing the ^{1}H-NMR and IR spectra with those of authentic samples, and the optical rotation was measured. Optical purities (% ee) were determined by HPLC analyses of the resulting secondary alcohols.

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