Synthesis and Reaction of 1-Azabicyclo[3.1.0]hexane

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The effective formation of 1-azabicyclo[3.1.0]hexane (5) by treatment of 2-(bromomethyl)pyrrolidine hydrobromide (4) with *n*-BuLi was established, with the reaction occurring by a rational reaction pathway *via* the open chain transition state 8 based on intermolecular Br···Li$^+$ coordination (S*N*2 process). The reaction of 5 with electrophiles 13a—n gave the corresponding pyrrolidines 14a—n and piperidine 6, 15a—g, i—n. The selectivity of the products in this reaction appeared to be controlled by equilibrium.

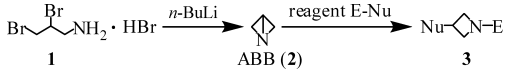
Key words 1-azabicyclo[3.1.0]hexane; lithium coordination; 3-halopiperidine; X-ray crystallographic analysis; 2-(halomethyl)-pyrrolidine

We have recently established an efficient method for synthesis of 1-azabicyclo[1.1.0]butane (ABB) (**2**) with *n*-BuLi from 2,3-dibromopropylamine hydrobromide (**1**), and developed a facile synthetic method for various 3-substituted azetidine derivatives (**3**), as represented in Chart 1.[1—7] We have also reported that a lithium cation of *n*-BuLi promoted the cyclization of **1** to ABB (**2**) bearing a highly strained bicyclic structure.[1,4] This effect of a lithium cation prompted us to synthesize other strained bicyclic systems using this method. We focus herein on the synthesis of 1-azabicyclo[3.1.0]-hexane (ABH) (**5**), which is known as a strained azabicyclic compound,[8,9] and describe the results and the mechanistic considerations of the cyclization of 2-(bromomethyl)pyrrolidine hydrobromide (**4**)[10,11] with a lithium cation, as well as the reaction of ABH (**5**) with some electrophiles.

The cyclization of **4** was attempted in the presence of various bases, as shown in Chart 2. Due to the difficulty of direct ABH analysis, the reactions were evaluated instead by HPLC analysis of 1-benzyl-3-bromopiperidine (**6**), which was formed by the reaction of ABH (**5**) with benzyl bromide. All results are summarized in Table 1.

First, the reaction of **4** was examined in aqueous solution (entries 1—3), since ABH (**5**) was prepared in 25% yield from 2-(chloromethyl)pyrrolidine hydrochloride with aqueous NaOH by Buyle.[12] The cyclization of **4** proceeded dramatically with the use of LiOH as a base, compared with the use of NaOH and KOH (entries 1—3). A lithium cation also increased the yield of ABH (**5**) in the reaction with hydride reagents (NaH, LiH) and amide reagents ($NaNH_2$, $LiNH_2$, LDA) as bases (entries 4—7, 9). The employment of *n*-BuLi gave rise to ABH (**5**) in quantitative yield and showed the best result (entry 11). The addition of a crown ether, 12-crown-4, trapping a lithium cation into the reaction with $LiNH_2$ decreased the yield of ABH (**5**), and its yield was almost the same as that of $NaNH_2$ (entries 6, 8). The similar results were obtained in the reaction with *n*-BuLi and *n*-BuMgCl (entries 10, 12). These results described above indicate that a lithium cation activated the C–Br bond in **4** by coordination to the Br atom and promoted the cyclization of **4**.[1,4,13] The reaction pathway was first estimated to involve the five-membered cyclic transition state **7** based on the intramolecular Br···Li$^+$ coordination (S*Ni* process), because the intramolecular Br···Li$^+$ coordination in **7** seems to be stronger than that in **8**, as shown in Chart 3.[4] However, it cannot be denied that the cyclization proceeded *via* the open chain transition state **8** based on the intermolecular Br···Li$^+$ coordination (S*N*2 process). Thus, the reaction of two diastereoisomers of *N*-benzyl-2-bromo-1,2-diphenylethylamine hydrobromide (**10**, **12**) with *n*-BuLi was examined to clarify the transition state in this cyclization.

Compounds **10** and **12** were prepared by the ring-opening



E-Nu: HX (X=halogen), AcSH, HCO_2H, Ac_2O, *etc.*

Chart 1

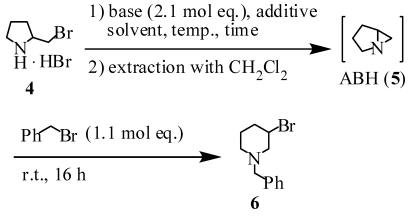


Chart 2

Table 1. Cyclization of **4** with Various Bases

Entry	Base	Additive (mol eq)	Solvent	Temp.	Time	Yield (%)[a] of **6**
1	NaOH	None	H_2O	r.t.	18 h	4
2	KOH	None	H_2O	r.t.	18 h	N.D.[b]
3	$LiOH \cdot H_2O$	None	H_2O	r.t.	18 h	68
4	NaH	None	THF	r.t.	18 h	31
5	LiH	None	THF	r.t.	18 h	64
6	$NaNH_2$	None	THF	r.t.	18 h	33
7	$LiNH_2$	None	THF	r.t.	18 h	90
8	$LiNH_2$	12-Crown-4 (2.1)	THF	r.t.	18 h	27
9	LDA	None	THF	r.t.	18 h	90
10	*n*-BuMgCl	None	THF	−78 °C	1 h	69
11	*n*-BuLi	None	THF	−78 °C	1 h	Quant.
12	*n*-BuLi	12-Crown-4 (2.1)	THF	−78 °C	1 h	64

a) Determined by HPLC analysis. *b*) Not detected.

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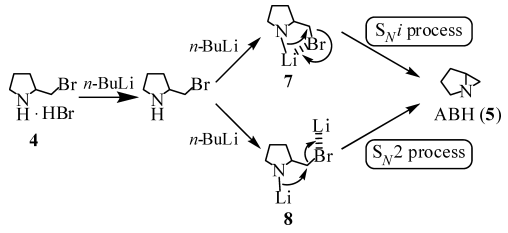
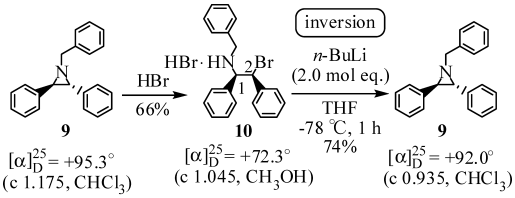


Chart 3



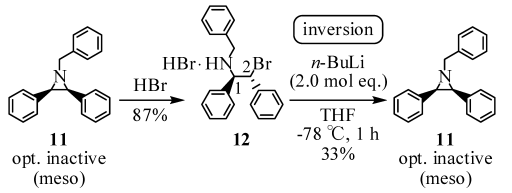


Chart 4

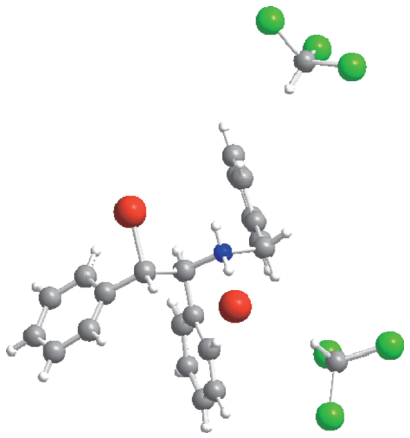


Fig. 1. Computer-Generated Drawing Derived from the X-Ray Coordinates of Compound **12**

reaction of the corresponding aziridines **9**[14,15] and **11**[14,15] with HBr (Chart 4). The structures of **10** and **12** were confirmed by ^{1}H- and ^{13}C-NMR analyses and X-ray crystallographic analysis of **12** (Fig. 1). The reactions of **10** and **12** with *n*-BuLi at −78 °C for 1 h afforded the aziridines **9** and **11** having an inverted configuration at the 2-position carbon, respectively, as shown in Chart 4. These results suggest that the cyclization proceeded in the S$_N$2 process by a back-side approach of the nitrogen anion. We therefore altered the S$_N$*i* process proposed previously to an S$_N$2 process.

Subsequently, the reaction of **4** with *n*-BuLi was performed at −78 °C for 1 h (entry 11, Table 1), and ABH (**5**) was isolated in 69% yield by distillation, as shown in Chart 5. The resulting ABH (**5**) was allowed to react with acyl chlorides **13a**—**f** and alkyl halides **13g**—**n** (Chart 6), as the reaction with electrophiles has rarely been reported.[17—23] All results are summarized in Table 2. The reaction with acyl

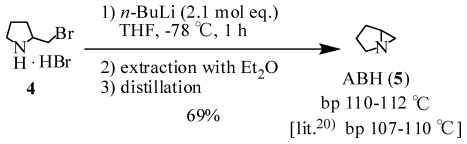


Chart 5

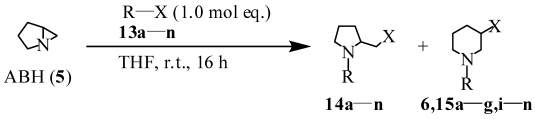


Chart 6

Table 2. Reaction of ABH (**5**) with **13a**—**n**

Entry	R	X	Yield (%)[a] of **14a**—**n**		Yield (%)[a] of **6**, **15a**—**g**, **i**—**n**	
1		Cl	**14a**	60	**15a**	26
2		Cl	**14b**	73	**15b**	24
3		Cl	**14c**	72	**15c**	19
4		Cl	**14d**	76	**15d**	24
5		Cl	**14e**	35	**15e**	18
6		Cl	**14f**	72	**15f**	23
7		Cl	**14g**	N.D.[b]	**15g**	7
8		Br	**14h**	N.D.[b]	**6**	Quant.
9		Br	**14i**	72	**15i**	18
10		Br	**14j**	N.D.[b]	**15j**	74
11		Br	**14k**	N.D.[b]	**15k**	72
12		Br	**14l**	N.D.[b]	**15l**	81
13		Br	**14m**	N.D.[b]	**15m**	69
14		Br	**14n**	N.D.[b]	**15n**	9

a) Isolated yields. *b*) Not detected.

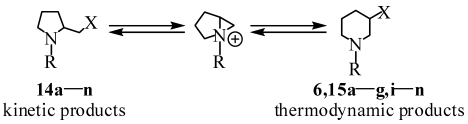
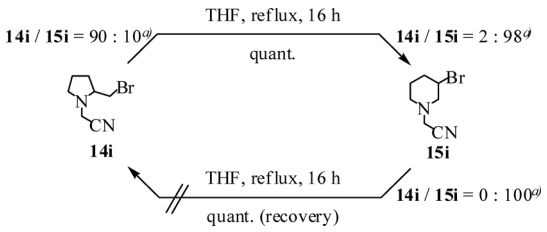


Chart 7

chlorides **13a**—**f** gave the corresponding pyrrolidines **14a**—**f** as the major product (entries 1—6). The piperidines **6**, **15g**, **j**—**n** were formed as the major product in the reaction with alkyl halides **13g**—**n**, except for **15i** (entries 7—14). The selectivity of products in the reaction of ABH (**5**) with electrophiles was rationalized by equilibrium, as Harding and Burks have proposed[24] and as shown in Chart 7. Although the kinetic products of the ring opening of ABH (**5**) may be the pyrrolidines **14a**—**n**, equilibrium leads to the thermodynamically favored piperidines **6**, **15a**—**g**, **i**—**n**. The generation of piperidines **6**, **15g**, **j**—**n** as major products in the reac-



a) Determined by ^{1}H-NMR analysis.

Chart 8

tion with alkyl halides **13g**—**n** was explained to be due to rapid equilibrium by the stronger nucleophilicity of the N atoms in **14g**, **h**, **j**—**n**, which were formed first, rather than by that of the N atoms in **14a**—**f**. The above hypothesis was supported by the fact that the pyrrolidine **14i** dissolved in tetrahydrofuran (THF) was completely converted to the piperidine **15i** under reflux for 16 h, though the piperidine **15i** was not transformed to **14i** under the same conditions, as shown in Chart 8.

In conclusion, we have established an efficient method for synthesizing 1-azabicyclo[3.1.0]hexane (**5**) by the cyclization of 2-(bromomethyl)pyrrolidine hydrobromide (**4**) with *n*-BuLi, and propose a rational S*N*2 process for this reaction involving the open chain transition state **8** based on the intermolecular Br$\cdots$Li$^+$ coordination. In addition, the reactions of ABH (**5**) with acyl chlorides **13a**—**f** and alkyl halides **13g**—**n** were demonstrated to give the pyrrolidines **14a**—**n** and the piperidines **6**, **15a**—**g**, **i**—**n**. The selectivity of the products in this reaction appears to have been controlled by equilibrium.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained on a JASCO FT/IR-420 or JASCO FT/IR-4100 IR Fourier transform spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-ECA500 (500 MHz) or JEOL JNM-AL400 (400 MHz) spectrometer. ^{13}C-NMR spectra were recorded on a JEOL JNM-ECA500 (125 MHz) or JEOL JNM-AL400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as an internal standard. Electron spray ionization (ESI)-MS were recorded on a Waters LCT Premier spectrometer. Fast atom bombardment mass spectra (FAB-MS) and electron ionization mass spectra (EI-MS) were recorded on a JEOL JMS SX-102A spectrometer. Elementary combustion analyses were performed on a Yanaco CHN CORDER MT-5. All reactions were monitored by TLC employing 0.25 mm silica gel plates (Merck 5715; 60 F_{254}). Preparative TLC (PTLC) was performed on 0.5 mm silica gel plates (Merck 5744; 60 F_{254}). Column chromatography was carried out on silica gel [Kanto Chemical 60N; 63—210 μm]. All reagents were used as purchased.

General Procedure for HPLC Analysis (Table 1) The reaction were performed by using a suspension of **4** (122.5 mg, 0.50 mmol) and each bases (1.05 mmol) in THF (1.5 ml) under the conditions shown in Table 1. After the reaction was completed, the reaction mixture was quenched with a phosphate buffer solution (pH 7.0, 1/15 mol/l, 3 ml), extracted with CH_2Cl_2, and then dried over $MgSO_4$. To the resulting CH_2Cl_2 solution was added benzyl bromide (65 μl, 0.55 mmol) at 0 °C, and the mixture was stirred at room temperature for 16 h to afford a crude reaction solution, which was analyzed by HPLC under the following conditions. Mobile phase: phosphate buffer solution (pH 7.0, 1/15 mol/l)/MeCN=5/5, UV: 230 nm, flow rate: 1.0 ml/min, column: TOSOH TSK-GEL 80Ts (4.6 mmϕ×15 cm). 1-Benzyl-3-bromopiperidine (**6**) (retention time=22 min) was used as the standard sample.

Preparation of (+)-(1*R*,2*S*)-*N*-Benzyl-2-bromo-1,2-diphenylethylamine Hydrobromide (10) To a solution of **9**[14,15] ($[\alpha]_D^{25}$ +95.3° (*c*=1.175, $CHCl_3$), 503 mg, 1.75 mmol) in MeCN (5 ml) was added hydrobromic acid (48%, 1.18 ml) at 0 °C. After being stirred for 1.5 h at room temperature, Et_2O was added to the reaction mixture and the precipitate was filtered off. The filtrate was washed with Et_2O to give **10** (519 mg, 66%) as a white solid, mp 169 °C. $[\alpha]_D^{25}$ +72.3° (*c*=1.045, MeOH), ^{1}H-NMR (400 MHz, CD_3OD) δ: 4.08 (1H, d, *J*=13.4 Hz), 4.15 (1H, d, *J*=13.4 Hz), 4.83 (1H, d, *J*=6.6 Hz), 5.78 (1H, d, *J*=6.6 Hz), 7.2—7.3 (2H, m), 7.3—7.4 (7H, m), 7.4—7.5 (5H, m), 7.52 (1H, tt, *J*=1.5, 7.3 Hz). ^{13}C-NMR (100 MHz, CD_3OD) δ: 51.8, 54.3, 67.0, 130.2, 130.29, 130.30, 130.5, 130.9, 131.0, 131.2, 131.67, 131.69, 131.72, 132.6, 137.7. IR (KBr) cm^{-1}: 2960, 1541, 1506, 1456, 1394. FAB-MS *m*/*z*: 368.0825 $[M+1]^+$ (Calcd for $C_{21}H_{21}NBr$: 368.0837). *Anal.* Calcd for $C_{21}H_{21}NBr_2$: C, 56.40; H, 4.73; N, 3.13. Found: C, 56.71; H, 4.77; N, 3.15.

Cyclization of (+)-(1*R*,2*S*)-*N*-Benzyl-2-bromo-1,2-diphenylethylamine Hydrobromide (10) To a suspension of **10** (50 mg, 0.112 mmol) in THF (0.5 ml) was added *n*-BuLi (1.58 mol/l, 0.142 ml, 0.224 mmol) at −78 °C under N_2 atmosphere. After being stirred for 1 h at −78 °C, the reaction mixture was quenched with a phosphate buffer solution (pH 6.0, 0.05 mol/l, 10 ml) and then extracted with AcOEt. The AcOEt extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by PTLC (eluent *n*-hexane–AcOEt, 9/1) to give **9** (24 mg, 74%) as a white solid. The *cis* azetidine **11** was not detected by TLC. $[\alpha]_D^{25}$ +92.0° (*c*=0.935, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.20 (1H, br s), 3.34 (1H, d, *J*=14.2 Hz), 3.42 (1H, br s), 3.66 (1H, d, *J*=14.2 Hz), 7.1—7.5 (15H, m) [lit.,[15] ^{1}H-NMR ($CDCl_3$) δ: 3.32 (2H, br s), 3.38 (1H, d, *J*=14 Hz), 3.66 (1H, d, *J*=14 Hz), 7.1—7.5 (15H, m)]. IR (KBr) cm^{-1}: 3020, 1651, 1522, 1421, 1215. EI-MS *m*/*z*: 285.1512 $[M^+]$ (Calcd for $C_{21}H_{19}N$: 285.1517).

Preparation of (±)-(1*R*,2*R*)-*N*-Benzyl-2-bromo-1,2-diphenylethylamine Hydrobromide (12) To a solution of **11** (414 mg, 1.45 mmol) in MeCN (4 ml) was added hydrobromic acid (48%, 0.65 ml) at −35 °C. After being stirred for 30 h at −35 °C, Et_2O was added to the reaction mixture and the precipitate was filtered off. The filtrate was recrystallized from MeOH–Et_2O to give **12** (519 mg, 66%) as colorless prisms, mp 142—143 °C. ^{1}H-NMR (400 MHz, CD_3OD) δ: 4.15 (1H, d, *J*=13.7 Hz), 4.20 (1H, d, *J*=13.7 Hz), 5.05 (1H, d, *J*=11.0 Hz), 5.73 (1H, d, *J*=11.0 Hz), 7.1—7.2 (3H, m), 7.2—7.3 (4H, m), 7.3—7.4 (5H, m), 7.4—7.5 (3H, m). ^{13}C-NMR (100 MHz, CD_3OD) δ: 51.4, 54.4, 68.9, 129.6, 130.1, 130.5, 130.6, 130.9, 131.2, 131.4, 131.7, 132.1, 132.7, 138.9. IR (KBr) cm^{-1}: 2931, 1541, 1506, 1456, 1404, 1267. FAB-MS *m*/*z*: 368.0847 $[M+1]^+$ (Calcd for $C_{21}H_{21}NBr$: 368.0837). *Anal.* Calcd for $C_{21}H_{21}NBr_2$: C, 56.40; H, 4.73; N, 3.13. Found: C, 56.26; H, 4.79; N, 3.04.

X-Ray Crystallographic Analysis of (±)-(1*R*,2*R*)-*N*-Benzyl-2-bromo-1,2-diphenylethylamine Hydrobromide (12) The crystalline compound **12** was recrystallized from $CHCl_3$ in order to subject to the X-ray crystallographic analysis. The measurement was made on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo$K\alpha$ radiation. The data were processed using the PROCESS-AUTO program package. The linear absorption coefficient, μ, for Mo$K\alpha$ radiation is 1.0 cm^{-1}. A symmetry-related absorption correction using the program ABSCOR was applied.[25] The data were corrected for Lorentz and polarization effects. The structure was solved by directed methods and expanded using Fourier techniques.[26,27] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. Natural atom scattering factors were taken from Cromer and Waber.[28] The values for the mass attenuation coefficients are those of Creagh and Hubbel.[29] All calculations were performed using the teXsan crystallographic software package.[30]

Crystallographic Data for **12**: $C_{21}H_{21}NBr_2\cdot 2CHCl_3$, MW=685.97, colorless prism crystal, triclinic, space group *P*-1(#2), *a*=9.995(1) Å, *b*=11.019(1) Å, *c*=14.201(1) Å, α=100.379(7)°, β=93.704(7)°, γ=111.722(6)°; *V*=1414.4(3) Å^3; *Z*=4, D_{calcd}=1.611 g/cm^3, *R*=0.079, *Rw*=0.171; GOF=1.060.

Cyclization of (±)-(1*R*,2*R*)-*N*-Benzyl-2-bromo-1,2-diphenylethylamine Hydrobromide (12) To a suspension of **12** (50 mg, 0.112 mmol) in THF (0.5 ml) was added *n*-BuLi (1.58 mol/l, 0.142 ml, 0.224 mmol) at −78 °C under N_2 atmosphere. After being stirred for 1 h at −78 °C, the reaction mixture was quenched with a phosphate buffer solution (pH 6.0, 0.05 mol/l, 10 ml) and then extracted with AcOEt. The AcOEt extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by PTLC (eluent *n*-hexane–AcOEt, 9/1) to give **11** (10 mg, 33%) as a white solid. The *trans* azetidine **9** was not detected by TLC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.06 (2H, s), 3.89 (2H, s), 7.0—7.3 (11H, m), 7.32 (2H, t, *J*=7.6 Hz), 7.43 (2H, d, *J*=7.6 Hz) [lit.,[16] ^{1}H-NMR ($CDCl_3$) δ: 3.08 (2H, s), 3.90 (2H, s), 7.05—7.55 (15H, m)]. IR (KBr) cm^{-1}: 3020, 1558, 1522, 1419, 1215, 928. EI-MS *m*/*z*: 285.1512 $[M^+]$ (Calcd for $C_{21}H_{19}N$: 285.1517).

Isolation of ABH (5)[12,20,21] To a suspension of **4** (25.0 g, 0.102 mol) in THF (300 ml) was added *n*-BuLi (2.64 mol/l, 81.2 ml, 0.214 mol) at −78 °C under N_2 atmosphere. After being stirred for 1 h at −78 °C, the reaction mixture was quenched with 1 N HCl (100 ml) and washed with Et_2O. The resultant HCl solution was made alkaline with 50% KOH, and extracted with Et_2O. The Et_2O layer was dried over $MgSO_4$, and distilled at atmospheric pressure to give **5** (5.87 g, 69%) as a colorless oil, bp 110—112 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.16 (1H, d, J=3.4 Hz), 1.36—1.50 (1H, m), 1.52 (1H, d, J=5.2 Hz), 1.60 (1H, dt, J=13.4, 7.6 Hz), 1.80—1.92 (1H, m), 2.05 (1H, dd, J=13.2, 8.6 Hz), 2.33 (1H, ddd, J=8.6, 5.2, 3.4 Hz), 2.86 (1H, dt, J=11.6, 7.6 Hz), 2.95 (1H, dd, J=11.6, 8.6 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 19.3, 25.7, 26.4, 39.3, 52.4. IR (neat) cm^{-1}: 2940, 2793, 1457, 1339, 1096. ESI-MS *m/z*: 106.0641 [M$^+$+Na] (Calcd for C_5H_9NNa: 106.0633).

General Procedure for the Reaction of ABH (5) with Electrophiles 13a—f (Table 2, Entry 1) To a solution of ABH (**5**) (42 mg, 0.50 mmol) in THF (5 ml) was added benzoyl chloride (**13a**) (59 μl, 0.50 mmol) at 0 °C under N_2 atmosphere. After being stirred for 16 h at room temperature, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent *n*-hexane–AcOEt, 4/1) to give **14a** (67 mg, 60%) as a colorless oil and **15a** (30 mg, 26%) as a colorless oil.

1-Benzoyl-2-chloromethylpyrrolidine (14a) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.56—2.26 (4H, m), 3.36—3.61 (2H, m), 3.82 (1H, dd, J=10.7, 2.0 Hz), 4.08 (1H, dd, J=10.7, 5.8 Hz), 4.43—4.61 (1H, m), 7.33—7.59 (5H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.1, 28.2, 45.9, 51.3, 57.6, 127.4, 128.3, 130.2, 136.8, 170.2. IR (neat) cm^{-1}: 2974, 2876, 1629, 1447, 1410, 1212, 719, 700, 656. ESI-MS *m/z*: 246.0665 [M$^+$+Na] (Calcd for $C_{12}H_{14}ClNNaO$: 246.0662).

1-Benzoyl-3-chloropiperidine (15a)[31] Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.32—2.42 (4H, m), 3.08—4.62 (5H, m), 7.41 (5H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 22.6/24.6, 34.3, 42.2, 47.6/49.3, 54.5/55.4, 127.0, 128.5, 129.8, 135.6, 170.9. IR (neat) cm^{-1}: 2949, 2860, 1635, 1428, 1273, 702. ESI-MS *m/z*: 246.0664 [M$^+$+Na] (Calcd for $C_{12}H_{14}ClNNaO$: 246.0662).

2-Chloromethyl-1-(4-methylbenzoyl)pyrrolidine (14b)[32] Colorless plates (THF–*n*-hexane). mp 85.0—87.0 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.64—1.82 (1H, m), 1.88—2.02 (1H, m), 2.02—2.23 (2H, m), 3.38 (3H, s), 3.43—3.62 (2H, m), 3.82 (1H, d, J=10.6 Hz), 4.05 (1H, dd, J=10.6, 5.8 Hz), 4.46—4.60 (1H, m), 7.20 (2H, d, J=7.7 Hz), 7.44 (2H, d, J=7.7 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.4, 25.2, 28.2, 46.0, 51.3, 57.5, 127.5, 128.9, 133.9, 140.4, 170.3. IR (KBr) cm^{-1}: 2980, 2953, 2885, 1624, 1416, 843, 758. ESI-MS *m/z*: 238.0997 [M$^+$+H] (Calcd for $C_{13}H_{17}ClNO$: 238.0999). *Anal.* Calcd for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.78; N, 5.89. Found. C, 65.56; H, 6.72; N, 5.94.

3-Chloro-1-(4-methylbenzoyl)piperidine (15b) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.35—2.33 (4H, m), 2.38 (3H, s), 3.03—4.70 (5H, m), 7.21 (2H, d, J=8.0 Hz), 7.31 (2H, d, J=8.0 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.4, 22.7/24.6, 34.4, 42.3, 47.6/49.5, 54.7/55.3, 127.1, 129.1, 132.7, 140.0, 171.1. IR (neat) cm^{-1}: 2949, 2861, 1634, 1427, 1273, 830, 752. ESI-MS *m/z*: 238.1006 [M$^+$+H] (Calcd for $C_{13}H_{16}ClNO$: 238.0999).

2-Chloromethyl-1-(4-methoxybenzoyl)pyrrolidine (14c) Colorless needles (THF–*n*-hexane). mp 84.0—85.0 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.53—1.88 (1H, m), 1.89—2.29 (3H, m), 3.44—4.15 (4H, m), 3.84 (3H, s), 4.44—4.66 (1H, m), 6.88—6.94 (2H, m), 7.45—7.64 (2H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.3, 28.3, 46.0, 51.5, 55.4, 57.6, 113.5, 128.9, 129.5, 161.2, 169.9. IR (KBr) cm^{-1}: 2977, 2950, 2883, 2840, 1625, 1424, 1406, 1253, 1184, 1027, 852, 769. ESI-MS *m/z*: 276.0767 [M$^+$+Na] (Calcd for $C_{13}H_{16}ClNNaO_2$: 276.0767).

3-Chloro-1-(4-methoxybenzoyl)piperidine (15c) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.42—2.34 (4H, m), 3.12—4.56 (5H, m), 3.81 (3H, s), 6.89 (2H, d, J=8.9 Hz), 7.38 (2H, d, J=8.9 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 23.4, 34.4, 42.9, 47.8/50.2, 55.2, 55.4, 113.8, 127.7, 129.1, 160.8, 170.9. IR (neat) cm^{-1}: 2950, 2859, 1631, 1608, 1426, 1251, 1174, 1027, 841, 763. ESI-MS *m/z*: 254.0973 [M$^+$+H] (Calcd for $C_{13}H_{17}ClNO_2$: 254.0948).

1-(4-Chlorobenzoyl)-2-chloromethylpyrrolidine (14d) Colorless prisms (THF–*n*-hexane). mp 87.5—88.5 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.69—1.85 (1H, m), 1.92—2.27 (3H, m), 3.41—3.61 (2H, m), 3.79 (1H, d, J=10.7 Hz), 4.09 (1H, dd, J=10.7, 5.6 Hz), 4.48—4.60 (1H, m), 7.39 (2H, d, J=8.3 Hz), 7.50 (2H, d, J=8.3 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.2, 28.1, 45.8, 51.3, 57.6, 128.6, 128.9, 135.1, 136.3, 169.1. IR (KBr) cm^{-1}: 2952, 2886, 1626, 1417, 1091, 848, 753, 714. ESI-MS *m/z*: 258.0454 [M$^+$+H] (Calcd for $C_{12}H_{14}Cl_2NO$: 258.0452). *Anal.* Calcd for $C_{12}H_{13}Cl_2NO$: C, 55.83; H, 5.08; N, 5.43. Found. C, 55.82; H, 5.04; N, 5.35.

3-Chloro-1-(4-chlorobenzoyl)piperidine (15d) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.39—2.38 (4H, m), 3.12—4.50 (5H, m), 7.34—7.45 (4H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 22.0/24.3, 33.9, 42.4, 47.6/49.3, 54.4/55.5, 128.6, 128.8, 134.0, 135.8, 169.9. IR (neat) cm^{-1}: 2950, 2861, 1637, 1430, 1273, 1092, 840, 754. ESI-MS *m/z*: 258.0451 [M$^+$+H] (Calcd for $C_{12}H_{14}Cl_2NO$: 258.0452).

2-Chloromethyl-1-(4-nitrobenzoyl)pyrrolidine (14e) Pale yellow prisms (THF–*n*-hexane). mp 79.5—80.5 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.73—1.89 (1H, m), 1.96—2.29 (3H, m), 3.32—3.60 (2H, m), 3.79 (1H, dd, J=11.2, 2.0 Hz), 4.16 (1H, dd, J=11.2, 5.4 Hz), 4.49—4.63 (1H, m), 7.71 (2H, d, J=8.6 Hz), 8.28 (2H, d, J=8.6 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.1, 28.1, 45.6, 51.1, 57.8, 123.7, 128.4, 142.7, 148.7, 167.9. IR (KBr) cm^{-1}: 2991, 2883, 1625, 1599, 1520, 1421, 1349, 851, 721. ESI-MS *m/z*: 291.0504 [M$^+$+Na] (Calcd for $C_{12}H_{13}ClN_2O_3Na$: 291.0512). *Anal.* Calcd for $C_{12}H_{13}ClN_2O_3$: C, 53.64; H, 4.88; N, 10.43. Found. C, 53.51; H, 4.87; N, 10.35.

3-Chloro-1-(4-nitrobenzoyl)piperidine (15e) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.46—1.75 (1H, m), 1.84—2.32 (3H, m), 3.17—3.77 (3H, m), 3.94—4.34 (2H, m), 7.55—7.66 (2H, m), 8.29 (2H, d, J=8.6 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.4/23.9, 33.4/34.1, 42.4/47.5, 49.2/54.1, 54.4/55.6, 123.9, 127.9/128.3, 141.8, 148.4, 168.4/168.8. IR (neat) cm^{-1}: 2951, 2862, 1637, 1521, 1439, 1349, 1274, 861, 725. ESI-MS *m/z*: 291.0532 [M$^+$+Na] (Calcd for $C_{12}H_{13}ClN_2NaO_3$: 291.0512).

2-Chloromethyl-1-(2-naphthoyl)pyrrolidine (14f) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.69—1.85 (1H, m), 1.91—2.29 (3H, m), 3.44—3.72 (2H, m), 3.86 (1H, d, J=10.3 Hz), 4.13 (1H, dd, J=10.3, 6.0 Hz), 4.54—4.67 (1H, m), 7.48—7.67 (3H, m), 7.82—7.94 (3H, m), 8.03 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.1, 28.2, 45.9, 51.3, 57.7, 124.4, 126.6, 127.2, 127.3, 127.7, 128.1, 128.5, 132.5, 133.9, 134.0, 170.2. IR (neat) cm^{-1}: 2973, 2876, 1623, 1472, 1411, 1349, 1197, 826, 777, 760. ESI-MS *m/z*: 296.0825 [M$^+$+Na] (Calcd for $C_{16}H_{16}ClNNaO$: 296.0818).

3-Chloro-1-(2-naphthoyl)piperidine (15f) Colorless plates (THF–*n*-hexane). mp 115.2—116.0 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.40—2.36 (4H, m), 3.04—4.66 (5H, m), 7.46—7.58 (3H, m), 7.81—7.95 (4H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 22.8/24.6, 34.4, 42.4, 47.7/49.4, 54.7/55.6, 124.3, 126.7, 126.9, 127.1, 127.8, 128.4, 128.4, 132.7, 132.9, 133.7, 170.9. IR (KBr) cm^{-1}: 2955, 2923, 2857, 1627, 1478, 1444, 1268, 1065, 867, 834, 808, 757. ESI-MS *m/z*: 296.0830 [M$^+$+Na] (Calcd for $C_{16}H_{16}ClNNaO$: 296.0818). *Anal.* Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12. Found. C, 70.04; H, 5.84; N, 5.14.

1-Benzyl-3-chloropiperidine (15g) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.49—1.67 (2H, m), 1.73—1.82 (1H, m), 2.01—2.26 (3H, m), 2.65—2.75 (1H, m), 2.99—3.09 (1H, m), 3.54 (2H, s), 3.93—4.04 (1H, m), 7.22—7.35 (5H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 24.8, 34.9, 52.8, 56.1, 61.3, 62.7, 127.1, 128.3, 129.0, 137.9. IR (neat) cm^{-1}: 2945, 2800, 1454, 1154, 757, 739, 698. ESI-MS *m/z*: 210.1032 [M$^+$+H] (Calcd for $C_{12}H_{17}ClN$: 210.1050).

1-Benzyl-3-bromopiperidine (6) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.53—1.84 (3H, m), 2.04—2.43 (3H, m), 2.66—2.82 (1H, m), 3.00—3.17 (1H, m), 3.53 (2H, d, J=2.3 Hz), 4.06—4.19 (1H, m), 7.22—7.38 (5H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.9, 35.7, 48.4, 52.8, 61.8, 62.6, 127.1, 128.3, 129.0, 137.9. IR (neat) cm^{-1}: 2943, 2798, 1455, 1149, 739, 712, 698. ESI-MS *m/z*: 254.0547 [M$^+$+H] (Calcd for $C_{12}H_{17}BrN$: 254.0544). *Anal.* Calcd for $C_{12}H_{16}BrN$: C, 56.71; H, 6.35; N, 5.51. Found. C, 56.57; H, 6.31; N, 5.43.

2-Bromomethyl-1-cyanomethylpyrrolidine (14i) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.74—1.92 (3H, m), 2.07 (1H, dq, J=12.0, 8.0 Hz), 2.74 (1H, q, J=8.6 Hz), 2.98—3.14 (2H, m), 3.30 (1H, dd, J=10.3, 6.3 Hz), 3.39 (1H, dd, J=10.3, 4.6 Hz), 3.70 (1H, d, J=17.6 Hz), 3.81 (1H, d, J=17.6 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 22.9, 30.3, 35.5, 41.1, 54.0, 61.8, 115.3. IR (neat) cm^{-1}: 2962, 2817, 1420, 1217, 1122, 860, 634. ESI-MS *m/z*: 203.0182 [M$^+$+H] (Calcd for $C_7H_{12}BrN_2$: 203.0184).

3-Bromo-1-cyanomethylpiperidine (15i) Colorless plates (Et_2O–*n*-hexane). mp 57.5—58.5 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.58—1.98 (3H, m), 2.08—2.24 (1H, m), 2.40—2.56 (1H, m), 2.60—2.76 (2H, m), 2.96—3.10 (1H, m), 3.55 (2H, d, J=1.7 Hz), 4.08—4.22 (1H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 24.6, 34.0, 46.0, 46.6, 51.6, 60.1, 114.3. IR (KBr) cm^{-1}: 2947, 2800, 1465, 1420, 1158, 878, 721, 635. ESI-MS *m/z*: 203.0172 [M$^+$+H] (Calcd for $C_7H_{12}BrN_2$: 203.0184). *Anal.* Calcd for $C_7H_{11}BrN_2$: C, 41.40; H, 5.46; N, 13.79. Found. C, 41.44; H, 5.25; N, 13.61.

3-Bromo-1-ethoxycarbonylmethylpiperidine (15j) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=6.9 Hz), 1.60—1.85 (3H, m), 2.18—2.41 (2H, m), 2.54—2.64 (1H, m), 2.79—2.88 (1H, m), 3.17—3.24 (1H, m), 3.26 (2H, d, J=2.3 Hz), 4.12—4.23 (1H, m), 4.18 (2H, q,

J=6.9 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.3, 25.7, 35.1, 47.5, 52.3, 58.9, 60.6, 61.3, 170.2. IR (neat) cm^{-1}: 2944, 2817, 1739, 1449, 1166, 1101, 714, 559. ESI-MS m/z: 250.0442 [M$^+$+H] (Calcd for $C_9H_{17}BrNO_2$: 250.0443).

3-Bromo-1-phenacylpiperidine (15k) Pale yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.60—1.94 (3H, m), 2.20—2.42 (2H, m), 2.52—2.66 (1H, m), 2.82—2.96 (1H, m), 3.18—3.34 (1H, m), 3.85 (2H, s), 4.14—4.27 (1H, m), 7.46 (2H, t, J=7.8 Hz), 7.58 (1H, t, J=7.8 Hz), 7.99 (2H, d, J=7.8 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.7, 35.2, 47.4, 52.9, 61.9, 63.9, 128.2, 128.6, 133.3, 135.8, 196.4. IR (neat) cm^{-1}: 2944, 2796, 1697, 1448, 1218, 754, 714, 689. ESI-MS m/z: 282.0492 [M$^+$+H] (Calcd for $C_{13}H_{17}BrNO$: 282.0494).

3-Bromo-1-(2-propenyl)piperidine (15l) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.56—1.86 (3H, m), 2.00—2.40 (3H, m), 2.68—2.83 (1H, m), 3.02 (2H, d, J=6.6 Hz), 3.04—3.18 (1H, m), 4.06—4.18 (1H, m), 5.11—5.24 (2H, m), 5.84 (1H, ddt, J=17.2, 10.3, 6.6 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.8, 35.6, 48.1, 52.9, 61.4, 61.7, 118.2, 134.7. IR (neat) cm^{-1}: 2944, 2789, 1644, 1150, 995, 922, 715, 638. ESI-MS m/z: 204.0372 [M$^+$+H] (Calcd for $C_8H_{15}BrN$: 204.0388).

3-Bromo-1-(2-propynyl)piperidine (15m) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.54—1.90 (3H, m), 2.14—2.42 (3H, m), 2.51—2.64 (1H, m), 2.69—2.80 (1H, m), 3.08—3.18 (1H, m), 3.35 (2H, t, J=2.2 Hz), 4.09—4.22 (1H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.4, 34.9, 46.8, 47.8, 51.5, 60.5, 73.5, 78.2. IR (neat) cm^{-1}: 3294, 2944, 2804, 1467, 1438, 1152, 1089, 717, 638. ESI-MS m/z: 202.0224 [M$^+$+H] (Calcd for $C_8H_{13}BrN$: 202.0231).

3-Bromo-1-(3-butenyl)piperidine (15n) Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.57—1.84 (3H, m), 2.04—2.54 (7H, m), 2.69—2.91 (1H, m), 3.05—3.26 (1H, m), 4.07—4.22 (1H, m), 5.01 (1H, dd, J=1.1, 10.3 Hz), 5.06 (1H, dd, J=1.1, 17.2 Hz), 5.79 (1H, ddt, J=17.2, 10.3, 6.6 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.8, 29.7, 31.2, 35.7, 52.8, 57.6, 61.8, 115.9, 136.2. IR (neat) cm^{-1}: 2925, 2853, 1457, 1153, 912, 712. ESI-MS m/z: 218.0546 [M$^+$+H] (Calcd for $C_9H_{17}BrN$: 218.0544).

Equilibrium of 14i and 15i (Chart 8) To a solution of **14i** (**14i**/**15i**=90/10, 20 mg, 0.10 mmol) in THF (1 ml) was refluxed for 16 h under Ar atmosphere. The mixture was concentrated *in vacuo* to give **15i** (**14i**/**15i**=2/98, 20 mg, quantitative yield) as a colorless oil. Then, a solution of **15i** (**14i**/**15i**=0/100, 27 mg, 0.13 mmol) in THF (1 ml) was treated in the same manner, and **15i** (**14i**/**15i**=0/100, 27 mg, quantitative recovery) was recovered as a colorless solid. The resultant oil and solid were analyzed by ^{1}H-NMR (500 MHz, $CDCl_3$).

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