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New chiral 1,4-aminoalcohols derived from (+)-camphor and (−)-fenchone for the enantioselective addition of diethylzinc to aldehyde

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Abstract

Various optically active 1,4-aminoalcohols were synthesized from (+)-camphor and (−)-fenchone. The aminoalcohols **5** or **6**-mediated enantioselective addition reactions of diethylzinc to benzaldehyde resulted in the formation of the optically active secondary alcohol in good yield. When the catalyst derived from (+)-camphor was used, the (*S*)-alcohol was obtained in high ee, while the (*R*)-alcohol was obtained in the reaction with the catalyst derived from (−)-fenchone. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

The catalytic enantioselective addition reaction of an organometallic reagent to aldehydes affording optically active secondary alcohols is an important synthetic procedure because enantiomerically pure or enriched alcohols are valuable intermediates for the synthesis of natural products.[1] Since Noyori and co-workers demonstrated the catalytic activity and efficiency of (−)-3-*exo*-(dimethylamino)isoborneol (DAIB) as a chiral catalyst,[2] a wide variety of aminoalcohols, mostly 1,2-aminoalcohols, have been prepared and used as chiral catalysts for the enantioselective addition reaction of diethylzinc to aldehydes.[3] However, only a few examples of the use of chiral 1,4-aminoalcohols have been reported.[4] Recently, we reported that 1,4-aminoalcohols **5b** and **6b** prepared from lactone **1** or **2** were efficient chiral catalysts for the addition reaction of diethylzinc to aldehydes.[5] In this paper, we have synthesized a series of 1,4-aminoalcohols **5** and **6** through aluminum reagent-mediated amidation of lactones, and aminoalcohol **5** or **6**-catalyzed enantioselective addition of diethylzinc to benzaldehyde is described.

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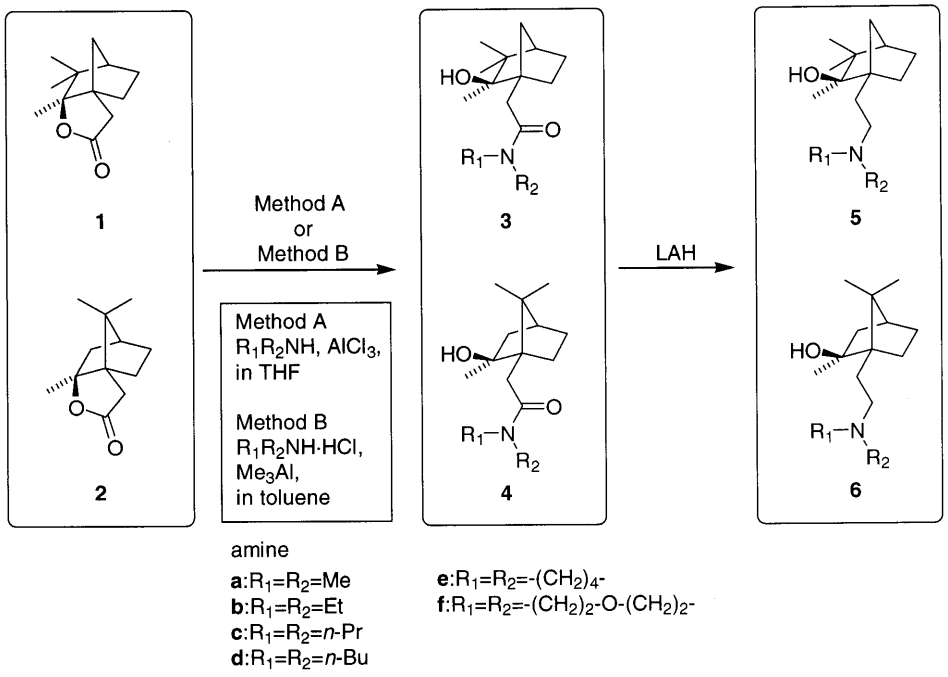
2. Results and discussion

Initially, we attempted aluminum chloride-mediated amidation of lactone **1** (Scheme 1).[6] When diethylamine, dipropylamine and dibutylamine were used as substrates, the amidation proceeded smoothly, and hydroxy amides **3** were obtained in high yield. However, cyclic amines, such as pyrrolidine and morpholine, did not react with **1**. This might be due to the reactivity of the aluminum amide, which was initially formed from aluminum chloride and the amine. Thus, we prepared the aluminum amide reagent from trimethylaluminum and amine hydrochloride,[7] then lactone **1** was added to the amide solution and the corresponding hydroxy amide **3** was obtained. Hydroxy amide **3** was easily reduced by lithium aluminum hydride to form aminoalcohol **5**. The yields of amidation and reduction are shown in Table 1. The reaction of **1** with morpholine resulted in the formation of **3f** in relatively low yield, because of the dehydration of **3f**. In the case of lactone **2**, though the addition reaction of amine was relatively slow and 10 days were needed to complete the reaction of **2** with diethylamine, hydroxy amide **4b** was obtained in 46% yield. On the other hand, the reaction of **2** with pyrrolidine or morpholine resulted in high yields relative to the reaction of **1**, and **4e** and **4f** were obtained in 72 and 47% yields, respectively. This might be due to the steric hindrance of the geminal dimethyl group. Hydroxy amide **4** was also reduced by lithium aluminum hydride to form aminoalcohol **6** in good yield. The structures of **3d** and **4f** were confirmed by X-ray structural analysis and the ORTEP views are shown in Fig. 1.[8]



Scheme 1.

The enantioselective addition reaction of diethylzinc to benzaldehyde catalyzed by **5** or **6** was conducted, and the results are shown in Table 2. The reaction was carried out in dry toluene in the presence of 5 mol% of a chiral catalyst at room temperature. The reaction was followed by

Table 1
Yield of hydroxy amide and aminoalcohol

Lactone	Amine	Method	Yield of **3** or **4** (%)[a]	Yield of **5** or **6** (%)[a]
1	**a**	B	53	89
1	**b**	A	81	86
1	**c**	A	92	87
1	**d**	A	84	88
1	**e**	B	46	92
1	**f**	B	18	75
2	**a**	B	58	84
2	**b**	A	46[b]	96
2	**e**	B	72	96
2	**f**	B	47	83

[a] Isolated yield.
[b] The reaction was carried out for 10 days.

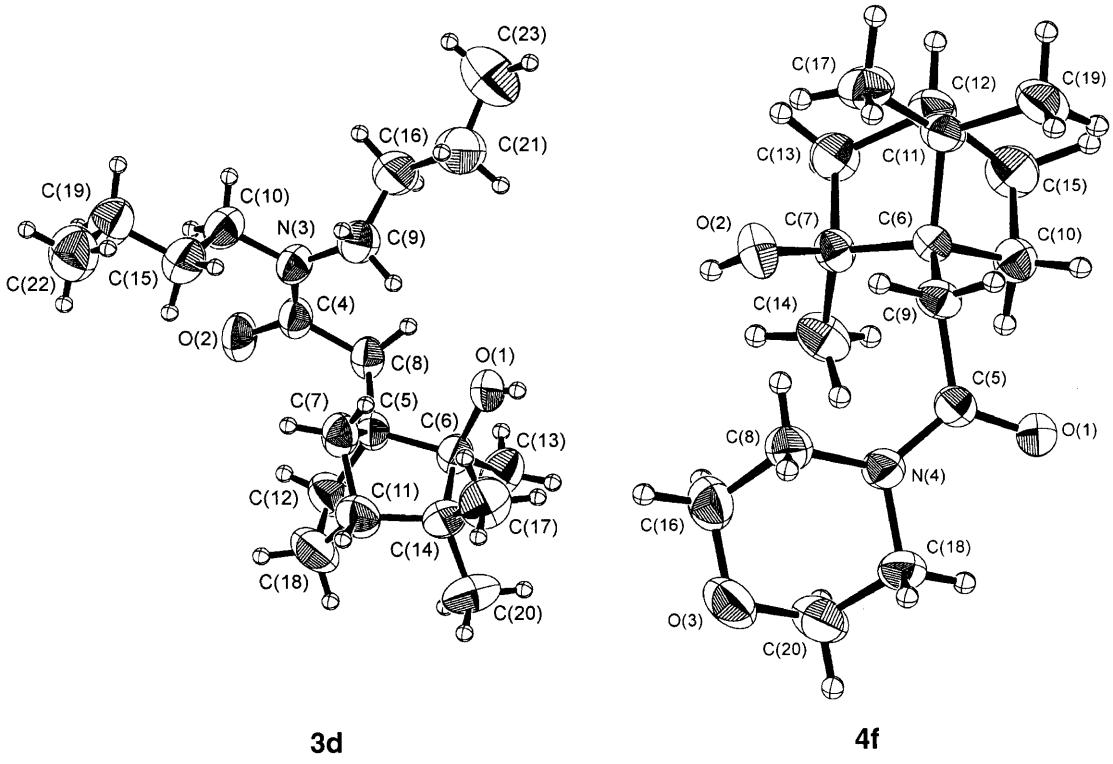
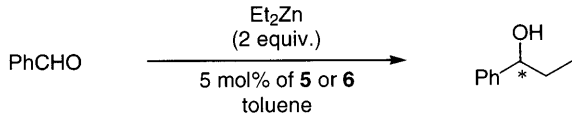


Figure 1. ORTEP views of hydroxy amides **3d** and **4f**

GC to determine the reaction time. After the appropriate time, the reaction mixture was quenched by 5% aqueous HCl, and 1-phenyl-1-propanol was isolated by extraction and purified by column chromatography over silica gel and the ee was determined by HPLC analysis using a chiral stationary phase. When chiral catalyst **5** was used as a catalyst, the addition reaction proceeded quantitatively, and (*S*)-1-phenyl-1-propanol was obtained in high enantiomeric

Table 2
Enantioselective addition reaction of diethylzinc to benzaldehyde with chiral catalyst **5** or **6**

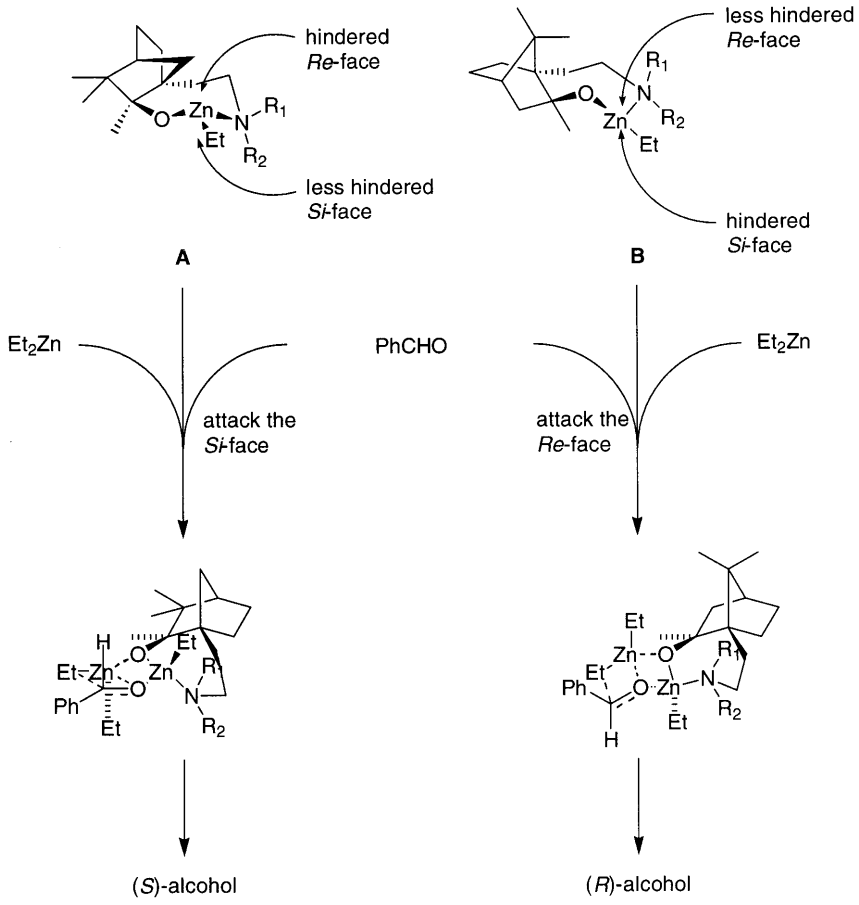


Catalyst	Time (h)[a]	Yield (%)[b]	Ee (%)[c]	Config.[d]
5a	2	98	91	*S*
5b	3	99	93	*S*
5c	2	99	95	*S*
5d	2	99	94	*S*
5e	2	99	94	*S*
5f	3	99	90	*S*
6a	3	99	56	*R*
6b	2	99	60	*R*
6e	3	99	55	*R*
6f	3	99	79	*R*

[a] Reaction was followed by GC.
[b] Determined by GC.
[c] Determined by HPLC using a Chiralcel OD-H column.
[d] Determined by the sign of the specific optical rotation.

excess. The maximum value of 95% ee was obtained with *N*,*N*-dipropyl substituted aminoalcohol **5c**. In the case of chiral catalyst **6**, the reaction also proceeded quantitatively, but moderate ee of 1-phenyl-1-propanol was obtained with *R*-configuration. The length of the nitrogen substituents had virtually no effect on the reaction (catalysts **6a**, **6b** and **6e**) and (*R*)-alcohol was obtained in 55–60% ee. On the other hand, if the catalyst **6f**, which was prepared from morpholine, was used, the ee value was increased to 79%.

In the postulated mechanism reported previously,[5] in situ formed zinc aminoalkoxide **A** or **B** acted as an actual catalyst (Scheme 2). When aldehyde oxygen coordinated with zinc aminoalkoxide **A**, aldehyde oxygen attacked the less hindered *Si*-face of the zinc atom and 7/4/4 tricyclic intermediate was formed;[9] then the zinc ethyl group reacted with aldehyde from the *Si* aldehyde face and (*S*)-enriched product was obtained. In the case of zinc aminoalkoxide **B**, aldehyde oxygen coordinated with zinc aminoalkoxide from the less hindered *Re*-face of the zinc atom and (*R*)-enriched product was obtained. In the reaction with catalyst **5**, there is no significant difference in the ee value among the nitrogen substituents, or it slightly decreased when **5f** was used. Thus, the stereogenic center of the fenchone skeleton plays the major role for the asymmetric induction. However, if the chiral aminoalcohol **6** was used as a catalyst, nitrogen substituents affected the enantioselectivity and the enantiomeric excess was increased to 79% ee when **6f** was used. In the case of chiral catalysts **5f** and **6f**, the methylene group, which was substituted on the nitrogen atom, of the *Re* zinc face side located on the pseudoaxial position due to the steric hindrance of the norbornane skeleton, and the ether oxygen coordinated weakly with zinc from the *Re* zinc face side; thus, the *Re* zinc face was consequently more hindered (Fig. 2). This factor may result in low selectivity of the reaction with **5f** and relatively high ee value of the reaction with **6f**.



Scheme 2.

Figure 2.

In conclusion, we have synthesized a series of 1,4-aminoalcohols from lactone **1** or **2**, which were prepared from (+)-camphor or (−)-fenchone, respectively. Aminoalcohols **5** and **6** were effective chiral catalysts for the enantioselective addition reaction of diethylzinc to aldehyde, and optically active secondary alcohol was obtained quantitatively with good enantiomeric excess.

3. Experimental

3.1. General

NMR spectra were recorded on a JEOL GSX-400 system or a Bruker DPX-300 system with TMS as an internal standard. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. Mass spectra were recorded on a JEOL JMS-HX110. Optical rotations were measured on a JASCO DIP-370 or a HORIBA SEPA-300. Elemental analyses were performed on an Elementar vario EL. Tetrahydrofuran (THF) was distilled from calcium hydride and stored under sodium wire. Toluene was distilled from phosphorus pentoxide. Diethylzinc was purchased from KANTO as 1.02 M solution in hexane and used as received. Other materials were obtained commercially.

3.1.1. Aluminum chloride-mediated amidation of lactones (Method A)

A solution of amine in THF was added dropwise to aluminum chloride in THF at 0°C and agitated for 20 minutes. The reaction mixture was maintained at the same temperature during the addition. After an additional 30 minutes, the cooling bath was removed and a solution of lactone in THF was added dropwise over 15 minutes and stirred for the appropriate number of hours. The reaction mixture was quenched with water (100 mL) under external cooling, stirred for 30 minutes and extracted three times with diisopropyl ether. The combined organic layers were washed twice with water and dried over sodium sulfate. After filtration and evaporation, the crude product was purified by silica gel column chromatography using hexane and ethyl acetate (8:1) as an eluent to give the corresponding hydroxy amide.

3.1.2. Trimethylaluminum-mediated amidation of lactones (Method B)

3.1.2.1. Preparation of aluminum amide solution. A well-dried Schlenk flask was charged with amine hydrochloride. The Schlenk flask was evacuated twice and flushed with argon, and toluene was added via a syringe. Trimethylaluminum (1.02 M in toluene) was added dropwise to the suspension at 0°C over 15 minutes. After the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for 2 hours until gas evolution had ceased.

3.1.2.2. Amidation of lactones. A well-dried Schlenk flask was charged with lactone. The Schlenk flask was evacuated twice, flushed with argon and toluene was added via syringe. The aluminum amide reagent was added dropwise to the solution at room temperature. After addition, the solution was refluxed for 8 hours and cooled to room temperature. To the reaction mixture, 5% aqueous hydrochloric acid (100 mL) was carefully added and extracted three times with diisopropyl ether. The combined organic layers were washed twice with water and dried over sodium sulfate. After filtration and evaporation, the crude product was purified by silica gel column chromatography using hexane and ethyl acetate (8:1) as an eluent to give corresponding hydroxy amide.

3a: Following Method B, **3a** was prepared from 0.93 g of dimethylamine hydrochloride (11 mmol), 11.6 mL of trimethylaluminum (1.02 M in toluene, 11 mmol) and 1.0 g of **1** (5.2 mmol). 53% yield (0.65 g, 2.7 mmol), colorless crystals; ^{1}H NMR (δ, $CDCl_3$): 0.93 (3H, s), 1.00 (3H, s), 1.08 (3H, s), 1.12–1.16 (1H, m), 1.32–1.63 (4H, m), 1.66–1.70 (1H, m), 2.17–2.26 (1H, m), 2.45

(1H, d, $J=14.8$ Hz), 2.70 (1H, d, $J=14.8$ Hz), 2.95 (3H, s), 3.08 (3H, s), 3.39 (1H, br s); ^{13}C NMR (δ, $CDCl_3$): 19.28, 23.75, 24.62, 25.35, 31.35, 34.25, 35.63, 38.31, 38.34, 45.10, 48.34, 54.40, 80.76, 173.86; IR: 3324, 2950, 1604 cm^{-1}; $[\alpha]_D^{25}$: −32.7 ($c=1.06$, $CHCl_3$); mp: 136–137°C. Anal. calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.28; H, 10.61; N, 5.82.

3c: Following Method A, **3c** was prepared from 4.8 g of dipropylamine (47 mmol), 2.1 g of aluminum chloride (17 mmol) and 1.0 g of **1** (5.2 mmol). The reaction mixture was stirred for 72 hours. 92% yield (1.42 g, 4.8 mmol), colorless crystals; ^{1}H NMR (δ, $CDCl_3$): 0.89 (3H, t, $J=7.2$ Hz), 0.93 (3H, s), 0.93 (3H, t, $J=7.2$ Hz), 1.00 (3H, s), 1.07 (3H, s), 1.12 (1H, dd, $J=10.2$ and 1.4 Hz), 1.36–1.42 (2H, m), 1.53–1.65 (6H, m), 1.68–1.69 (1H, m), 2.16 (1H, dd, $J=10.0$ and 1.8 Hz), 2.46 (1H, d, $J=14.7$ Hz), 2.63 (1H, d, $J=14.7$ Hz), 3.18–3.34 (4H, m), 3.85 (1H, br s); ^{13}C NMR (δ, $CDCl_3$): 11.66, 11.84, 19.83, 21.32, 22.77, 24.12, 25.11, 25.85, 32.28, 34.35, 38.69, 45.50, 48.43, 48.69, 50.88, 54.72, 80.89, 173.82; IR: 3352, 2964, 1620 cm^{-1}; $[\alpha]_D^{25}$: −22.4 ($c=1.03$, $CHCl_3$); mp: 120–121°C. Anal. calcd for $C_{18}H_{33}NO_2$: C, 73.17; H, 11.26; N, 4.74. Found: C, 73.14; H, 11.07; N, 4.67.

3d: Following Method A, **3d** was prepared from 6.1 g of dibutylamine (47 mmol), 2.1 g of aluminum chloride (17 mmol) and 1.0 g of **1** (5.2 mmol). The reaction mixture was stirred for 72 hours. 84% yield (1.42 g, 4.4 mmol), colorless crystals; ^{1}H NMR (δ, $CDCl_3$): 0.92 (3H, t, $J=7.3$ Hz), 0.93 (3H, s), 0.96 (3H, t, $J=7.3$ Hz), 1.00 (3H, s), 1.07 (3H, s), 1.09–1.17 (1H, m), 1.21–1.65 (12H, m), 1.66–1.72 (1H, m), 2.11–2.21 (1H, m), 2.45 (1H, d, $J=14.7$ Hz), 2.62 (1H, d. $J=14.7$ Hz), 3.18–3.39 (4H, m), 3.82 (1H, br s); ^{13}C NMR (δ, $CDCl_3$): 14.25, 14.31, 19.84, 20.50, 20.73, 24.14, 25.13, 25.86, 30.26, 31.71, 32.27, 34.38, 38.69, 45.50, 46.56, 48.71, 48.98, 54.74, 80.90, 173.66; IR: 3377, 2931, 1620 cm^{-1}; $[\alpha]_D^{25}$: −20.1 ($c=0.97$, $CHCl_3$); mp: 118–119°C. Anal. calcd for $C_{20}H_{37}NO_2$: C, 74.25; H, 11.53; N, 4.33. Found: C, 74.15; H, 11.54; N, 4.35.

3e: Following Method B, **3e** was prepared from 1.2 g of pyrrolidine hydrochloride (11 mmol), 11.6 mL of trimethylaluminum (1.02 M in toluene, 11 mmol) and 1.0 g of **1** (5.2 mmol). 46% yield (0.64 g, 2.4 mmol), colorless crystals; ^{1}H NMR (δ, $CDCl_3$): 0.93 (3H, s), 1.01 (3H, s), 1.07 (3H, s), 1.14 (1H, dd, $J=9.9$ and 1.2 Hz), 1.32–1.42 (2H, m), 1.52–1.62 (2H, m), 1.68–1.71 (1H, m), 1.82–1.98 (4H, m), 2.23–2.26 (1H, m), 2.40 (1H, d, $J=15.1$ Hz), 2.63 (1H, d, $J=15.1$ Hz), 3.43–3.53 (4H, m), 3.91 (1H, br s); ^{13}C NMR (δ, $CDCl_3$): 19.39, 23.56, 24.37, 25.31, 26.12, 31.97, 36.10, 38.12, 45.12, 45.69, 47.35, 48.21, 48.80, 54.09, 80.40, 172.28; IR: 3423, 2966, 1612 cm^{-1}; $[\alpha]_D^{25}$: −32.7 ($c=1.01$, $CHCl_3$); mp: 119–120°C. Anal. calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.37; H, 10.23; N, 5.31.

3f: Following Method B, **3f** was prepared from 1.4 g of morpholine hydrochloride (11 mmol), 11.6 mL of trimethylaluminum (1.02 M in toluene, 11 mmol) and 1.0 g of **1** (5.2 mmol). 18% yield (0.26 g, 0.94 mmol), colorless crystals; ^{1}H NMR (δ, $CDCl_3$): 0.93 (3H, s), 0.99 (3H, s), 1.09 (3H, s), 1.15 (1H, dd, $J=9.8$ and 1.3 Hz), 1.32–1.41 (1H, m), 1.46–1.64 (3H, m), 1.70–1.71 (1H, m), 2.09 (1H, dd, $J=9.8$ and 1.7 Hz), 2.40 (1H, d, $J=14.2$ Hz), 2.66 (1H, br s), 2.76 (1H, d, $J=14.2$ Hz), 3.55–3.70 (8H, m); ^{13}C NMR (δ, $CDCl_3$): 19.56, 24.22, 25.09, 25.62, 30.66, 33.89, 38.81, 42.34, 45.38, 47.41, 48.74, 54.88, 67.09, 67.36, 81.42, 172.64; IR: 3357, 2933, 1620 cm^{-1}; $[\alpha]_D^{25}$: −32.0 ($c=1.00$, $CHCl_3$); mp: 122–123°C. Anal. calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.27; H, 9.57; N, 4.99.

4a: Following Method B, **4a** was prepared from 0.93 g of dimethylamine hydrochloride (11 mmol), 11.6 mL of trimethylaluminum (1.02 M in toluene, 11 mmol) and 1.0 g of **2** (5.2 mmol). 58% yield (0.73 g, 3.0 mmol), colorless crystals; ^{1}H NMR (δ, $CDCl_3$): 0.87 (3H, s), 1.05–1.18 (1H, m), 1.21 (6H, s), 1.28 (1H, d, $J=12.6$ Hz), 1.50–1.85 (4H, m), 2.13 (1H, dt, $J=12.6$ and 3.6 Hz), 2.44 (1H, d, $J=13.0$ Hz), 2.57 (1H, d, $J=13.0$ Hz), 2.99 (3H, S), 3.14 (3H, s), 4.66 (1H,

br s); ^{13}C NMR (δ, $CDCl_3$): 21.20, 21.41, 27.07, 28.53, 29.83, 31.38, 35.80, 38.77, 44.71, 47.53, 50.76, 55.54, 78.57, 174.58; IR: 3383, 2939, 1612 cm^{-1}; $[\alpha]_D^{25}$: −45.9 ($c=1.00$, $CHCl_3$); mp: 77.5–79.0°C. Anal. calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.27; H, 10.60; N, 5.82.

4e: Following Method B, **4e** was prepared from 1.2 g of pyrrolidine hydrochloride (11 mmol), 11.6 mL of trimethylaluminum (1.02 M in toluene, 11 mmol) and 1.0 g of **2** (5.2 mmol). 72% yield (0.98 g, 3.7 mmol), colorless crystals; ^{1}H NMR (δ, $CDCl_3$): 0.87 (3H, s), 1.07–1.18 (1H, m), 1.22 (3H, s), 1.24 (3H, s), 1.27 (1H, d, $J=12.7$ Hz), 1.45–2.02 (8H, m), 2.13 (1H, dt, $J=12.7$ and 3.6 Hz), 2.28 (1H d, $J=12.8$ Hz), 2.59 (1H, d, $J=12.8$ Hz), 3.36–3.60 (4H, m), 4.82 (1H, br s); ^{13}C NMR (δ, $CDCl_3$): 21.19, 21.47, 24.43, 26.28, 27.09, 28.63, 30.20, 33.54, 44.77, 46.05, 47.53, 47.74, 50.70, 55.55, 78.50, 172.97; IR: 3332, 2931, 1604 cm^{-1}; $[\alpha]_D^{25}$: −18.1 ($c=1.00$, $CHCl_3$); mp: 77.5–79.0°C. Anal. calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.36; H, 10.26; N, 5.31.

4f: Following Method B, **4f** was prepared from 1.4 g of morpholine hydrochloride (11 mmol), 11.6 mL of trimethylaluminum (1.02 M in toluene, 11 mmol) and 1.0 g of **2** (5.2 mmol). 47% yield (0.68 g, 2.4 mmol), colorless crystals; ^{1}H NMR (δ, $CDCl_3$): 0.87 (3H, s), 1.07–1.17 (1H, m), 1.22 (3H, s), 1.23 (3H, s), 1.29 (1H, d, $J=12.8$ Hz), 1.43–1.54 (1H, m), 1.56–1.65 (1H, m), 1.68–1.84 (2H, m), 2.13 (1H, dt, $J=12.8$ and 3.5 Hz), 2.37 (1H, d, $J=13.0$ Hz), 2.62 (1H, d, $J=13.0$ Hz), 3.51–3.86 (8H, m), 4.33 (1H, br s); ^{13}C NMR (δ, $CDCl_3$): 21.22, 21.38, 27.06, 28.55, 29.69, 30.89, 42.16, 44.66, 47.41, 47.59, 50.84, 55.36, 66.88, 66.97, 78.65, 173.09; IR: 3382, 2931, 1608 cm^{-1}; $[\alpha]_D^{25}$: −41.6 ($c=1.00$, $CHCl_3$); mp: 140.5–142.0°C. Anal. calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.38; H, 9.57; N, 5.03.

3.2. Preparation of 1,4-aminoalcohols

A solution of amide in THF was added dropwise to a suspension of lithium aluminum hydride in THF at 0°C for 30 minutes. The reaction mixture was refluxed for 8 hours, then cooled and quenched with water. 10% aqueous sodium hydroxide (100 mL) was added and the mixture was stirred for 30 minutes. The aqueous layer was extracted three times with diisopropyl ether and the combined organic layers were washed twice with water and dried over sodium sulfate. After filtration and evaporation, the crude product was purified by alumina column chromatography using hexane and ethyl acetate (3:1) as an eluent to give the corresponding 1,4-aminoalcohol.

5a: **5a** was prepared from 0.5 g of **3a** (2.1 mmol) and 0.24 g of lithium aluminum hydride (6.3 mmol). 89% yield (0.41 g, 1.8 mmol), viscous oil; ^{1}H NMR (δ, $CDCl_3$): 0.83–0.89 (1H, m), 0.88 (3H, s), 0.99 (3H, s), 1.05 (3H, s), 1.08–1.19 (1H, m), 1.25–1.68 (5H, m), 1.86 (1H, ddd, $J=14.6$, 11.2 and 3.4 Hz), 2.08–2.16 (2H, m), 2.22 (6H, s), 2.44–2.55 (1H, m); ^{13}C NMR (δ, $CDCl_3$): 19.38, 24.20, 25.61, 25.79, 30.17, 33.17, 37.42, 44.34, 44.66, 48.54, 56.60, 57.05, 78.70; IR: 3427, 3126, 2958 cm^{-1}; $[\alpha]_D^{25}$: −19.4 ($c=0.92$, $CHCl_3$); HRMS (FAB) calcd for $C_{14}H_{28}NO$ $[M+H]^+$: 226.2172. Found: m/z 226.2174.

5c: **5c** was prepared from 0.5 g of **3c** (1.7 mmol) and 0.19 g of lithium aluminum hydride (5.1 mmol). 87% yield (0.41 g, 1.6 mmol), viscous oil; ^{1}H NMR (δ, $CDCl_3$): 0.87 (6H, t, $J=7.5$ Hz), 0.89 (3H, s), 0.91 (1H, d, $J=1.5$ Hz), 0.99 (3H, s), 1.04 (3H, s), 1.13 (1H, dt, $J=3.0$ and 12.2 Hz), 1.27–1.65 (9H, m), 1.92 (1H, ddd, $J=15.4$, 11.4 and 3.6 Hz), 2.10 (1H, dd, $J=9.4$ and 1.9 Hz), 2.21–2.34 (3H, m), 2.48–2.62 (3H, m), 6.22 (1H, br s); ^{13}C NMR (δ, $CDCl_3$): 12.44, 19.27, 19.95, 24.50, 25.90, 26.27, 30.04, 33.79, 37.70, 44.80, 49.08, 52.28, 55.68, 57.29, 79.19; IR: 3458, 3099, 2960 cm^{-1}; $[\alpha]_D^{25}$: +12.9 ($c=1.02$, $CHCl_3$); HRMS (FAB) calcd for $C_{18}H_{36}NO$ $[M+H]^+$: 282.2797. Found: m/z 282.2801.

5d: **5d** was prepared from 0.5 g of **3d** (1.5 mmol) and 0.17 g of lithium aluminum hydride (4.5 mmol). 88% yield (0.42 g, 1.4 mmol), viscous oil; ^{1}H NMR (δ, $CDCl_3$): 0.88 (3H, s), 0.92 (6H, t, $J=7.2$ Hz), 1.00 (3H, s), 1.04 (3H, s), 1.10–1.18 (1H, m), 1.18–1.69 (14H, m), 1.84–1.98 (1H, m), 2.08–2.14 (1H, m), 2.21–2.35 (3H, m), 2.50–2.63 (3H, m); ^{13}C NMR (δ, $CDCl_3$): 14.47, 19.96, 21.30, 24.51, 25.92, 26.29, 28.13, 30.17, 33.93, 37.68, 44.76, 49.07, 52.27, 53.32, 57.37, 79.06; IR: 3445, 3097, 2958 cm^{-1}; $[\alpha]_D^{25}$: −11.7 ($c=0.97$, $CHCl_3$); HRMS (FAB) calcd for $C_{20}H_{40}NO$ [M+H]$^+$: 310.3110. Found: m/z 310.3106.

5e: **5e** was prepared from 0.5 g of **3e** (1.9 mmol) and 0.21 g of lithium aluminum hydride (5.7 mmol). 92% yield (0.44 g, 1.7 mmol), viscous oil; ^{1}H NMR (δ, $CDCl_3$): 0.86 (1H, d, $J=9.4$ Hz), 0.89 (3H, s), 1.00 (3H, s), 1.06 (3H, s), 1.13 (1H, dt, $J=3.1$ and 12.3 Hz), 1.24–1.35 (1H, m), 1.45–1.52 (2H, m), 1.56–1.61 (1H, m), 1.64–1.66 (1H, m), 1.74–1.78 (4H, m), 1.83–1.90 (1H, m), 2.14–2.17 (1H, m), 2.24–2.29 (1H, ddd, $J=12.3$, 5.8 and 3.4 Hz), 2.45–2.47 (2H, m), 2.61–2.63 (2H, m), 2.73–2.80 (1H, m), 6.24 (1H, br s); ^{13}C NMR (δ, $CDCl_3$): 19.53, 23.34, 24.17, 25.54, 25.81, 31.58, 33.07, 37.55, 37.61, 44.34, 48.54, 48.62, 53.49, 53.73, 56.65, 78.85; IR: 3413, 3116, 2960 cm^{-1}; $[\alpha]_D^{25}$: −5.1 ($c=1.02$, $CHCl_3$); HRMS (FAB) calcd for $C_{16}H_{30}NO$ [M+H]$^+$: 252.2327. Found: m/z 252.2329.

5f: **5f** was prepared from 0.15 g of **3f** (0.5 mmol) and 0.06 g of lithium aluminum hydride (1.5 mmol). 75% yield (0.11 g, 0.40 mmol), viscous oil; ^{1}H NMR (δ, $CDCl_3$): 0.90 (3H, s), 0.93 (1H, dd, $J=9.5$ and 1.0 Hz), 0.99 (3H, s), 1.06 (3H, s), 1.18 (1H, dt, $J=3.8$ and 12.7 Hz), 1.28–1.37 (1H, m), 1.41–1.50 (2H, m), 1.57–1.62 (1H, m), 1.58–1.68 (1H, m), 1.91 (1H, ddd, $J=15.2$, 10.5 and 4.5 Hz), 2.05–2.08 (1H, m), 2.28–2.34 (1H, m), 2.35–2.43 (2H, m), 2.48–2.55 (1H, m), 2.55–2.2.66 (2H, m), 3.70–3.76 (4H, m); ^{13}C NMR (δ, $CDCl_3$): 19.98, 24.42, 25.77, 26.14, 28.59, 32.94, 38.01, 44.95, 49.03, 53.80, 56.70, 56.87, 67.09, 79.94; IR: 3485, 3165, 2958 cm^{-1}; $[\alpha]_D^{25}$: −6.2 ($c=0.83$, $CHCl_3$); HRMS (FAB) calcd for $C_{16}H_{30}NO_2$ [M+H]$^+$: 268.2277. Found: m/z 268.2260.

6a: **6a** was prepared from 0.5 g of **4a** (2.1 mmol) and 0.24 g of lithium aluminum hydride (6.3 mmol). 84% yield (0.40 g, 1.8 mmol), viscous oil; ^{1}H NMR (δ, $CDCl_3$): 0.85 (3H, s), 1.05 (1H, ddd, $J=12.3$, 9.1 and 5.4 Hz), 1.22–1.45 (3H, m), 1.23, (3H, s), 1.26 (3H, s), 1.52–1.80 (4H, m), 2.06 (1H, dt, $J=12.6$ and 3.6 Hz), 2.22 (6H, s), 2.26–2.46 (2H, m); ^{13}C NMR (δ, $CDCl_3$): 21.23, 22.17, 26.34, 26.84, 29.27, 31.19, 44.86, 46.27, 47.70, 50.04, 54.81, 55.89, 77.73; IR: 3391, 3203, 2949 cm^{-1}; $[\alpha]_D^{25}$: +16.0 ($c=1.02$, $CHCl_3$); HRMS (FAB) calcd for $C_{14}H_{28}NO$ [M+H]$^+$: 226.2172. Found: m/z 226.2177.

6e: **6e** was prepared from 0.5 g of **4e** (1.9 mmol) and 0.21 g of lithium aluminum hydride (5.7 mmol). 96% yield (0.45 g, 1.8 mmol), colorless crystals; ^{1}H NMR (δ, $CDCl_3$): 0.84 (3H s), 1.06 (1H, ddd, $J=12.4$, 9.1 and 5.6 Hz), 1.23 (3H, s), 1.29 (3H, s), 1.25–1.32 (2H, m), 1.43 (1H, ddd, $J=15.2$, 7.8 and 2.7 Hz), 1.53–1.83 (8H, m), 2.04–2.04 (1H, m), 2.44–2.53 (3H, m), 2.54–2.63 (2H, m), 2.63–2.72 (1H, m); ^{13}C NMR (δ, $CDCl_3$): 21.12, 21.96, 23.21, 26.80, 27.49, 29.28, 30.98, 46.10, 47.58, 49.97, 52.33, 53.41, 54.77, 77.65; IR: 3332, 2931 cm^{-1}; $[\alpha]_D^{25}$: +17.6 ($c=1.00$, $CHCl_3$); mp: 82–83°C. Anal. calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.43; H, 11.49; N, 5.46.

6f: **6f** was prepared from 0.5 g of **4f** (1.8 mmol) and 0.21 g of lithium aluminum hydride (5.4 mmol). 83% yield (0.39 g, 1.5 mmol), colorless crystals; ^{1}H NMR (δ, $CDCl_3$): 0.85 (3H s), 1.02–1.13 (1H, m), 1.21 (3H, s), 1.29 (3H, s), 1.22–1.45 (3H, m), 1.52–1.86 (4H, m), 2.02–2.11 (1H, m), 2.37–2.65 (6H, m), 3.66–3.76 (4H, m); ^{13}C NMR (δ, $CDCl_3$): 21.23, 22.04, 24.66, 26.81, 29.39, 30.79, 46.12, 47.63, 50.15, 53.53, 54.91, 55.11, 66.74, 78.01; IR: 3307, 2964 cm^{-1}; $[\alpha]_D^{25}$: +11.4 ($c=1.03$, $CHCl_3$); mp: 49–50°C. Anal. calcd for $C_{16}H_{29}NO_2$: C, 71.87; H, 10.93; N, 5.24. Found: C, 71.83; H, 10.76; N, 5.08.

3.3. Typical procedure for addition reaction of diethylzinc to aldehydes

A well-dried Schlenk flask was charged with aminoalcohol (0.05 mmol). The Schlenk flask was evacuated twice and flushed with argon. Toluene (2.0 mL) was added and the solution was cooled to 0°C followed by addition of diethylzinc (1.02 M solution in hexane, 2.0 mL, 2.0 mmol). The reaction mixture was stirred at room temperature for 30 minutes and the reaction temperature was changed to the appropriate degree. Then, aldehyde (1.0 mmol) was added directly via a syringe and stirred for the appropriate number of hours. The reaction was quenched by addition of 2.0 M aqueous hydrochloric acid (10 mL) and the resulting mixture was extracted three times with diisopropyl ether. The combined organic layers were washed twice with water and dried over sodium sulfate. After filtration and evaporation, the crude product was purified by silica gel column chromatography using hexane and ethyl acetate (8:1) as an eluent to give the corresponding alcohol. The enantiomeric excess of the product was determined by analytical HPLC using *n*-hexane and 2-propanol (95:5) as an eluent and flow rate was 0.5 mL/min.

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