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An Efficient Synthesis of Bicyclic Amidines via Intramolecular Cyclization of Azide to Lactam

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Experimental Section

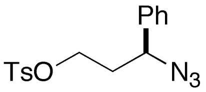
General: Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported downfield from TMS (= 0) or in the scale relative to $CHCl_3$ (7.24 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CHCl_3$ (77.0 ppm for ^{13}C NMR) as an internal reference. Chemical shifts in CD_3OD were reported in the scale relative to CH_3OH (3.30 ppm for ^{1}H NMR, 49.0 ppm for ^{13}C NMR) as an internal reference. Optical rotations were measured on a JASCO P-1010 polarimeter. FAB mass spectra were measured on JEOL JMS-BU20 GCmate or JEOL JMS-MS700V. ESI mass spectra were measured on Waters-ZQ4000. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). In situ IR spectra were recorded on a ReactIR 4000 instrument from ASI applied Systems fitted with SiComp probe. 1,2-Dichloroethane was distilled from CaH_2. Oxalyl chloride was purchased from Wako Pure Chemical Co., Ltd. and used as received. 2.0 M CH_2Cl_2 solution of Oxalyl bromide was purchased from Aldrich and used as received. Amberite IRA 400 in Cl form was purchased from Aldrich.

Procedure for azide lactam 1: (not optimized)

To a THF solution of lactam (0.3 M), was added NaH (1.1 equiv. to lactam , 60% dispersion of mineral oil) at 0 °C and stirred for 30 min at room temperature. The requisite azidoalkyl tosylate (1.0 equiv.) in THF and tetrabutylammonium iodide (0.2 eq.) were added to the resulting mixture and stirred at room temperature. DMF was added when the reaction mixture became highly viscous or the reaction rate was too slow. After starting materials disappeared on TLC (1-12 h), the reaction mixture was quenched by saturated NH_4Cl aq. at 0 °C and extracted with CH_2Cl_2. The combined organic extract was washed with H_2O and brine, then dried over Na_2SO_4. Evaporation of the organic solvent gave the crude mixture of azido lactam. The resulting residue was purified by flash silica gel column chromatography (SiO_2, hexane/ethyl acetate 4/1–1/1) to afford azido lactam **1**.

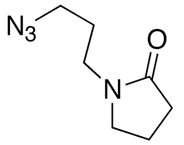
(*S*)-3-Azido-3-phenylpropyl tosylate:

Colorless oil; IR (neat) 2099, 1360, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$)



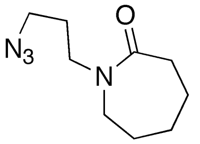
□1.98-2.03 (m, 2H), 2.44 (s, 3H), 3.99 (ddd, *J* = 10.4, 5.5, 5.1 Hz, 1H), 4.13 (ddd, *J* = 10.4, 7.6, 5.2 Hz, 1H), 4.54 (dd, *J* = 8.5, 6.4 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.30-7.36 (m, 5H), 7. 78 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (CDCl$_3$) □21.6, 35.6, 62.0, 66.9, 126.8, 127.9, 128.6, 129.0, 129.9, 132.7, 138.3, 145.0; ESI-MS *m/z* 354 [M+Na]$^+$; HRMS (FAB): calcd. for $C_{16}H_{17}CsN_3O_3S$ 464.0045 [M+Cs]$^+$, found 464.0046 [M+Cs]$^+$; [□]$_D^{24}$ –92.6 (*c* 0.4, CHCl$_3$).

1-(3-Azidopropyl)pyrrolidin-2-one (1a):



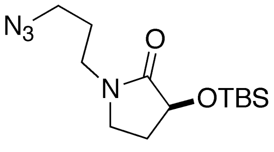
Colorless oil; IR (neat) □ 2098, 1671 cm^{-1}; ^{1}H NMR (CDCl$_3$) □1.78 (tt, *J* = 7.5, 7.0 Hz, 2H), 2.01 (tt, *J* = 8.3, 7.0 Hz, 2H), 2.36 (t, *J* = 8.3 Hz, 2H), 3.27-3.38 (m, 6H); ^{13}C NMR (CDCl$_3$) □17.9, 26.8, 30.9, 40.1, 47.4, 49.1, 175.2; ESI-MS *m/z* 191 [M+Na]$^+$; HRMS (FAB): calcd. for $C_7H_{13}N_4O$ 169.1089 [M+H]$^+$, found 169.1089 [M+H]$^+$.

***N*-(3-Azidopropyl)-□-caprolactam (1b):**



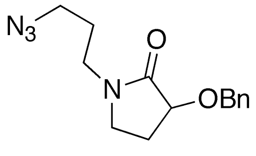
Colorless oil; IR (neat) □ 2096, 1635 cm^{-1}; ^{1}H NMR (CDCl$_3$) □1.59-1.66 (m, 3H), 1.68-1.73 (m, 3H), 1.77 (dddd, *J* = 7.0, 7.0, 6.7, 6.7 Hz, 2H), 2.48-2.51 (m, 2H), 3.30 (dd, *J* = 6.7, 6.7 Hz, 1H), 3.32-3.34 (m, 2H), 3.41 (dd, *J* = 7.0, 7.0 Hz, 2H); ^{13}C NMR (CDCl$_3$) □23.4, 27.6, 28.7, 29.9, 37.2, 45.9, 49.2, 50.0, 175.9; ESI-MS *m/z* 219 [M+Na]$^+$; HRMS (FAB): calcd. for $C_9H_{17}N_4O$ 197.1402 [M+H]$^+$, found 197.1402 [M+H]$^+$.

(*S*)-1-(3-Azidopropyl)-3-(*t*-butyldimethylsilyloxy) pyrrolidin-2-one (1c):



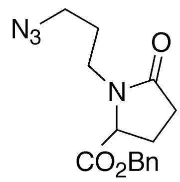
Colorless oil; IR (neat) □ 2098, 1703 cm^{-1}; ^{1}H NMR (CDCl$_3$) □0.00 (s, 3H), 0.15 (s, 3H), 0.77 (s, 9H), 1.66 (tt, *J* = 7.0, 7.0 Hz, 2H), 1.79 (dddd, *J* = 12.8, 7.6, 7.6, 7.6 Hz, 1H), 2.18 (dddd, *J* = 12.8, 7.6, 7.6, 3.4 Hz, 1H), 3.07-3.12 (m, 1H), 3.16-3.24 (m, 5H), 4.51(dd, *J* = 7.6, 7.6 Hz, 1H); ^{13}C NMR (CDCl$_3$) □–5.1, –4.5, 18.3, 25.8, 26.7, 29.4, 40.6, 43.7, 49.1, 71.0, 173.6; ESI-MS *m/z* 321 [M+Na]$^+$; HRMS (FAB): calcd. for $C_{13}H_{27}N_4O_2Si$ 299.1903 [M+H]$^+$, found 299.1904 [M+H]$^+$; [□]$_D^{24}$ –33.6 (*c* 1.1, CHCl$_3$).

1-(3-Azidopropyl)-3-benzyloxypyrrolidin-2-one (1d):



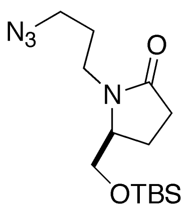
Colorless oil; IR (neat) □ 2096, 1685 cm^{-1}; ^{1}H NMR (CDCl$_3$) □1.76 (dddd, *J* = 6.7, 6.7, 6.7, 6.7 Hz, 2H), 1.93-2.01 (m, 1H), 2.22-2.30 (m, 1H), 3.18-3.38 (m, 6H), 4.06 (dd, *J* = 7.0, 7.0 Hz, 1H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.92 (d, *J* = 11.9 Hz, 1H), 7.22-7.36 (m, 5H); ^{13}C NMR (CDCl$_3$) □26.4, 26.5, 40.1, 44.0, 48.8, 71.9, 75.6, 127.6, 127.9, 128.2, 137.7, 179.7; ESI-MS *m/z* 297 [M+Na]$^+$; HRMS (FAB): calcd. for $C_{14}H_{19}N_4O_2$ 275.1508 [M+H]$^+$, found 275.1500 [M+H]$^+$.

1-(3-Azidopropyl)-5-(benzyloxycarbonyl)pyrrolidin-2-one (1e):



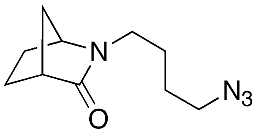
Colorless oil; IR (neat) ν 2098, 1692, 1170 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.60-1.80 (m, 2H), 1.98-2.09 (m, 1H), 2.26-2.37 (m, 2H), 2.44-2.52 (m, 1H), 3.06 (ddd, *J* = 14.0, 7.3, 7.3 Hz, 1H), 3.23-3.30 (m, 2H), 3.60 (ddd, *J* = 14.0, 7.3, 6.8 Hz, 1H), 4.20 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.18 (s, 2H), 7.32-7.37 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 23.0, 26.6, 29.3, 39.7, 49.0, 60.1, 67.3, 128.3, 128.6, 128.6, 134.9, 175.6; ESI-MS *m/z* 325 [M+Na]$^+$; HRMS (FAB): calcd. for $C_{15}H_{19}N_4O_3$ 303.1457 [M+H]$^+$, found 303.1459 [M+H]$^+$.

(5*S*)-1-(3-Azidopropyl)-5-(*t*-butyldimethylsilyloxymethyl)pyrrolidin-2-one (1f):



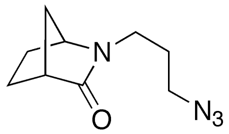
Colorless oil; IR (neat) ν 2097, 1687 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ -0.37 (s, 6H), 0.86 (s, 9H), 1.72-1.90 (m, 3H), 2.03-2.10 (m, 1H), 2.27 (ddd, *J* = 16.2, 10.0, 5.2 Hz, 1H), 2.42 (ddd, *J* = 16.2, 7.4, 7.4 Hz, 1H), 3.12-3.18 (m, 1H), 3.31 (ddd, *J* = 6.8, 6.8, 2.2 Hz, 2H), 3.55-3.59 (m, 2H), 3.61-3.66 (m, 1H), 3.69 (dd, *J* = 10.4, 3.4 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ -5.6, 18.1, 21.6, 25.8, 27.1, 30.3, 38.6, 49.3, 59.6, 64.2, 175.7; ESI-MS *m/z* 335 [M+Na]$^+$; HRMS (FAB): calcd. for $C_{14}H_{29}N_4O_2Si$ 313.2060 [M+H]$^+$, found 313.2060 [M+H]$^+$; $[\alpha]_D^{23}$ +11.4 (*c* 0.55, CHCl$_3$).

(1*R*,4*S*)-3-(4-Azidobutyl)-3-azabicyclo[2.2.1]heptan-2-one (1g):



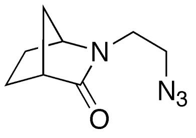
Colorless oil; IR (neat) ν 2096, 1695 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.33 (d, *J* = 9.2 Hz, 1H), 1.50-1.62 (m, 6H), 1.72-1.84 (m, 3H), 2.77 (brd, *J* = 2.2 Hz, 1H), 2.78-2.88 (m, 1H), 3.26-3.32 (m, 2H), 3.36-3.43 (M, 1H), 3.77 (brs, 1H); ^{13}C NMR (CDCl$_3$) δ 24.5, 25.6, 26.2, 27.4, 39.5, 40.1, 45.7, 50.9, 59.0, 178.1; ESI-MS *m/z* 231 [M+Na]$^+$; HRMS (FAB): calcd. for $C_{10}H_{16}N_4O$ 209.1402 [M+H]$^+$, found 209.1407 [M+H]$^+$; $[\alpha]_D^{23}$ –38.9 (*c* 0.69, CHCl$_3$).

(1*R*,4*S*)-3-(3-Azidopropyl)-3-azabicyclo[2.2.1]heptan-2-one (1h):



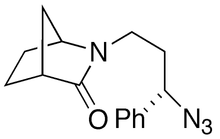
Colorless oil; IR (neat) ν 2096, 1694 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.35 (d, *J* = 9.2 Hz, 1H), 1.52-1.62 (m, 2H), 1.72-1.85 (m, 5H), 2.78 (brd, *J* = 2.2 Hz, 1H), 2.86 (ddd, *J* = 14.0, 7.0, 7.0 Hz, 1H), 3.31 (dd, *J* = 7.0, 7.0 Hz, 2H), 3.46 (ddd, *J* = 14.0, 7.0, 7.0 Hz, 1H), 3.78 (brs, 1H); ^{13}C NMR (CDCl$_3$) δ 24.4, 27.4, 28.0, 37.8, 40.0, 45.7, 49.0, 59.6, 178.3; ESI-MS *m/z* 217 [M+Na]$^+$; HRMS (FAB): calcd. for $C_9H_{15}N_4O$ 195.1246 [M+H]$^+$, found 195.1249 [M+H]$^+$. $[\alpha]_D^{20}$ –67.5 (*c* 2.00, CHCl$_3$).

(1*R*,4*S*)-3-(2-Azidoethyl)-3-azabicyclo[2.2.1]heptan-2-one (1i):



Colorless oil; IR (neat) ν 2101, 1874 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.37 (d, *J* = 9.5 Hz, 1H), 1.52-1.68 (m, 2H), 1.72-1.90 (m, 3H), 2.79 (brs, 1H), 2.95 (ddd, *J* = 14.3, 7.0, 5.0 Hz, 1H), 3.34-3.32 (m, 2H), 3.58 (ddd, *J* = 14.3, 5.2, 5.2 Hz, 1H), 3.90 (brs, 1H); ^{13}C NMR (CDCl$_3$) δ 24.4, 27.5, 39.9, 40.3, 45.5, 50.5, 60.5, 178.5; ESI-MS *m/z* 203 $[M+Na]^+$; HRMS (FAB): calcd. for $C_8H_{13}N_4O$ 181.1089 $[M+H]^+$, found 181.1093 $[M+H]^+$; $[□]_D^{25}$ –96.8 (*c* 0.76, $CHCl_3$).

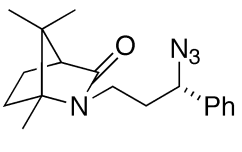
(1*R*,4*S*)-3-{(3*S*)-3-Azido-3-phenylpropyl}-3-azabicyclo[2.2.1]heptan-2-one (1j):



Colorless oil; IR (neat) □ 2096, 1696 cm^{-1}; ^1H NMR ($CDCl_3$) □ 1.34 (d, *J* = 9.2 Hz, 1H), 1.49-1.57 (m, 2H), 1.69-1.76 (m, 1H), 1.79-1.85 (m, 2H), 1.96 (ddd, *J* = 7.0, 7.0, 7.0 Hz, 2H), 2.77 (brd, *J* = 2.5 Hz, 1H), 2.85 (ddd, *J* = 14.0, 7.0, 7.0 Hz, 1H), 3.43 (ddd, *J* = 14.0, 7.0, 7.0 Hz, 1H), 3.78 (brs, 1H), 4.43 (dd, *J* = 7.0, 7.0 Hz, 1H), 7.28-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) □ 23.4, 26.5, 34.2, 36.9, 39.0, 44.7, 58.9, 63.0, 125.9, 127.4, 127.9, 137.9, 177.2; ESI-MS *m/z* 293 $[M+Na]^+$; HRMS (FAB): calcd. for $C_{15}H_{19}N_4O$ 271.1559 $[M+H]^+$, found 271.1558 $[M+H]^+$; $[□]_D^{23}$ –169.4 (*c* 0.70, $CHCl_3$).

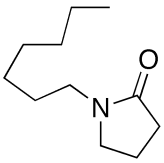
(1*S*,4*R*)-3-(3-Azidopropyl)-3-aza-4,7,7-trimethylbicyclo[2.2.1]heptan-2-one (1k):
Known compound (ref. [3a]).

(1*S*,4*R*)-3-{(3*S*)-3-Azido-3-phenylpropyl}-3-aza-4,7,7-trimethylbicyclo[2.2.1]heptan-2-one (1l):



Colorless oil; IR (neat) □ 2097, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) □ 0.84 (s, 3H), 0.91 (s, 3H), 1.23 (s, 3H), 1.42-1.53 (m, 2H), 1.74 (ddd, *J* = 9.5, 9.5, 3.4 Hz, 1H), 1.83-1.95 (m, 3H), 2.26 (d, *J* = 4.0 Hz, 1H), 3.04 (ddd, *J* = 14.4, 8.8, 5.2 Hz, 1H), 3.28 (ddd, *J* = 14.4, 8.6, 6.7 Hz, 1H), 4.46 (dd, *J* = 9.2, 5.2 Hz, 1H), 7.26-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) □ 12.1, 18.0, 18.4, 23.5, 33.5, 36.0, 36.6, 49.7, 54.9, 64.3, 70.7, 126.7, 128.3, 128.8, 139.4, 178.4; ESI-MS *m/z* 335 $[M+Na]^+$; HRMS (FAB): calcd. for $C_{18}H_{25}N_4O$ 313.2028 $[M+H]^+$, found 313.2029 $[M+H]^+$; $[□]_D^{25}$ –64.1 (*c* 1.1, $CHCl_3$).

1-Heptylpyrrolidin-2-one (1m):



Colorless oil; IR (neat) □ 1683 cm^{-1}; ^1H NMR ($CDCl_3$) □ 0.85 (t, *J* = 7.4 Hz, 3H), 1.20-1.30 (m, 8H), 1.45-1.51 (m, 2H), 1.95-2.01 (m, 2H), 2.36 (dd, *J* = 8.3, 8.3 Hz, 2H), 3.24 (dd, *J* = 7.3, 7.3 Hz, 2H), 3.35 (dd, *J* = 7.0, 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) □ 14.0, 17.9, 22.6, 26.8, 27.3, 29.0, 31.1, 31.7, 45.5, 47.1, 174.8; ESI-MS *m/z* 206 $[M+Na]^+$; HRMS (FAB): calcd. for $C_{11}H_{22}NO$ 184.1701 $[M+H]^+$, found 184.1701 $[M+H]^+$.

Bicyclic amidine synthesis via intramolecular cyclization of azide to lactam.

Procedure A:

To a 1,2-dichloroethane solution of azido lactam **1** (0.1 M), was added oxalyl bromide (2.0 M solution in dichloromethane) dropwise at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was warmed to room temperature and stirred for the designated time at the designated temperature (see Table 2). The resulting mixture was quenched with anisole (2 equiv. to **1**) and MeOH (one fifth volume to 1,2-dichloroethane) at 0 °C and stirred for 30 min at room temperature. The resulting mixture was extracted with 5% HCl aq., and aqueous layer was washed with dichloromethane. To the aqueous extract was added NaOH at 0 °C and extracted by dichloromethane. The organic extract was dried over Na_2SO_4. Evaporation of the solvent gave the pure amidine **2**.

Procedure B:

To a 1,2-dichloroethane solution of azido lactam **1** was added oxalyl bromide (2.0 M solution in dichloromethane) dropwise at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was warmed to room temperature and stirred for the designated time at the designated temperature (see Table 2). The resulting mixture was quenched with anisole (2 equiv. to **1**) and MeOH (one fifth volume to 1,2-dichloroethane) at 0 °C and then stirred for 30 min at room temperature. The resulting mixture was evaporated to half volume and extracted with 1N HCl aq. The aqueous extract was washed with CH_2Cl_2 and evaporated under reduced pressure. The resulting residue was passed through the amberlite IRA 400 (OH^-) with MeOH as eluent. Evaporation of the organic solvent gave the pure amidine **2**.

Procedure C:

To a 1,2-dichloroethane solution of azido lactam **1** was added oxalyl bromide (2.0 M solution in dichloromethane) dropwise at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was warmed to room temperature and stirred for the designated time at the designated temperature (see Table 2). The resulting mixture was quenched with anisole (2 equiv. to **1**) and MeOH (one fifth volume to 1,2-dichloroethane) at 0 °C and then stirred for 30 min at room temperature. The resulting mixture was evaporated to half volume and purified by silica gel column chromatography (SiO_2, ethyl acetate, CH_2Cl_2/MeOH 100/0–10/1) to afford amidine salt.

Procedure D:

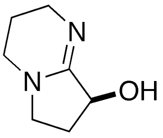
To a CH_2Cl_2 solution of azido lactam **1** was added oxalyl chloride (1.0 equiv. to **1**) dropwise at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was warmed to room temperature and and stirred for the designated time at the designated temperature (see Table 2). The resulting mixture was quenched and extracted with 1N HCl aq. The aqueous extract was washed with CH_2Cl_2 and evaporated under reduced pressure. The resulting residue was passed through the amberlite IRA 400 (OH^-) with MeOH as eluent. Evaporation of the organic solvent gave the pure amidine **2**.

1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) (2a):

Prepared by procedure A or B.

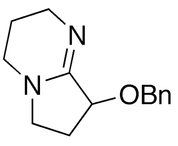
1.8-Diazabicyclo[5.3.0]undec-ene (DBU) (2b):
Prepared by procedure A or B.

(*S*)-7-Hydroxy-1,5-diazabicyclo[4.3.0]non-5-ene (2c):



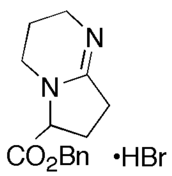
Prepared by procedure B; colorless solid; IR (neat) □ 1691 cm^{-1}; ^{1}H NMR ($CDCl_3$) □1.63-1.77 (m, 2H), 1.84-1.91 (m, 1H), 2.15-2.22 (m, 1H), 3.06-3.16 (m, 4H), 3.21-3.25 (m, 1H), 3.30 (ddd, *J* = 8.5, 8.5, 4.6 Hz, 1H), 4.41 (dd, *J* = 7.0, 7.0 Hz, 1H), 6.35 (brs, 1H); ^{13}C NMR ($CDCl_3$) □20.3, 29.3, 42.6, 43.0, 48.4, 70.4, 163.0; ESI-MS *m/z* 141 [M+H]$^+$; [□]$_D^{24}$ –74.7 (*c* 1.2, $CHCl_3$).

7-Benzyloxy-1,5-diazabicyclo[4.3.0]non-5-ene (2d):



Prepared by procedure B, D; colorless oil; IR (neat) □ 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) □1.73-1.79 (m, 2H), 1.96 (ddd, *J* = 13.4, 7.3, 3.6 Hz, 1H), 2.12 (dddd, *J* = 13.4, 6.7, 6.7, 6.7 Hz, 1H), 3.10-3.22 (m, 3H), 3.34-3.42 (m, 3H), 4.18 (dd, *J* = 6.7, 3.6 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.89 (d, *J* = 11.7 Hz, 1H), 7.24 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.31 (dd, *J* = 7.3, 7.4 Hz, 2H), 7.36 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) □20.5, 28.3, 43.1, 43.8, 48.6, 71.5, 78.4, 127.4, 127.8, 128.2, 138.4, 159.3; ESI-MS *m/z* 231 [M+H]$^+$; HRMS (FAB): calcd. for $C_{14}H_{19}N_2O$ 231.1497 [M+H]$^+$, found 231.1500 [M+H]$^+$.

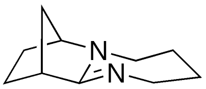
9-Benzyloxycarbonyl-1,5-diazabicyclo[4.3.0]non-5-ene•HBr (2e):



Prepared by procedure C; colorless oil; IR (neat) □ 1741, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$) □1.97-2.02 (m, 2H), 2.15 (dddd, *J* = 13.4, 9.1, 4.0, 3.4 Hz, 1H), 2.47 (dddd, *J* = 13.4, 9.5, 9.5, 8.9 Hz, 1H), 3.06 (ddd, *J* = 17.7, 9.1, 8.5 Hz, 1H), 3.27-3.35 (m, 2H), 3.40-3.50 (m, 3H), 4.41 (dd, *J* = 9.5, 3.4 Hz, 1H), 5.13 (d, *J* = 11.9 Hz, 1H), 5.19 (d, *J* = 11.9 Hz, 1H), 7.27-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) □18.5, 24.1, 29.2, 38.2, 42.5, 66.5, 68.2, 128.6, 128.9, 129.1, 134.4, 165.8, 169.1; ESI-MS *m/z* 259 [M+H]$^+$; HRMS (FAB): calcd. for $C_{15}H_{19}N_2O_2$ 259.1446 [M+H]$^+$, found 259.1446 [M+H]$^+$.

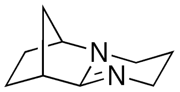
(*S*)-9-Hydroxymethyl-1,5-diazabicyclo[4.3.0]non-5-ene (2f):
Prepared by procedure B; Known compound (ref. [6c]).

(1*S*,9*R*)-2,7-Diazatricyclo[7.2.1.0^{2,8}]dodec-7-ene (2g):



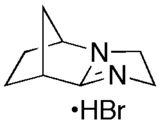
Prepared by procedure B, D; colorless oil; IR (neat) □ 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$) □1.14-1.20 (m, 1H), 1.27 (d, *J* = 9.5 Hz, 1H), 1.43-1.67 (m, 3H), 1.74-1.90 (m, 5H), 2.57 (ddd, *J* = 11.9, 11.9, 2.5 Hz, 1H), 2.78 (brs, 1H), 2.97-3.05 (m, 2H), 3.57 (brs, 1H) 3.60-3.65 (m, 1H); ^{13}C NMR ($CDCl_3$) □25.2, 25.8, 28.6, 29.1, 38.7, 47.7, 48.0, 50.7, 65.2, 168.9; ESI-MS *m/z* 165 [M+H]$^+$; HRMS (FAB): calcd. for $C_{10}H_{16}N_2$ 165.1392 [M+H]$^+$, found 165.1396 [M+H]$^+$; [□]$_D^{26}$ –152.2 (*c* 0.4, $CHCl_3$).

(1*S*,8*R*)-2,6-Diazatricyclo[6.2.1.$0^{2,7}$]undec-6-ene (2h):



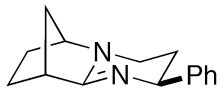
Prepared by procedure D; colorless oil; IR (neat) □ 1659 cm^{-1}; ^{1}H NMR (CDCl$_3$) □ 1.21 (d, *J* = 9.2 Hz, 1H), 1.34-1.48 (m, 2H), 1.48-1.62 (m, 2H), 1.64-1.67 (m, 1H), 1.70-1.80 (m, 2H), 2.73 (brd, *J* = 1.5 Hz, 1H), 2.92-2.97 (m, 1H), 3.02 (ddd, *J* = 11.3, 8.8, 6.1 Hz, 1H), 3.11 (ddd, *J* = 14.4, 8.3, 3.6 Hz, 1H), 3.25 (ddd, *J* = 14.4, 4.3, 4.3 Hz, 1H), 3.50 (brs, 1H); ^{13}C NMR (CDCl$_3$) □ 21.1, 25.9, 26.5, 38.0, 39.3, 43.3, 44.1, 60.5, 164.8; ESI-MS *m/z* 151 [M+H]$^+$; HRMS (FAB): calcd. for $C_9H_{15}N_2$ 151.1285 [M+H]$^+$, found 151.1289 [M+H]$^+$; [□]$_D^{23}$ –35.4 (*c* 1.5, CHCl$_3$).

(1*S*,7*R*)-2,5-Diazatricyclo[5.2.1.$0^{2,6}$]dec-5-ene•HBr (2i):



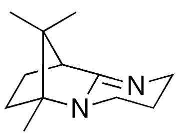
Prepared by procedure C; colorless solid; IR (neat) □ 1627 cm^{-1}; ^{1}H NMR (CD$_3$OD) □ 1.42-1.48 (m, 1H), 1.70-1.76 (m, 1H), 1.80 (d, *J* = 10.0 Hz, 1H), 1.91-1.95 (m, 1H), 2.13 (d, *J* = 10.0 Hz, 1H), 2.16-2.23 (m, 2H), 3.43 (brs, 1H), 3.44-3.52 (m, 1H), 3.80-3.86 (m, 1H), 4.11 (dd, *J* = 12.2, 6.1 Hz, 1H), 4.21 (brs, 1H); ^{13}C NMR (CD$_3$OD) □ 25.7, 27.3, 41.6, 44.5, 45.6, 51.0, 62.2, 181.3; ESI-MS *m/z* 137 [M+H]$^+$; HRMS (FAB): calcd. for $C_8H_{13}N_2$ 137.1079 [M+H]$^+$, found 137.1076 [M+H]$^+$; [□]$_D^{22}$ +23.0 (*c* 0.78, MeOH).

(1*S*,5*S*,8*R*)-5-Phenyl-2,6-diazatricyclo[6.2.1.$0^{2,7}$]undec-6-ene (2j):



Prepared by procedure B; colorless oil; IR (neat) □ 1651 cm^{-1}; ^{1}H NMR (CDCl$_3$) □ 1.31 (d, *J* = 9.2 Hz, 1H), 1.56-1.72 (m, 3H), 1.75-1.92 (m, 4H), 2.92-2.97 (m, 2H), 3.14 (ddd, *J* = 11.6, 6.7, 5.5 Hz, 1H), 3.59 (brs, 1H), 4.47 (dd, *J* = 6.5, 5.5 Hz, 1H), 7.14-7.18 (m, 1H), 7.22-7.28 (m, 4H); ^{13}C NMR (CDCl$_3$) □ 27.2, 27.2, 29.9, 38.8, 39.1, 45.1, 57.3, 61.5, 126.3, 126.6, 128.1, 144.8, 165.0; ESI-MS *m/z* 227 [M+H]$^+$; HRMS (FAB): calcd. for $C_{15}H_{19}N_2$ 227.1548 [M+H]$^+$, found 227.1552 [M+H]$^+$; [□]$_D^{24}$ +48.1 (*c* 0.48, CHCl$_3$).

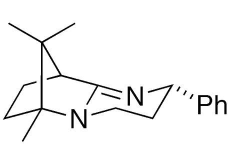
(1*R*,8*S*)-2,6-Diaza-1,11,11-trimethyltricyclo[6.2.1.$0^{2,7}$]undec-6-ene (2k):



Prepared by procedure D; colorless oil; IR (neat) □ 1660 cm^{-1}; ^{1}H NMR (CDCl$_3$) □ 0.84 (s, 3H), 0.89 (s, 3H), 1.02 (s, 3H), 1.36-1.51 (m, 3H), 1.63 (ddd, *J* = 10.0, 10.0, 3.6 Hz, 1H), 1.76-1.84 (m, 1H), 1.85-1.92 (m, 1H), 2.21 (d, *J* = 3.6 Hz, 1H), 2.94 (dd, *J* = 6.7, 5.5 Hz, 2H), 3.13 (ddd, *J* = 14.4, 8.6, 3.4 Hz, 1H), 3.28 (ddd, *J* = 14.4, 4.5, 4.5 Hz, 1H); ^{13}C NMR (CDCl$_3$) □ 11.2, 18.2, 18.2, 21.6, 25.8, 31.9, 36.9, 43.8, 48.3, 53.8, 69.8, 165.6; ESI-MS *m/z* 193 [M+H]$^+$; HRMS (FAB): calcd. for $C_{12}H_{21}N_2$ 193.1705 [M+H]$^+$, found 193.1706 [M+H]$^+$; [□]$_D^{24}$ +75.3 (*c* 0.82, CHCl$_3$).

(1*R*,5*S*,8*S*)-2,6-Diaza-1,11,11-trimethyl-5-phenyltricyclo[6.2.1.$0^{2,7}$]undec-6-ene (2l):

Prepared by procedure B; colorless oil; IR (neat) □ 1656 cm^{-1}; ^{1}H



NMR ($CDCl_3$) □0.91 (s, 3H), 0.97 (s, 3H), 1.11 (s, 3H), 1.44-1.48 (m, 1H), 1.54-1.57 (m, 2H), 1.69-1.74 (m, 1H), 2.00-2.08 (m, 2H), 2.47 (brd, *J* = 3.6 Hz, 1H), 2.94 (ddd, *J* = 11.3, 6.1, 4.3 Hz, 1H), 3.03-3.08 (m, 1H), 4.29 (dd, *J* = 8.5, 3.6 Hz, 1H), 7.17-7.19 (m, 1H), 7.26-7.29 (m, 4H); ^{13}C NMR ($CDCl_3$) □11.5, 18.4, 18.5, 26.3, 30.1, 32.1, 35.8, 49.1, 54.0, 56.3, 70.5, 126.4, 126.7, 128.2, 145.9, 166.2; ESI-MS *m/z* 269 $[M+H]^+$; HRMS (FAB): calcd. for $C_{18}H_{25}N_2$ 269.2017 $[M+H]^+$, found 269.2023 $[M+H]^+$; $[□]_D^{22}$ +74.0 (*c* 0.35, $CHCl_3$).

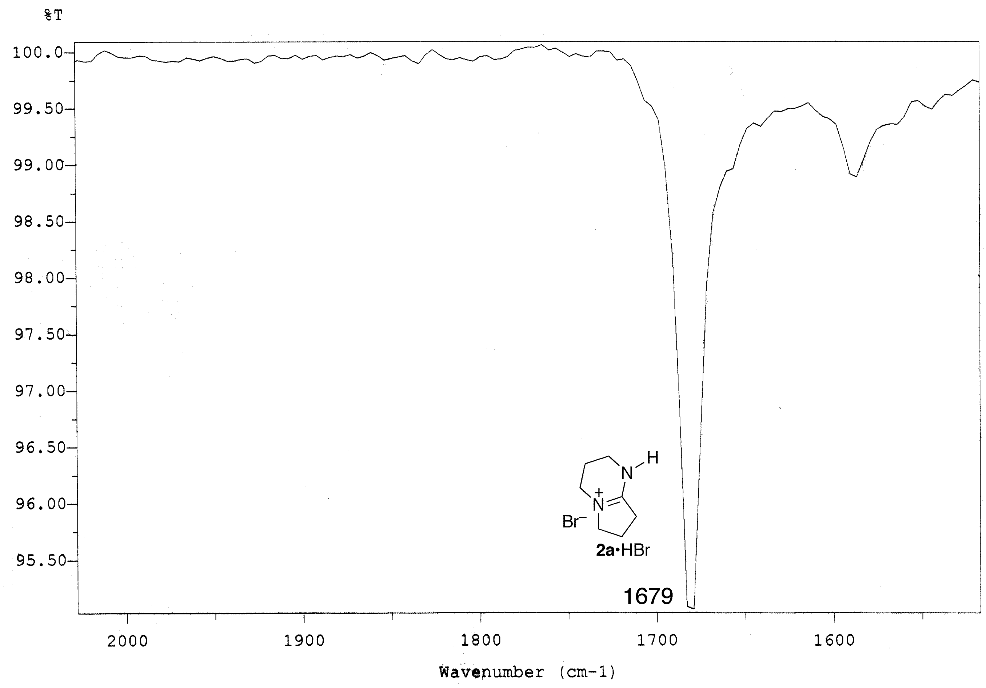
Procedure for in situ IR study.

Procedure for Figure 1 (a), (b):

To a 1,2-dichloroethane (10 mL) solution of **1a** (168.2 mg, 1 mmol) in 3-neck flask with a magnetic stirring bar, was equipped with ReactIR SiComp probe. The reaction mixture was cooled to 0 °C and IR scan was started (the spectra were acquired 16 scans per spectrum at a resolution of 16, scan rate: every 30 seconds for the first 1 hour, then every 1 minute). Oxalyl bromide (0.5 mL, 1 mmol, 2.0 M dichloromethane solution) was slowly added in the period of 2 min to 8 min. The reaction mixture was stirred at the same temperature until the reaction time reached 60 min. At 60 min, the reaction mixture was warmed to 25 °C and IR scan was continued.

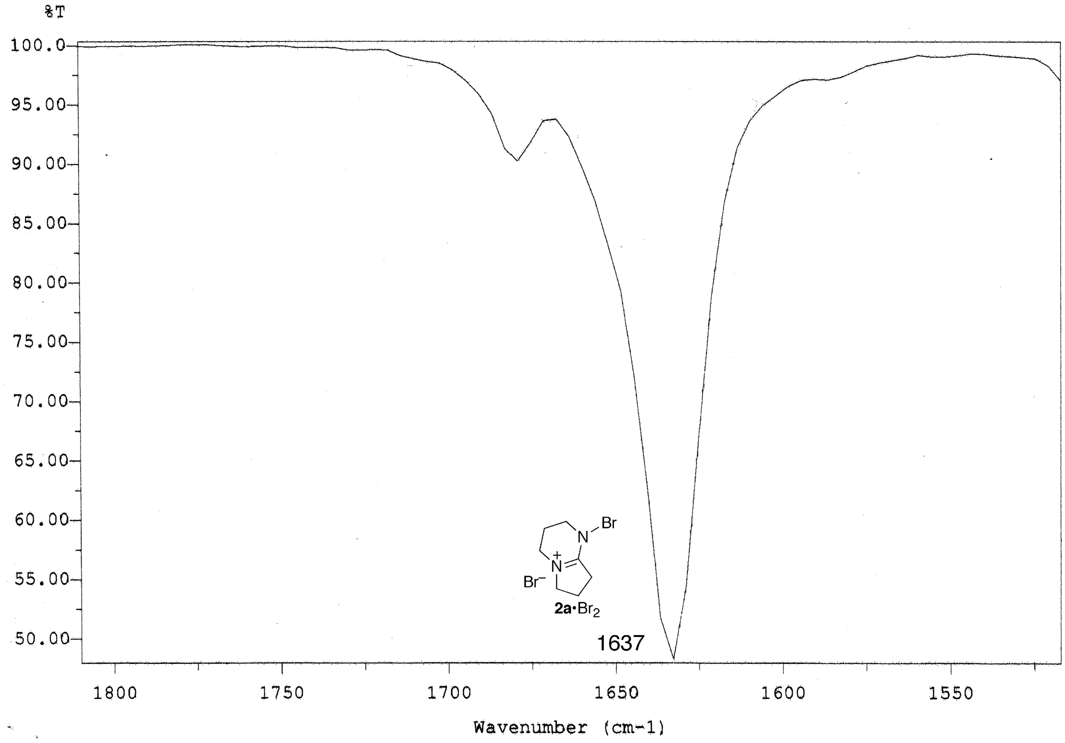
IR chart of 2a•HBr in 1,2-dichloroethane:

To a methanol (0.5 mL) solution of **2a** (247 □L, 2 mmol), was added 20% HBr in EtOH (0.5 mL) at room temperature . After stirring for 10 min at the same temperature, ether (4.0 ml) was added to the reaction mixture. The resulting white solid was filtered and washed with diethyl ether and dried in vacuo to give **2a**•HBr as a white solid (hygroscopic).

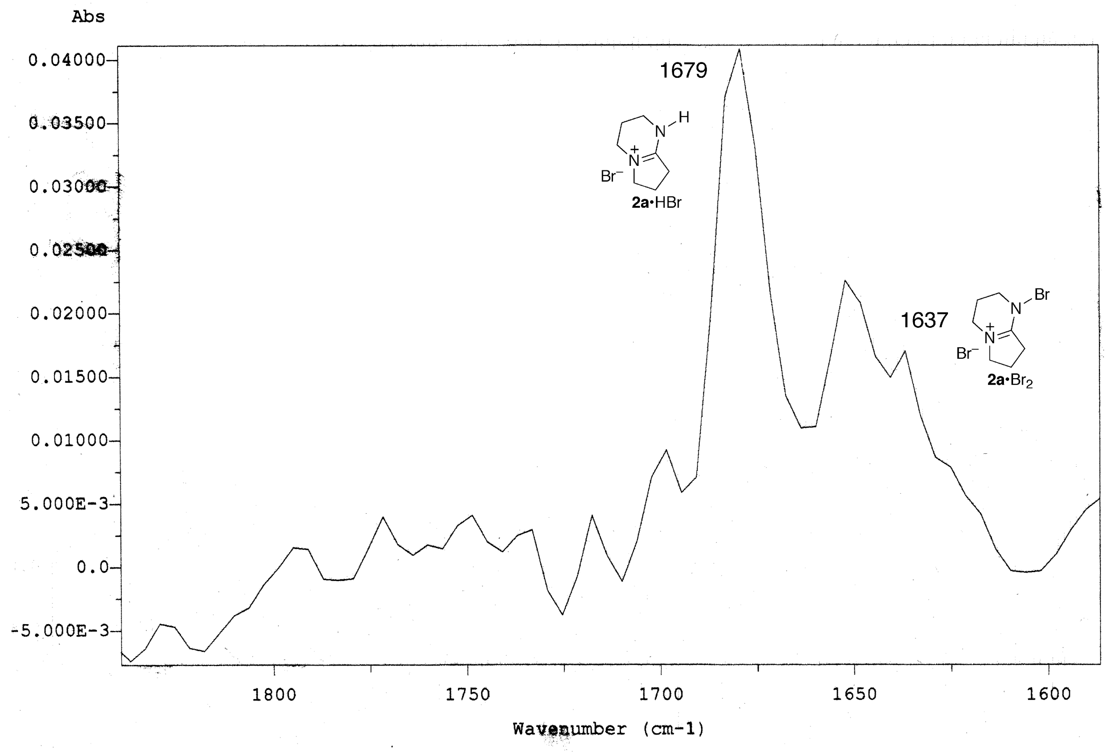


IR chart of $2a{\bullet}Br_2$ in 1,2-dichloroethane:

To a 1,2-dichloroethane (10 mL) solution of **2a** (247 μL, 2 mmol), was slowly added bromine (102 μL, 2 mmol) at 25 °C to give **2a•**Br.



The peak derived from **2a**•Br$_2$ was detected in Figure 1 (b). The magnified chart is shown below.



Procedure for Figure 1 (c):

To a 1,2-dichloroethane (10 mL) solution of **1m** (366.6 mg, 2 mmol) in 3-neck flask with a magnetic stirring bar, was equipped with ReactIR SiComp probe. The reaction mixture was cooled to 0 °C and IR scan was started (the spectra were acquired 16 scans per spectrum at a resolution of 16, scan rate: every 30 seconds for the first 1 hour, then every 1 minute). Oxalyl bromide (1.0 mL, 2 mmol, 2.0 M dichloromethane solution) was slowly added in the period of 2 min to 8 min. The reaction mixture was stirred at the same temperature until the reaction time reached 50 min. At 50 min, the reaction mixture was warmed to 25 °C and IR scan was continued.

Procedure for Figure 1 (d):

To a 1,2-dichloroethane (10 mL) solution of **2a** (247 □L, 2 mmol) in 3-neck flask with a magnetic stirring bar, was equipped with ReactIR SiComp probe. Bromine (102 □L, 2 mmol) was added slowly at 25 °C to give **2a**•Br. Then, IR scan was started (the spectra were acquired 16 scans per spectrum at a resolution of 16, scan rate: every 30 seconds) and MeOH (162 mL, 4 mmol) was added to this mixture at 2 min.