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Tetrahedron: Asymmetry

New β-amino alcohols with a bicyclo[3.3.0]octane scaffold in an asymmetric Henry reaction

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Abstract—A new category of β-amino alcohols with a bicyclo[3.3.0]octane scaffold has been synthesized and used in the direct asymmetric nitroaldol reaction (Henry reaction). Up to 74% ee was obtained with the addition of nitromethane to relatively bulky aldehydes.

1. Introduction

Since its discovery in 1895,[1] the nitroaldol reaction (Henry reaction), one of the most powerful carbon–carbon bond forming transformations, has been widely used in the synthesis of numerous natural products and other useful compounds.[2] However, the asymmetric version of this reaction promoted by chiral catalysts had not appeared until the last decade. Shibasaki et al.[3] first reported the highly enantioselective and diastereoselective Henry reaction employing their elegant heterobimetallic system.[4] Jørgensen et al.[5] disclosed the enantioselective Henry reaction of α-keto esters with nitromethane catalyzed by copper salts in combination with chiral bisoxazoline ligands. Ma et al.[6] and Najera et al.,[7] using chiral guanidine as the organo catalyst, developed another case for a direct asymmetric Henry reaction.

Recently, a novel type of dinuclear zinc catalyst[8,9] (Fig. 1) developed by Trost has successfully been utilized in an asymmetric Henry reaction.[10] Following Trost's work, Reiser et al.[11] disclosed in detail that the Henry reaction could be promoted by diethylzinc in the presence of either diamines or amino alcohols. However, initial investigations with chiral amino alcohols to make this process asymmetric were unsuccessful.

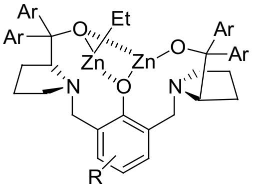
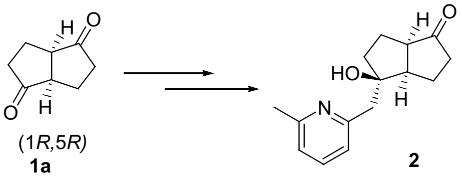


Figure 1. Trost's catalyst.

In recent years, we have been interested in the synthesis of chiral auxiliaries and ligands with a *cis*-bicyclo[3.3.0]octane framework.[12] Pyridyl alcohol **2**, derived from chiral diketone (1*R*,5*R*)-**1a**,[13] was found to induce high enantioselectivities in the asymmetric addition of diethylzinc to aldehydes (Scheme 1).[12a] The semi-caged structure of the *cis*-bicyclo[3.3.0]octane was expected to form a unique chiral environment for this asymmetric process. It occurred to us that the chiral diketone **1a** could be converted into its analogous epoxide, and subsequently attacked by amines, which is one of the common procedures for the preparation of β-amino alcohols.[14]



Scheme 1.

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Herein we report the synthesis of this new kind of β-amino alcohol with a bicyclo[3.3.0]octane framework. Inspired by Trost's work, the asymmetric Henry reaction catalyzed by the Brönsted base–Lewis acid complex generated from diethylzinc and these β-amino alcohols was then tried. Although amino alcohols have been widely used in asymmetric reactions, especially the addition of organozinc reagents to aldehydes,[15] there are few reports about their use in asymmetric Henry reactions. It is worth noting that Sundararajan has already reported an asymmetric Michael reaction catalyzed by a chiral amino alcohol–Al (or Na) complex, employing the Brönsted base–Lewis acid catalysis.[16]

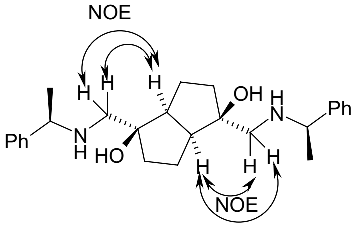


Figure 2. The NOE analysis of **4b**.

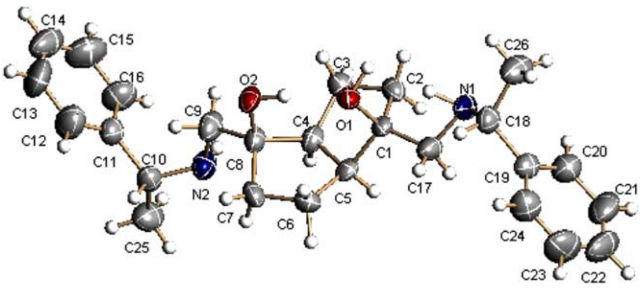
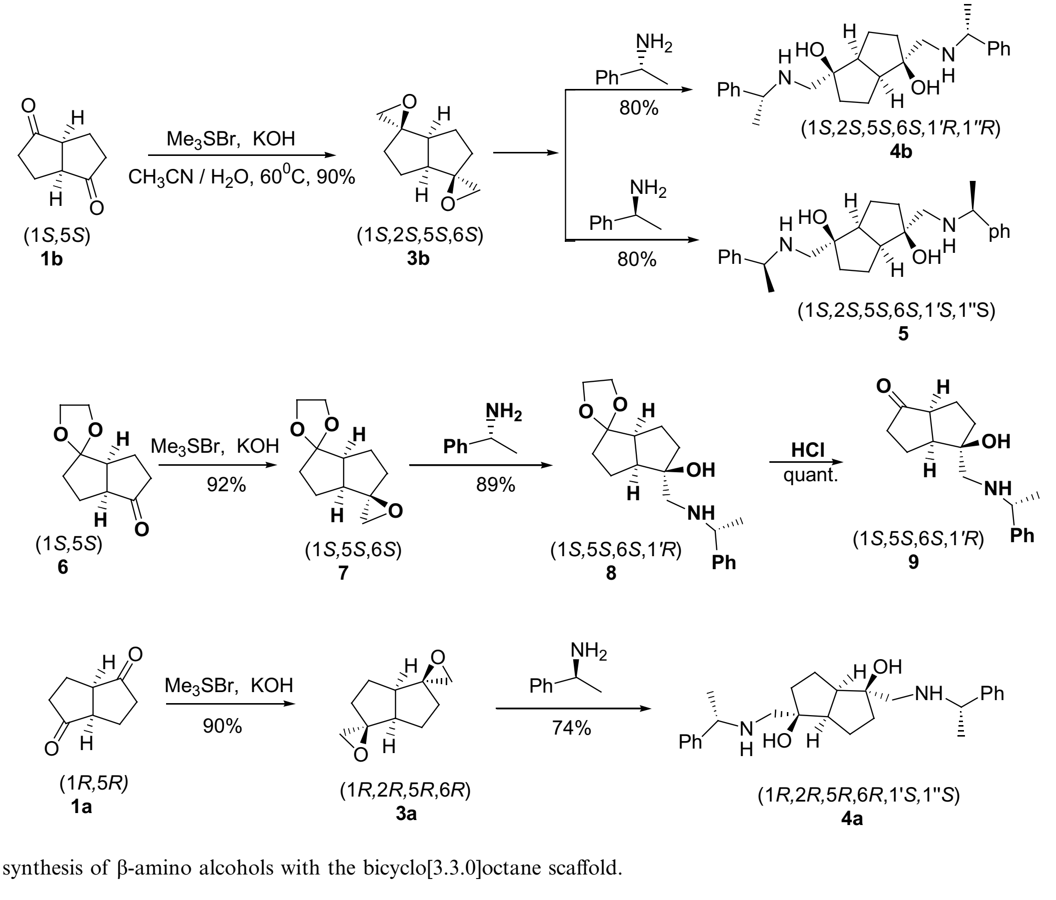


Figure 3. The X-ray analysis of **4b**.

2. Results and discussion

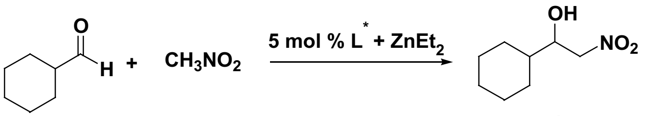
As shown in Scheme 2, treatment of the diketone (1*S*,5*S*)-**1b**[13] (the enantiomer of **1a**) with trimethylsulfonium bromide[17] furnished bis-oxirane **3b**. Due to its wide availability and ample use in asymmetric synthesis,[18] homochiral (*R*) or (*S*)-1-phenylethylamine was then chosen as the nucleophile to open the epoxide ring of **3b**, thus producing the bis-β-amino alcohols **4b** and **5** as two diastereomers. The relative configuration of **4b** was determined by its NOE (Fig. 2) and X-ray analysis (Fig. 3). In another part, mono-β-amino alcohol **8** was obtained via the same procedure as described above from mono-ketone (1*S*,5*S*)-**6**.[12a] Deprotection of **8** gave amino alcohol **9** with an unmasked carbonyl group.

Amino alcohols **4b**, **5**, **8**, and **9** were then tested in the asymmetric Henry reaction under the conditions[10] described by Trost with minor modifications. The reaction



Scheme 2. The synthesis of β-amino alcohols with the bicyclo[3.3.0]octane scaffold.

between cyclohexanecarboxaldehyde and nitromethane was selected as the representative reaction (Eq. 1). The catalyst was prepared in situ from 5 mol % of one of the above mentioned amino alcohols with two (for **8** and **9**) or three (for **4b** and **5**) equivalents of diethylzinc in THF in the presence of 4 Å MS at 0 °C, into which 6 equiv of nitromethane was added, followed by the addition of the aldehyde.



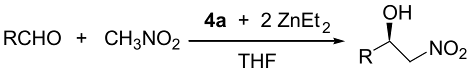
10

(1)

As can be seen from Table 1, in combination with diethylzinc, all four amino alcohols catalyzed the addition of nitromethane to cyclohexanecarboxaldehyde to produce the product with good to high yields. Considering the relatively low reaction temperature, shorter reaction time, and higher yield, bis-amino alcohols **4b** and **5** (entries 1 and 2) were more active than the mono-amino alcohols **8** and **9** (entries 3 and 4). As far as the enantioselectivitiy was concerned, **4b** was the most effective among the four amino alcohols (entry 1, 38% ee). It seems that the bis-amino alcohols catalyze this reaction via a different mechanism compared to that of the mono-amino alcohols. The bis-amino alcohol **4b** provided **10** in an (*S*)-configuration (entry 1), while the mono-amino alcohol **8** or **9**, with the same configuration both on the bicyclo[3.3.0]octane scaffold and the phenylethylamine moiety, afforded **10** in an (*R*)-configuration (entries 3 and 4). Perhaps the two amino alcohol–zinc complex moieties in **4b** operated cooperatively.

Compound **4b** was then chosen as the standard ligand for optimizing further the reaction conditions. We later found that the molar ratio between **4b** and diethylzinc was crucial for the ee value of the product (entries 5–7). The optimal result was obtained when 2 equiv of diethylzinc were used (entry 6, 46% ee). A further improvement in enantioselectivity was achieved by lowering the reaction temperature to −25 °C (entry 8, 59% ee). Attempts to increase the ee value by changing the number of equivalents of nitromethane and the reaction medium failed. The use of additives such as Ph_3PS and C_2H_5OH also proved to be unbeneficial.[20] When the ligand was **4a** (the enantiomer of **4b**, prepared from **1a** as shown in Scheme 1), almost the same ee value of the product was obtained, while the absolute configuration of the product reversed as expected as indicated by the sign of the specific rotation (entry 9).

Under the optimal conditions (Table 1, entry 9), the complex formed in situ between 5 mol % of **4a** and 10 mol % of diethylzinc, was used to catalyze the addition of nitromethane to a variety of aldehydes (Eq. 2), with the results summarized in Table 2. Moderate enantioselectivities were obtained for the relatively bulky aldehydes, such as *iso*-butyraldehyde (entry 3), pivalaldehyde (entry 4), and 2-ethylbutyraldehyde (entry 5). α,α-Dimethylhydrocinnamaldehyde[21] was shown to produce the highest ee among all the substrates examined (entry 6, 74% ee). When it came to the sterically less encumbered hydrocinnamaldehyde (entry 2), the ee value diminished to 37%. As far as aromatic aldehydes were concerned, the enantioselectivities were relatively poor (entries 7–9). However, a moderate ee of 49% was achieved in the case of *o*-methoxybenzaldehyde (entry 10). The absolute configuration of all the products in Table 2 is assigned as *R* based on the specific rotation when compared with the reported data by Shibasaki et al.[3a] and Trost et al.[10]



(2)

3. Conclusion

In summary, a new category of β-amino alcohols with a bicyclo[3.3.0]octane scaffold was synthesized and used in an asymmetric Henry reaction.[22] Moderate enantioselectivities were obtained for the relatively bulky aliphatic aldehydes. Although the detailed mechanism of this system calls for further investigation, it is reasonable to assume a mechanism in which at least two zinc atoms

Table 1. Optimization of the Henry reaction between cyclohexylcarboxaldehyde and nitromethane[a]

Entry	Ligand	L:$ZnEt_2$	Temperature	Time (h)	Yield (%)[b]	Ee (%)[c]	$[\alpha]_D^{20}$	Absolute configuration[d]
1	**4b**	1:3	0 °C	10	87	38	+6.9	*S*
2	**5**	1:3	0 °C	10	81	12	−2.8	*R*
3	**8**	1:2	0 °C to rt	24	70	27	−6.2	*R*
4	**9**	1:2	0 °C to rt	24	50	17	−4.0	*R*
5	**4b**	1:5	0 °C	7	93	25	+4.5	*S*
6	**4b**	1:2	0 °C	7	77	46	+8.3	*S*
7	**4b**	1:1	0 °C	9	59	38	+6.1	*S*
8	**4b**	1:2	−25 °C	8	75	59	+10.3	*S*
9	**4a**	1:2	−25 °C	8	90	52	−10.5	*R*

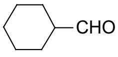
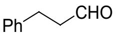
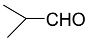
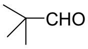
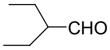
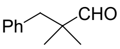
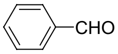
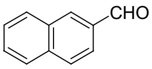
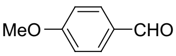
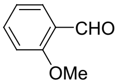
[a] All reactions were conducted on a 1 mmol scale of cyclohexylcarboxaldehyde.

[b] Isolated yield.

[c] The ee value of the product was determined by the chiral HPLC analysis.

[d] The absolute configuration of **10** was established according to the optical rotation in comparison with the reported data by Trost, see Ref. 19.

Table 2. Enantioselective Henry reaction between aldehydes and nitromethane[a]

Entry	Aldehyde	Reaction time (h)	Yield (%)[b]	Ee (%)[c]	$[\alpha]^{20}_{\mathrm{D}}$ in $CHCl_3$
1		8	90	52	−10.5 (*c* 5.40)
2		11	74	37	+4.6 (*c* 1.28)
3		10	90	66	−21.5 (*c* 1.75)
4		12	82	67	−19.7 (*c* 1.42)
5		20	50	69	−17.0 (*c* 1.20)
6		20	40	74	−4.1 (*c* 1.05)
7[d]		8	80	33	−15.4 (*c* 2.15)
8		36	81	25	−7.2 (*c* 1.70)
9		42	73	21	−7.1 (*c* 1.87)
10		23	75	49	−22.4 (*c* 3.75)

[a] All reactions were run on a 1 mmol scale of aldehyde using 5 mol% **4a**, 6 equiv of nitromethane in THF at −25 °C unless otherwise noted.

[b] Isolated yield.

[c] The ee value of the product was determined by chiral HPLC analysis.

[d] 10 mol% of **4a** and 20 mol% $ZnEt_2$ was used.

are involved, one acting as a Lewis acid center to activate the aldehyde, while the other functioning as a Brönsted base to generate a zinc-nitronate from nitromethane. Related works on the Brönsted base–Lewis acid zinc complex, which was prepared in situ from BINOL derivatives and $ZnEt_2$ has been reported by Shibasaki and co-workers.[23] Further work to modify the ligand in order to improve the enantioselectivities is currently in progress. Expansion of this system to other asymmetric reactions is also under investigation.

4. Experimental

4.1. General

Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer 241MC polarimeter. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ on 300 and 75 MHz FT-spectrometers, respectively, using TMS as the internal reference. IR spectra were recorded on a Digibal FT-IR spectrometer. Mass spectra were recorded by the EI method, and HRMS were measured on a Finnigan MAT-8430 mass spectrometer. Elemental analysis was performed on Heraeus Rapid-CHNO. Enantiomeric excess determination was carried out using HPLC with a Chiralcel OD, AS, AD, or OJ column. The silica gel used for flash chromatography was 300–400 mesh. All solvents were dried by standard method. Unless otherwise noted, commercially available reagents were used without further purification.

4.2. (1*S*,2*S*,5*S*,6*S*)-Bicyclo[3.3.0]octan-2,6-dione diepoxide, 3b

To 20 mL of CH_3CN was added Me_3SBr (3.27 g, 20.8 mmol), KOH (4.66 g, 83.3 mmol), and H_2O (68 μL). The resulting heterogeneous mixture was stirred for 5 min at 60 °C, followed by the addition of the solution of chiral dione **1b** (958 mg, 6.9 mmol) in CH_3CN (7 mL). The system was then stirred at 60 °C for 2 h, and filtered through a pad of Celite. The volatile solvent was removed under reduced pressure. Water (10 mL) was added to dissolve the residue. The mixture was extracted with ether, and purified by flash column chromatography to provide **3b** as oil (1.1 g, 90%). $[\alpha]^{20}_{\mathrm{D}} = +108.8$ (*c* 2.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.56–1.77 (m, 8H), 2.5 (m, 2H), 2.67 (d, $J = 5.1$ Hz, 2H), 2.78 (d, $J = 5.4$ Hz, 2H); FT-IR (film, cm^{-1}): 2961, 1459, 1164, 925; EIMS (*m*/*z*, %): 166 (M$^+$, 0.97), 79 (100.00), 91 (63.26), 109 (62.18), 108 (57.27), 110 (56.09), 77

(54.61), 135 (52.71), 105 (48.25); ^{13}C NMR (300 MHz, $CDCl_3$, ppm): δ 23.82, 32.62, 44.60, 52.58, 66.23; HRMS *m/z* calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.1005.

4.3. (1*S*,2*S*,5*S*,6*S*,1′*R*,1″*R*)-2,6-Bis(1-phenylethyl-amino-methyl)-bicyclo[3.3.0]octan-2,6-diol, 4b

Compound **3b** (500 mg, 3.0 mmol) and (*R*)-(+)-1-phenylethylamine (2.3 mL, 18 mmol) was refluxed in ethanol for 34 h under an argon atmosphere. The volatile solvent was removed under reduced pressure and the residue subjected to flash column chromatography to afford **4b** (980 mg, 80%) as a white solid. mp: 78 °C; $[\alpha]_D^{20} = +56.5$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.41 (d, $J = 6.3$ Hz, 6H), 1.59 (m, 4H), 1.78 (m, 2H), 1.93 (m, 2H), 2.31 (m, 2H), 2.41 (d, $J = 11.7$ Hz, 2H), 2.58 (d, $J = 11.7$ Hz, 2H), 2.50–3.40 (br, 4H), 3.80 (q, 2H), 7.29 (m, 10H); FT-IR (KBr, cm^{-1}): 3343, 3154, 2956, 1454, 1119, 761, 700; EI-MS (*m/z*, %): 408 (M^+, 1.69), 289 (7.96), 275 (9.71), 274 (23.49), 120 (18.20), 134 (22.27), 106 (13.50), 105 (100.00), 79 (10.99); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 20.66, 24.39, 41.34, 51.85, 55.09, 58.69, 78.91, 126.50, 126.89, 128.41, 145.30; HRMS M^+ calcd for $C_{16}H_{36}N_2O_2$: 408.2777, found: 408.2788. X-ray data of **3b**: $C_{26}H_{36}N_2O_2$ space group P212121. a 8.4987(9), b 9.4805(10), c 29.272(3). Crystallographic data for **3b** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 230028. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.4. (1*S*,2*S*,5*S*,6*S*,1′*S*,1″*S*)-2,6-Bis(1-phenylethyl-amino-methyl)-bicyclo[3.3.0]octan-2,6-diol, 5

Compound **5** was prepared from **3b** and (*S*)-(−)-1-phenylethylamine in a similar way as described in Section 4.3. Yield: 80%; $[\alpha]_D^{20} = -12.5$ (*c* 3.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.32 (d, $J = 6.6$ Hz, 6H), 1.52 (m, 4H), 1.71–1.84 (m, 4H), 2.22 (m, 2H), 2.36 (d, $J = 12.0$ Hz, 2H), 2.50 (d, $J = 11.7$ Hz, 2H), 2.00–3.40 (br, 4H), 3.72 (q, 2H), 7.28 (m, 10H); FT-IR (film, cm^{-1}): 3338, 3026, 2960, 1451, 1128, 762, 701; EI-MS (*m/z*, %): 408 (M^+, 1.59), 275 (8.73), 274 (21.53), 134 (20.60), 120 (18.58), 106 (14.02), 105 (100.00), 79 (13.22), 77 (9.60); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 20.89, 24.40, 41.58, 51.89, 55.03, 58.40, 78.88, 126.36, 126.73, 128.30, 145.43; HRMS M^+ calcd for $C_{16}H_{36}N_2O_2$: 408.2777, found: 408.2761.

4.5. (1*S*,5*S*,6*S*)-Bicyclo[3.3.0]octan-2,6-dione 2-epoxide 6-ethylene ketal, 7

Compound **7** was prepared from **6** and Me_3SBr in a similar way as described in Section 4.2. Yield: 92%; $[\alpha]_D^{20} = +63.6$ (*c* 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.72 (m, 8H), 2.55 (m, 2H), 2.70 (m, 1H), 2.84 (m, 1H), 3.90 (m, 4H); FT-IR (film, cm^{-1}): 2963, 1342, 1211, 1109; EI-MS (*m/z*, %): 196 (M^+, 0.66), 166 (21.76), 165 (55.09), 100 (22.43), 99 (100.00), 87 (9.81), 86 (13.89), 79 (12.69), 55 (14.92); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.1, 25.8, 33.5, 34.2, 42.8, 49.6, 50.8, 63.7, 64.8, 66.3, 118.8; HRMS M^+ calcd for $C_{11}H_{16}O_3$: 196.1099, found: 196.1120.

4.6. 1*S*,5*S*,6*S*,1′*R*)-6-Hydroxy-6-(1-phenylethyl-amino-methyl)-bicyclo[3.3.0]octan-2-one ethylene ketal, 8

Compound **8** was prepared from **6** and (*R*)-(+)-1-phenylethylamine in a similar way as described in Section 4.3. Yield: 89%; $[\alpha]_D^{20} = +70.7$ (*c* 1.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.40 (d, $J = 6.3$ Hz, 3H), 1.46 (m, 1H), 1.69 (m, 7H), 2.25 (m, 1H), 2.38 (m, 1H), 2.44 (d, $J = 11.1$ Hz, 1H), 2.59 (d, $J = 11.7$ Hz, 1H), 3.00 (br, 2H), 3.82 (q, 1H), 3.89 (m, 4H), 7.27 (m, 5H); FT-IR (film, cm^{-1}): 3477, 3026, 2961, 1107, 763, 702; EI-MS (*m/z*, %): 318 (M^++H, 38.11), 134 (30.10), 120 (31.54), 106 (12.47), 105 (100.00), 99 (16.93), 79 (15.97), 77 (11.81); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 21.68, 23.76, 24.42, 35.44, 38.71, 48.64, 49.23, 55.84, 58.44, 64.04, 64.75, 80.39, 118.26, 126.35, 126.81, 128.36, 145.44; HRMS (M^+-CH_3) calcd for $C_{18}H_{24}NO_3$: 302.1756, found: 302.1773.

4.7. (1*S*,5*S*,6*S*,1′*R*)-6-Hydroxy-6-(1-phenylethyl-amino-methyl)-bicyclo[3.3.0]octan-2-one, 9

To a solution of 5% HCl and acetone (10/1, v/v) was added **8**. The mixture was stirred at rt for 5 h. THF was evaporated under reduced pressure. Then, saturated aqueous $NaHCO_3$ solution was added to neutralize the mixture. The mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography to give **9** in quantitative yield. mp: 92 °C; $[\alpha]_D^{20} = +146.5$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.48 (d, $J = 6.6$ Hz, 3H), 1.50 (m, 1H), 1.90 (m, 5H), 2.17 (m, 1H), 2.26 (m, 2H), 2.40 (d, $J = 11.4$ Hz, 1H), 2.58 (m, 1H), 2.66 (d, $J = 12.0$ Hz, 1H), 3.48 (br, 2H), 3.84 (q, 1H), 7.29 (m, 5H); FT-IR (film, cm^{-1}): 3416, 3359, 3029, 2961, 1718, 766, 707; EI-MS (*m/z*, %): 274 (M^++H, 2.15), 134 (39.39), 106 (11.86), 105 (100.00), 103 (9.53), 79 (13.99), 77 (13.34), 57 (7.01), 41 (6.71); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 20.15, 23.48, 25.26, 37.97, 38.33, 48.50, 51.26, 54.47, 59.04, 80.96, 126.53, 127.50, 128.73, 143.68, 223.25; HRMS M^+ calcd for $C_{17}H_{23}NO_2$:273.1729, found: 273.1702.

4.8. (1*R*,2*R*,5*R*,6*R*)-Bicyclo[3.3.0]octan-2,6-dione diepoxide, 3a

Compound **3a** was prepared from **1a** and Me_3SBr in a similar way as described in Section 4.2. Yield: 90%; $[\alpha]_D^{20} = -111.6$ (*c* 1.20, $CHCl_3$).

4.9. (1*R*,2*R*,5*R*,6*R*,1′*S*,1″*S*)-2,6-Bis(1-phenylethyl-aminomethyl)-bicyclo[3.3.0]octan-2,6-diol, 4a

Prepared from **3a** and *S*-(−)-1-phenylethylamine in a similar way as described in Section 4.3. Yield: 74%; $[\alpha]_D^{20} = -53.0$ (*c* 1.55, $CHCl_3$).

4.10. Typical procedure for the asymmetric addition of nitromethane to aldehydes

Under an argon atmosphere, diethylzinc (91 μL of 1.1 M solution in toluene, 0.10 mmol) was added to **4a** (21 mg, 0.05 mmol) and pre-dried 4 Å MS (100 mg) in anhydrous THF (4 mL) at 0 °C. The mixture was stirred for 30 min, and then cooled to −25 °C. After the addition of the corresponding aldehyde (1.0 mmol) and nitromethane (0.32 mL, 6.0 mmol), the suspension was stirred for the indicated time and quenched by aqueous HCl (4 mL, 1.0 M). Extraction with diethyl ether and purification by flash column chromatography afforded the desired product.

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