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Selective reaction of camphor-derived *exo*-formyl [2.2.1]bicyclic carbinol with alkyl primary amines: application to the preparation of new chiral catalysts for asymmetric reduction of aryl ketones

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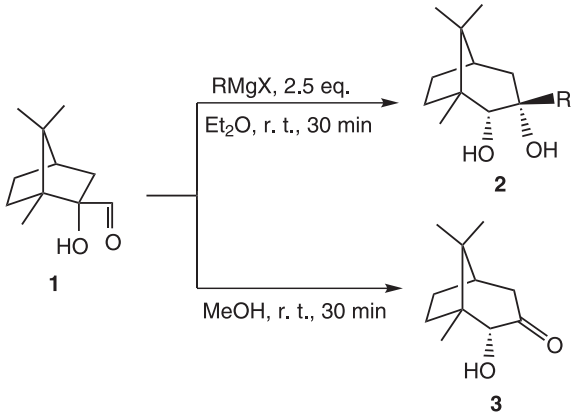
ABSTRACT

Reaction of camphor-derived *exo*-formyl [2.2.1]bicyclic carbinol with various alkyl primary amines gave regio- and stereo-specific [3.2.1]bicyclic α-amino ketones. A detailed mechanism of the reaction was discussed. This reaction was further applied to the preparation of some camphor-derived oxazaborolidines, one of which proved to be an efficient chiral catalyst for the asymmetric borane reduction of prochiral aryl ketones at room temperature.

1. Introduction

Several decades ago, it had been reported that α-hydroxy imines could rearrange in the presence of heat, forming α-amino ketones.[1] Later on, Preiss and co-workers had applied the thermal reaction to the conversion of 1-methylimino phenylmethyl cyclopentanols into 2-methylamino- 2-phenylcyclohexanone derivatives for medicinal purposes.[2] They concluded that ring expansion had occurred to the cyclopentyl moiety of the reactant. Furthermore, the enantio-controlled α-substituted α-amino cyclohexanones had been prepared also by utilizing thermal rearrangement, and starting from their corresponding imino cyclohexanols.[3] However, it was believed that the mechanism of this reaction involved a conventional 1,2-carbon migration instead of ring expansion. Recently, we had found that camphor-derived *exo*-formyl [2.2.1]bicyclic carbinol (**1**, Scheme 1) underwent consecutive ring expansion-alkylation in the presence of *C*-nucleophiles, and the regio- and stereo-specific alkyl [3.2.1] bicyclic diol **2** was furnished.[4] On the other hand, the solution of **1** in blank methanol afforded regio- and stereo-specific bicyclic hydroxy ketone **3**.[5]

All the interesting results mentioned above prompted us to further investigate the reaction of carbinol **1** with alkyl primary amines, which could be *N*-nucleophile donors. Herein, we report the results of the reaction as well as the application of products to the asymmetric reduction of prochiral aryl ketones.



Scheme 1. Ring expansion and alkylation of **1**.

2. Results and discussion

After being prepared from camphor in three steps using the procedures previously reported, carbinol **1**[4] was immediately treated with various alkyl primary amines individually in toluene at reflux for 3 h as shown in Table 1. Surprisingly, in each case, the

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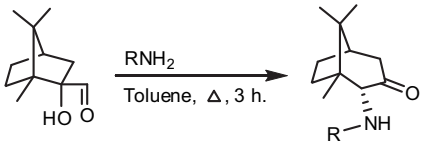
Table 1
Results of the reaction of *exo*-formyl [2.2.1]bicyclic carbinol **1** with alkyl primary amines



1 **4**

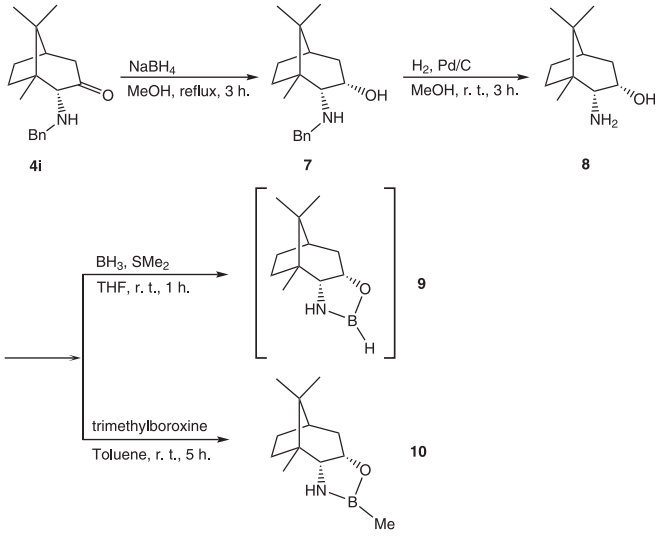
Entry	Primary amine	Product **4**	Yield[c] (%)
1	$MeNH_2$	**4a** (R=Me)[a]	64
2	$EtNH_2$	**4b** (R=Et)[b]	66
3	*n*-$PrNH_2$	**4c** (R=*n*-Pr)	75
4	*i*-$PrNH_2$	**4d** (R=*i*-Pr)	74
5	$CH_2CHCH_2NH_2$	**4e** ($R=CH_2CHCH_2$)	86
6	*n*-$BuNH_2$	**4f** (R=*n*-Bu)	77
7	*t*-$BuNH_2$	**4g** (R=*t*-Bu)[b]	82
8		**4h** (R=Cyclohexyl)	66
9	$BnNH_2$	**4i** (R=Bn)	85

[a] The structure of this compound was found to be unstable in the air at room temperature.
[b] Single crystal was obtained for the X-ray crystallography.
[c] Yield of isolated product.

reaction exclusively provided [3.2.1]bicyclic α-amino ketone **4**,[6] in which C-2 possesses the new amino group with *endo* orientation. The orientation of amino groups on **4b** and **4g** was determined with X-ray diffraction.[6b,c] Among all possible regio- and stereoisomers of product, structure **4** was the only one observed. The yield of **4** is approximately proportional to the number of carbon atoms contained in the alkyl moiety of amine (entries 1–5). It is deduced that the primary amine with larger alkyl group possesses higher electron density, which is necessary for the ring expansion to occur. Nevertheless, the reaction with cyclohexyl amine (entry 8), for some unknown reasons, did not give the product with high yield.

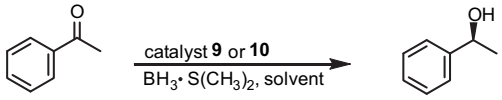
A plausible mechanism for the reaction shown in Table 1 is illustrated in Fig. 1. Presumably, an imino [2.2.1]bicyclic carbinol **5** was formed at the beginning of the reaction. Then the nitrogen atom on **5** abstracted the proton from hydroxyl group on C2, such that C1–C2 bond was forced to break, similar to the situation occurred in the solution of **1** in blank methanol (Scheme 1).[5] Thus, the C1 immediately attacked C3 from *re*-face, providing bicyclic α-amino ketone **4**. In order to confirm the mechanism of the reaction, carbinol **1** was particularly treated with benzyl amine in dichloromethane at room temperature for 30 min. Then, intermediate **6** was expected to be detected upon work up. Indeed, the existence of structure **6** was verified with NMR experiments. On the ^1H NMR spectrum of crude **6**, a singlet signal appeared at 7.97 ppm, corresponding to the proton atom of imino moiety. Furthermore, on the ^{13}C NMR of **6**, a signal appeared at 170 ppm, corresponding to the carbon atom of the imino group.

For one of the applications of the title reaction, bicyclic amino ketone **4i** (entry 9 in Table 1) was adopted as the precursor of some new oxazaborolidines (Scheme 2), which were then employed as chiral catalysts for the asymmetric reduction of prochiral ketones.[7–9] Reduction of **4i** with sodium borohydride in hot methanol smoothly gave amino alcohol **7**, in which the benzyl group was then removed under hydrogenolysis conditions, providing bicyclic amino alcohol **8**.[10,11] Consequently, the new oxazaborolidines were prepared using the procedures reported by Masui and Shioiri.[9] Treatments of **8** with borane in THF, and with trimethyl boroxine in toluene afforded oxazaborolidines **9** and **10**, respectively. Since **9** is unstable and may not be isolated, it was prepared in situ for the following reduction reaction of acetophenone (Table 2).[9,12]



Scheme 2. Preparation of oxazaborolidines **9** and **10**.

Table 2
Effects of chiral catalysts **9** and **10** on the asymmetric reduction of acetophenone



Entry	Catalyst (equiv)	Solvent	*T* (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	**9** (0.1)	THF	rt[c]	1	83	87
2	**10** (0.1)	THF	rt	1	93	91
3	**10** (0.1)	THF	−20	1	88	72
4	**10** (0.1)	THF	0	1	87	70
5	**10** (0.05)	THF	rt	1	93	86
6	**10** (0.2)	THF	rt	1	91	91
7	**10** (0.1)	CH_2Cl_2	rt	3	92	89
8	**10** (0.1)	Toluene	rt	8	84	61

[a] Yield of isolated product.
[b] A chiralcel OD-RH column was employed for HPLC analysis for the assignment of configuration of the product, and for the determination of enantiomeric excess (ee) value.
[c] Room temperature.

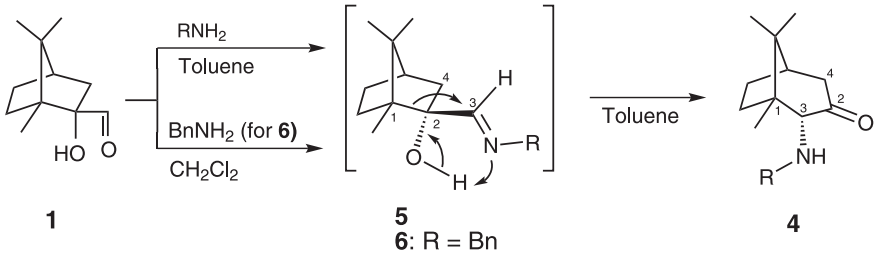
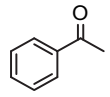
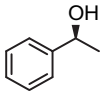
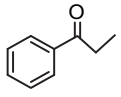
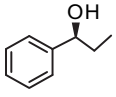
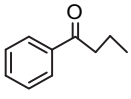
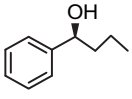
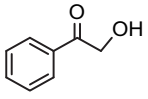
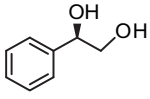
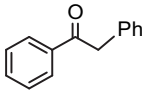
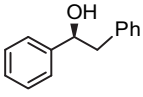
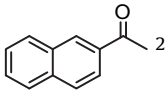
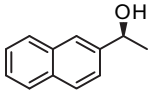
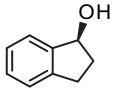
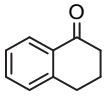
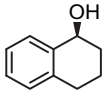


Fig. 1. Plausible mechanism for the reaction of formyl carbinol **1** with primary amines.

Masui and Shioiri had further reported the results of asymmetric reduction of ketones,[9] using α-pinene-derived oxazaborolidines as the catalysts. They concluded that the reaction could be carried out at 25–30 °C, and provide good results. Interestingly, we also found that room temperature was the most convenient and efficient condition for the reaction in the presence of oxazaborolidines **9** and **10**. Furthermore, as shown in Table 2, **10** turned out to be a better chiral catalyst than **9** for the asymmetric reduction of acetophenone in THF (entries 1 and 2). Both yield and stereoselectivity were decreased at low temperatures (entries 3 and 4). Increasing the amount of **10** could not raise the yield and ee (%) value of the secondary alcohol (entry 6). Non-polar solvent, such as CH_2Cl_2 and toluene, could not help increase the stereoselectivity (entries 7 and 8).

Finally, catalytic amount (0.1 equiv) of oxazaborolidine **10** was adopted for the reduction of various prochiral aryl ketones in THF at room temperature. As shown in Table 3, among the starting materials, hydroxy acetophenone (entry 4) was reduced in lowest enantioselectivity although the phenyl diol was obtained in high yield. Excitingly, on the other hand, (*S*)-1-indanol (entry 7) was furnished in almost excellent enantiomeric purity. In addition, the reduction of 1-tetralone (entry 8) also provided the corresponding product in both high chemical and high optical yields.

Table 3
Results of asymmetric reduction of aryl prochiral ketones in the presence of 0.1 equiv of 10 at room temperature

Entry	Ketone	Time (h)	Product[a]	Config.[b]	Yield (%)[c]	ee[d] (%)
1		1		S	93	91
2		1		S	93	80
3		2		S	90	86
4		2		S	98	78
5		4		S	87	82
6		2		S	92	80
7		3		S	97	99
8		3		S	96	98

[a] A chiralcel OD-RH column was used for HPLC analysis for the assignment of configuration of each product.
[b] Configuration.
[c] Yield of isolated product.
[d] In the HPLC analyses, the retention time of each product was compared with that of the corresponding commercially available chiral compound for the determination of ee value.

A plausible structure of the transition state for the reduction of the prochiral ketones in the presence of catalytic amount of oxazaborolidine **10** is shown in Fig. 2.[11] Once the stable double-chair conformation was formed,[13,14] the hydride might be released from borane, and primarily attack the ketone from *re*-face. Thus, a secondary alcohol with *S*-configuration was predominantly afforded.

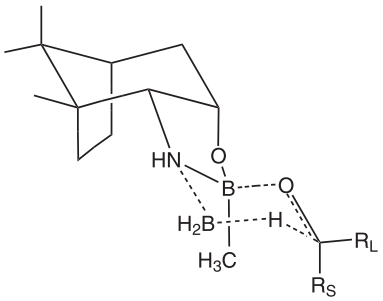


Fig. 2. Plausible structure of the transition state for the reduction of prochiral ketones.

3. Conclusion

In conclusion, the reaction of camphor-derived *exo*-formyl [2.2.1]bicyclic carbinol with alkyl primary amines proved to be regio- and stereoselective, providing [3.2.1]bicyclic α-amino ketones as the products. The reaction was composed of consecutive coupling and ring expansion. This reaction could be applied to the preparation of some oxazaborolidines, which demonstrated to be good chiral catalysts for the asymmetric borane reduction of aryl prochiral ketones at room temperature. Other applications of the title reaction to the synthesis of some more useful compounds are under investigation.

4. Experimental

4.1. General information

Round bottom flasks were employed for carrying out all the reactions. Moisture-sensitive solvents were dried with standard methods and transferred via a syringe when necessary. Crude product solutions were dried on Na_2SO_4, filtered, and then concentrated with a rotary evaporator below 40 °C at ~30 Torr. Flash column chromatography was performed employing 230–400 mesh silica gel. TLC was performed on silica gel sheets with organic binder and detected by 0.5% phosphor-molybdic acid solution in 95% ethanol. Melting points were measured on a Fargo MP-1D apparatus and were uncorrected. An FT/IR spectrophotometer (Perkin–Elmer-paragon 500) was used for obtaining the infrared spectra. Data were expressed as wave number of absorption (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were obtained using a 200 MHz (Varian) spectrometer. Chemical shifts (δ scale) were expressed in parts per million downfield from tetramethylsilane (δ=0.00). ^1H NMR data were presented as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, dd=doublet of doublet, t=triplet, m=multiplet and/or multiple resonances), coupling constant in Hz (Hertz), integration. Optical rotation ([α]) values were recorded at room temperature on JASCO (P-1010), digital polarimeter.

4.2. General procedure for the reaction of carbinol 1 with alkyl primary amines

To a solution of carbinol **1** (0.5 g, 3.23 mmol) in toluene (30 ml) was added alkyl primary amine (1.30 equiv, 4.20 mmol) at room temperature. The reaction mixture was heated at reflux for 3 h

under argon, then cooled to room temperature, and washed with water (30 ml×3). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified with flash column chromatography (*n*-hexanes/EtOAc=3:1) to give the corresponding [3.2.1]bicyclic α-amino ketone (**4**).

4.3. Data of [3.2.1]bicyclic α-amino ketones

4.3.1. Compound ***4a***. Syrup: R_f=0.70 (3:1, hexanes/EtOAc); $[\alpha]_D^{28}$ −55.9 (0.2, CH_2Cl_2); IR (film): 3333 (br), 2956, 2881, 2975, 1708, 1479, 1448 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.91 (s, 1H, C*H*NH), 2.72 (m, 1H), 2.41 (s, 3H, CH_3NH), 2.24 (dd, *J*=3.0, 15.4 Hz, 1H), 2.09 (br s, 1H, N*H*), 1.96–1.88 (m, 2H), 1.61 (m, 1H), 1.43–1.24 (m, 2H), 1.20 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.33, 73.97, 52.31, 46.23, 45.66, 44.50, 38.81, 30.14, 27.09, 24.62, 18.54, 17.60. HRMS calcd for $C_{12}H_{21}NO$: 195.1623; found: 195.1630.

4.3.2. Compound ***4b***. White solid: R_f=0.70 (3:1, hexanes/EtOAc); mp 39–40 °C; $[\alpha]_D^{28}$ −50.9 (0.2, CH_2Cl_2); IR (KBr): 3313 (br), 2962, 2881, 1708, 1479 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.03 (s, 1H, C*H*NH), 2.77–2.52 (m, 3H), 2.25 (dd, *J*=3.0, 15.4 Hz, 1H), 2.04 (br s, 1H), 1.98–1.89 (m, 2H), 1.95 (m, 1H), 1.41–1.14 (m, 2H), 1.21 (s, 3H), 1.07 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.00 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.69, 71.69, 52.19, 46.24, 46.13, 45.70, 44.47, 30.29, 27.11, 24.66, 18.51, 17.58, 15.52. HRMS calcd for $C_{13}H_{23}NO$: 209.1780; found: 209.1788.

4.3.3. Compound ***4c***. Syrup: R_f=0.72 (3:1, hexanes/EtOAc); $[\alpha]_D^{28}$ −48.7 (0.2, CH_2Cl_2); IR (film): 3315 (br), 2958, 2883, 1706, 1477, 1390 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.99 (s, 1H, C*H*NH), 2.70 (m, 1H), 2.49 (m, 2H), 2.21 (dd, *J*=3.0, 15.2 Hz, 1H), 1.93–1.79 (m, 2H), 1.66–1.00 (m, 6H), 1.17 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.88 (t, *J*=7.4 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.64, 71.72, 53.95, 52.26, 46.19, 45.65, 44.44, 30.32, 27.05, 24.61, 23.45, 18.48, 17.55, 11.67. HRMS calcd for $C_{14}H_{25}NO$: 223.1936; found: 223.1942.

4.3.4. Compound ***4d***. Syrup: R_f=0.78 (3:1, hexanes/EtOAc); 80% yield; $[\alpha]_D^{28}$ −4.3 (0.2, CH_2Cl_2); IR (film): 3312 (br), 2925, 2852, 1706, 1449 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.08 (s, 1H, C*H*NH), 2.74 (m, 1H), 2.57 (hept. *J*=6.4 Hz, 1H, MeC*H*Me), 2.24 (dd, *J*=3.2, 11.4 Hz, 1H), 1.96–1.82 (m, 3H), 1.53–1.46 (m, 1H), 1.39–1.13 (m, 2H), 1.21 (s, 3H), 1.02 (d, *J*=4.4 Hz, 3H, CH_3CHCH$_3$), 1.00 (s, 3H), 0.99 (d, *J*=4.4 Hz, 3H, CH$_3$CHCH_3), 0.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 215.46, 67.18, 49.95, 49.13, 46.68, 44.29, 35.54, 26.87, 25.14, 24.96, 23.43, 22.71, 20.93. HRMS calcd for $C_{14}H_{25}NO$: 223.1936; found: 223.1931.

4.3.5. Compound ***4e***. Syrup: R_f=0.74 (3:1, hexanes/EtOAc); $[\alpha]_D^{28}$ −15.2 (0.2, CH_2Cl_2); IR (film): 3320 (br), 3075, 2956, 2390, 1700, 1472, 1396 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.86 (m, 1H, CH_2=C*H*CH$_2$), 5.29–5.13 (m, 2H, CH_2=CHCH$_2$), 3.36 (m, 2H, CH_2=CHCH_2), 3.22 (s, 1H, C*H*NH), 2.76 (m, 1H), 2.34 (m, 1H), 1.99–1.03 (m, 6H), 1.20 (s, 3H), 1.08 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.33, 137.16, 115.59, 70.06, 53.71, 52.19, 46.16, 45.58, 44.43, 30.17, 26.97, 24.55, 18.37, 17.51. HRMS calcd for $C_{14}H_{23}NO$: 221.1780; found: 221.1782.

4.3.6. Compound ***4f***. Syrup: R_f=0.78 (3:1, hexanes/EtOAc); 77% yield; $[\alpha]_D^{28}$ −44.3 (0.2, CH_2Cl_2); IR (film): 3314, 2957, 2876, 1707, 1477 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.05 (s, 1H, C*H*NH), 2.74 (m, 1H), 2.58 (t, *J*=7.2 Hz, 2H, NHCH_2CH$_2$CH$_2$CH$_3$), 2.26 (dd, *J*=3.0, 15.4 Hz, 1H), 1.96–1.89(m, 1H), 1.64–1.16 (m, 9H), 1.21 (s, 3H), 01.02 (s, 3H), 0.98 (s, 3H), 0.90 (t, *J*=7.2 Hz, 3H, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.47, 71.66, 52.14, 51.64, 46.07, 45.53, 44.29, 32.46, 30.95, 26.94, 24.50, 20.21, 18.37, 17.43, 13.87. HRMS calcd for $C_{15}H_{27}NO$: 237.2093; found: 237.2100.

4.3.7. Compound ***4g***. White solid: R_f=0.78 (3:1, hexanes/EtOAc); mp 45–47 °C; 82%yield; $[\alpha]_D^{28}$ −5.5 (0.2, CH_2Cl_2); IR (film): 3352 (br), 2960, 2882, 1703, 1514 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.24 (s, 1H, C*H*NH), 2.74 (m, 1H), 2.24 (dd, *J*=1.4, 14.4 Hz, 1H), 1.99–1.80 (m, 3H), 1.42–1.13 (m, 3H), 1.26 (s, 3H), 0.99 (s, 3H), 0.98 (s, 12H, CH_3 and *t*-BuNH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 213.00, 65.04, 52.32, 50.61, 46.82, 45.93, 44.90, 30.82, 29.56, 27.16, 24.87, 18.53, 18.41. HRMS calcd for $C_{15}H_{27}NO$: 237.2093; found: 237.2096.

4.3.8. Compound ***4h***. Syrup: R_f=0.78 (3:1, hexanes/EtOAc); 66% yield; $[\alpha]_D^{28}$ −24.0 (0.2, CH_2Cl_2); IR (film): 3312, 2956, 2883, 1709, 1476 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.10 (s, 1H, C*H*NH), 2.70 (m, 1H), 2.14–2.03 (m, 2H), 2.20 (dd, *J*=3.0, 15.2 Hz, 1H), 1.97–1.64 (m, 7H), 1.57–1.10 (m, 6H), 1.18 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H), 0.92–0.80 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.42, 68.94, 57.94, 52.03, 46.19, 45.74, 44.52, 34.27, 33.72, 30.33, 27.04, 26.09, 25.23, 25.16, 24.65, 18.48, 17.64. HRMS calcd for $C_{17}H_{29}NO$: 263.2249; found: 263.2248.

4.3.9. Compound ***4i***. Syrup: R_f=0.78 (3:1, hexanes/EtOAc); 82% yield; $[\alpha]_D^{28}$ −8.8 (0.2, CH_2Cl_2); IR (film): 3510 (br), 3077, 2957, 2881, 1710, 1607, 1450 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.18 (m, 5H, $CH_2C_6H_5$), 3.81 (d, *J*=13.2 Hz, 1H, CH_ACH$_B$Ph), 3.73 (d, *J*=13.2 Hz, 1H, CH$_A$CH_BPh), 3.14 (s, 1H, C*H*NH), 2.70 (d, *J*=15.4 Hz, 1H), 2.46 (br s, 1H, CHN*H*), 2.23 (dd, *J*=2.8, *J*=15.4 Hz, 1H), 1.98–1.82 (m, 2H), 1.66 (m, 1H), 1.44–1.20 (m, 2H), 1.15 (s, 3H), 1.03 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.42, 140.61, 128.16, 128.06, 126.74, 70.29, 55.15, 52.41, 46.22, 45.66, 44.45, 30.21, 26.99, 24.55, 18.40, 17.16. HRMS calcd for $C_{18}H_{25}NO$: 271.1936; found: 271.1939.

4.4. Preparation of 7

To a solution of **4i** (0.5 g, 1.85 mmol) in methanol (20 ml) was added sodium borohydride (0.21 g, 5.55 mmol). The reaction mixture was heated at reflux for 3 h, then quenched with water (5 ml), and extracted with ethyl acetate (20 ml×3). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified with flash column chromatography (*n*-hexanes/EtOAc=3:1) to give [3.2.1]bicyclic α-amino alcohol **7** (0.48 g, 96%) as a syrup: R_f=0.80 (3:1, hexanes/EtOAc); $[\alpha]_D^{28}$ −60.9 (0.2, CH_2Cl_2); IR (film): 3377 (br), 3065, 2928, 1452 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.23 (m, 5H, $CH_2C_6H_5$), 3.83 (d, *J*=12.6 Hz, 1H, CH_ACH$_B$Ph), 3.84 (s, 1H, C*H*OH), 3.66 (d, *J*=12.6 Hz, 1H, CH$_A$CH_BPh), 2.63 (dd, *J*=1.2, 5.4 Hz, 1H, C*H*NH), 2.03–1.66 (m, 5H), 1.59 (m, 1H), 1.37–1.10 (m, 2H), 0.86 (s, 6H, 2CH$_3$), 0.84 (s, 3H, CH$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.91, 128.39, 128.17, 127.14, 63.26, 63.07, 52.76, 45.67, 44.18, 43.83, 33.76, 29.35, 26.10, 24.99, 18.78, 17.11. HRMS calcd for $C_{18}H_{27}NO$: 273.2093; found: 273.2089.

4.5. Preparation of 8

To a solution of **7** (0.35 g, 1.28 mmol) in methanol at room temperature was added Pd–C (10%, 0.05 g) and applied hydrogen. The system was stirred at room temperature for 3 h. The reaction mixture was then filtered through Celite, and the filtrate was collected, and concentrated under reduced pressure to give **8** (0.22 g, 92%) as a white solid: R_f=0.20 (3:1, hexanes/EtOAc); mp 124–126 °C; $[\alpha]_D^{28}$ −77.0 (0.2, CH_2Cl_2); IR (KBr): 3358 (br), 2927, 1620, 1430 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.80 (t, *J*=5.5 Hz, 1H, C*H*OH), 2.90 (dd, *J*=1.4, 5.5 Hz, 1H, C*H*NH$_2$), 2.10–1.11 (m, 10H), 0.88 (s, 6H, 2CH$_3$), 0.85 (s, 3H, CH$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 67.24, 55.45, 46.29, 44.14, 43.88, 34.68, 28.30, 26.24, 25.18, 18.65, 17.10. HRMS calcd for $C_{11}H_{21}NO$: 183.1623; found: 183.1621.

4.6. Preparation of 9

To a solution of **8** (0.18 g, 1.00 mmol) in THF (5 ml) was added borane–dimethyl sulfide complex (2.0 M, 5 ml). The reaction mixture was stirred at room temperature for 1 h, then used directly for the reduction of acetophenone as shown in Table 2.

4.7. Preparation of 10

To a solution of **8** (0.18 g, 1.00 mmol) in toluene (20 ml) was added trimethyl boroxine (0.10 g, 0.80 mmol). The reaction mixture was stirred at room temperature under argon for 5 h, then concentrated under reduced pressure to a volume of 5 ml. Toluene (20 ml) was added to the reaction mixture, which was then concentrated to 5 ml again. This process was repeated for two times. Finally, the solvent in the reaction mixture was removed under reduced pressure to give **10** (0.15 g, 90%) as a white solid: R_f=0.80 (3:1, hexanes/EtOAc); mp 130–131 °C; $[\alpha]_D^{28}$ −26.9 (0.2, CH_2Cl_2); IR (KBr): 3380 (br), 2925 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.35 (t, J=7.2 Hz, 1H, C*H*OH), 3.28 (d, J=7.6 Hz, 1H, C*H*NH), 2.63 (br s, 1H), 2.17–2.03 (m, 1H), 1.90–1.22 (m, 6H), 0.87 (s, 3H), 0.85 (s, 3H), 0.73 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 69.20, 62.10, 45.96, 43.42, 34.74, 28.65, 26.64, 24.65, 18.72, 18.61, 17.13, 0.13; ^{11}B NMR ($CDCl_3$) δ 31.1. HRMS calcd for $C_{12}H_{22}BNO$: 207.1794; found: 207.1788.

4.8. General procedure for the reduction of ketones

To a solution of the oxazaborolidine (**9** or **10**) in anhydrous THF (5 ml) was added BH_3–$S(CH_3)_2$ (0.70 ml, 10 M in THF, 1.70 mmol) under argon. The solution of prochiral aryl ketone (2.45 mmol) in anhydrous THF (5 ml) was then added dropwise to the mixture by using an automatic syringe pump over 2 h at room temperature. The reaction mixture was kept stirring at room temperature until the ketone was completely consumed. Hydrochloric acid (2 N) was then added dropwise to quench the reaction, and the system was extracted with diethyl ether (10 ml×3). The organic layers were combined, washed, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (*n*-hexanes/EtOAc=5:1) to give the chiral secondary alcohol.

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6. (a) The structure of compound **4a** was found to be unstable in the air at room temperature; (b) Since compounds **4a**, **4c**–**f**, **4h**, and **4i** are syrup at room temperature (see Experimental), the stereo structures of these compounds were inferred from the stereo structures of **4b** and **4g**, and from the principle of mechanism discussed for the formation of compound **3**, as shown in Scheme 1 and Ref. 5; (c) Crystallographic data for structures **4b** and **4g** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 778512 and CCDC 778513, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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10. The orientation of benzyl amino group on compound **7** was originated from compound **4i**. Furthermore, the NOESY NMR spectra of both **7** and **8** demonstrated that the proton on the carbon atom, which possesses hydroxyl group (C*H*OH) and the proton on the carbon atom, which possesses amino group (C*H*NH_2) are *syn* to each other. Thus, the stereo structure of compound **8** was confirmed.
11. As shown in Experimental Section, the ^1H NMR COSY spectrum of amino alcohol **8** revealed that the triplet signal at 3.80 ppm is corresponding to the proton on carbon atom, which possesses OH group. It is deduced that the triplet signal should be a doublet of doublet signal (dd), and the two coupling constants are identical (J_1=J_2=5.5 Hz). This proton is believed to couple to the proton on carbon atom, which possesses amino group, and also to couple to only one (H_A) of the two protons (H_A and H_B) in the adjacent ring-methylene group. The other proton (H_B) did not couple to the proton, which is corresponding to the signal at 3.80 ppm, according to vicinal Karplus correlation. On the other hand, the quartet signal at 2.90 ppm is corresponding to the proton on the carbon atom, which possesses amino group. This proton is believed to have long range coupling to one of the two protons (H_A and H_B) in the ring-methylene group, which was just mentioned above. Indeed, the possibility of the existence of boat form for amino alcohol **8** could not be excluded. However, based on our molecular model study, the possibility of the existence of chair form should be larger than that of boat form for amino alcohol **8**.
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