Supporting Informations

Strained Azetidinium Ylides: New Reagents for Cyclopropanation

François Couty,* Olivier David* Bénédicte Larmanjat and Jérôme Marrot

_Institut Lavoisier, Université de Versailles Saint-Quentin-en-Yvelines, 45 avenue des Etats-Unis, 78035 Versailles Cedex, France, odavid@chimie.uvsq.fr_

S2-S13 procedures for the preparation of compounds: 7, 8, 9, 10, 11, 12, 5, 6, 14, 15, 13, 16, 21, 25, 27, 31, 33, 35, 37.

S14: $^1$H and $^{13}$C NMR spectra of the azetidine 11
S15: $^1$H and $^{13}$C NMR spectra of the azetidine 12
S16: $^1$H and $^{13}$C NMR spectra of the azetidinium salt 5
S17: $^1$H and $^{13}$C NMR spectra of the azetidinium salt 3
S18: $^1$H and $^{13}$C NMR spectra of the pyrrolidinium salt 13
S19: $^1$H and $^{13}$C NMR spectra of the cyclopropane 16
S20: $^1$H and $^{13}$C NMR spectra of the cyclopropane 21
S21: $^1$H and $^{13}$C NMR spectra of the cyclopropane 25
S22: $^1$H and $^{13}$C NMR spectra of the cyclopropane 27
S23: $^1$H and $^{13}$C NMR spectra of the cyclopropane 31
S24: $^1$H and $^{13}$C NMR spectra of the cyclopropane 33a
S25: $^1$H and $^{13}$C NMR spectra of the cyclopropane 35a
S26: $^1$H and $^{13}$C NMR spectra of the cyclopropane 37a
S27: Crystal structures of compounds 27, 31, 33b and 35a
General comments

$^1$H and $^{13}$C spectra were recorded at 300 and 75 MHz respectively; chemical shifts are reported in ppm from TMS. All the reactions were carried out under argon. Column chromatography was performed on a silica gel 230-400 mesh by using various mixtures of diethyl ether (Et$_2$O), ethyl acetate (AcOEt) and petroleum ether (PE). The TLCs were run on Kieselgel 60F254 plates. The melting points are uncorrected. THF and ether were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. The composition of the stereoisomeric mixtures was determined by NMR analysis on crude products before any purification.

General procedure for cyanomethylation:

To a solution of amino alcohol (0.10 mol) in 90 mL of acetonitrile was added K$_2$CO$_3$ (19.2 g, 0.14 mol, 1.4 eq) and bromoacetonitrile (7.6 mL, 0.11 mol, 1.2 eq). The solution was stirred at room temperature for 36 h. The volatiles were evaporated and the residue was partitioned between water and dichloromethane. After extraction with dichloromethane and drying of the organic phases over MgSO$_4$, evaporation yielded the cyano-alcohols which were used without further purification.

[(2-Hydroxyethyl)-methyl-amino]-acetonitrile (7)

Using 5.01 g of 2-methylaminoethanol (67 mmol), 2.30 g of 7 were obtained as a yellow volatile liquid (30%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 3.65 (t, 2H, $J = 5.0$ Hz), 3.59 (s, 2H), 2.71 (bs, 1H, OH), 2.65 (t, 2H, $J = 5.0$ Hz), 2.40 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 114.7 (Cq), 58.7 (CH$_2$), 57.3 (CH$_2$), 45.5 (CH$_2$), 41.7 (CH$_3$). IR (CHBr$_3$, cm$^{-1}$) v: 3518, 3359, 2945, 2863, 2801, 2233. HRMS (ESI, TOF MS) m/z: calcd for [MH$^+$] 115.0871, found 115.0874.
[Benzyl-(2-hydroxyethyl)-amino]-acetonitrile (8)

Using 15 g of benzylaminoethanol (0.10 mol), 16 g of a yellow liquid were obtained (85%). (AcOEt/PE: 1/1, Rf = 0.32). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 7.40-7.30 (m, 5H), 3.73 (bs, 4H), 3.52 (s, 2H), 2.84 (t, 2H, $J$ = 5.3 Hz), 2.32 (bs, 1H, OH). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 136.7 (Cq), 129.2 (CH), 128.7 (CH), 128.3 (CH), 114.7 (Cq), 58.9 (CH$_2$), 58.1 (CH$_2$), 55.7 (CH$_2$), 41.8 (CH$_2$). IR (CHBr$_3$, cm$^{-1}$) v: 3426, 3087, 2960, 2939, 2878, 2832, 2233, 1654, 1598. HRMS (ESI, TOF MS) m/z: calcd for [MH$^+$] 191.1184, found 191.1194.

General procedure for the chlorination:

The alcohol (20 mmol) is dissolved in 50 mL of dichloromethane. At 0°C, SOCl$_2$ (2.9 mL, 40 mmol, 2 eq) was added and after 10 min of stirring, the mixture was heated to reflux for 3h. The solution was then neutralized with a saturated solution of NaHCO$_3$ (strong gas evolution!) to reach a basic pH, the aqueous phase was then extracted three times with dichloromethane, drying over MgSO$_4$ and evaporation of the solvent offered the chloro derivatives which were used as such.

[(2-Chloro-ethyl)-methyl-amino]-acetonitrile (9)

Starting with 2.30 g of [(2-Hydroxy-ethyl)-methyl-amino]-acetonitrile 7 (20 mmol). 1.44 g of a brown liquid was obtained (54%). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 3.61 (s, 2H), 3.59 (t, 2H, $J$ = 6.3 Hz), 2.85 (t, 2H, $J$ = 6.3 Hz), 2.44 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 114.6 (Cq), 57.0 (CH$_2$), 45.4 (CH$_2$), 41.8 (CH$_3$), 41.3 (CH$_2$). IR (CHBr$_3$, cm$^{-1}$) v: 2957, 2842, 2233.

[Benzyl-(2-chloroethyl)-amino]-acetonitrile (10)

Starting with 9.1 g of [Benzyl-(2-hydroxy-ethyl)-amino]-acetonitrile 8 (48 mmol), 9.5 g of an orange oil were obtained (95%). (Et$_2$O/Pentane: 3/7, Rf = 0.52). $^1$H NMR (300 MHz, CDCl$_3$)
\( \delta: 7.42-7.41 \) (m, 5H), 3.80 (s, 2H), 3.67 (t, 2H, \( J = 6.4 \) Hz), 3.57 (s, 2H), 3.05 (t, 2H, \( J = 6.4 \) Hz). \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta: 136.6 \) (Cq), 129.1 (CH), 128.9 (CH), 128.1 (CH), 114.9 (Cq), 58.3 (CH\(_2\)), 55.5 (CH\(_2\)), 41.7 (CH\(_2\)), 41.5 (CH\(_2\)). IR (CHBr\(_3\), cm\(^{-1}\)) \( \nu: 3087, 3024, 2955, 2832, 2228, 1611, 1599. \) HRMS (ESI, TOF MS) m/z: calcld for \([\text{MH}^+]\) 209.0846, found 209.0846.

**General procedure for the azetidine formation:**

To a solution of chlorinated compound (11 mmol) in 15 mL of dry THF, at -78°C, under argon, 14 mL of a LiHMDS solution [1M] in THF (14 mmol, 1.3 eq) were added dropwise. The solution was stirred while allowed to warm up to -10°C for 3h. The reaction was stopped by addition of a saturated solution of NH\(_4\)Cl, after addition of water and extraction with dichloromethane, drying over MgSO\(_4\) and evaporation yielded the title compound which was purified by flash chromatography on silica gel.

**1-Methyl-azetidine-2-carbonitrile (11)**

1.44 g of [(2-Chloro-ethyl)-methyl-amino]-acetonitrile (9) (11 mmol) were used. After chromatography using (Et\(_2\)O/Pentane: 2/8, \( \text{Rf} = 0.18 \)) as eluent, 346 mg of a colourless oil were isolated (33%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta: 3.83 \) (t, 1H, \( J = 10.9 \) Hz), 3.38 (q, 1H, \( J = 10.9 \) Hz), 3.08 (q, 1H, \( J = 10.9 \) Hz), 2.38 (q, 2H, \( J = 10.9 \) Hz), 2.35 (s, 3H). \(^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta: 118.9 \) (Cq), 54.5 (CH\(_2\)), 53.8 (CH), 43.3 (CH\(_3\)), 22.7 (CH\(_2\)). IR (CHBr\(_3\), cm\(^{-1}\)) \( \nu: 2960, 2878, 2791, 2176. \)

**1-Benzyl-azetidine-2-carbonitrile (12)**

Starting with 5.42 g of [Benzyl-(2-chloro-ethyl)-amino]-acetonitrile (10) (11 mmol) and after chromatographic purification (Et\(_2\)O/Pentane: 2/8, \( \text{Rf} = 0.18 \)), 3.7 g of a colorless oil were
obtained (82%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.15-7.12 (m, 5H), 3.78 (t, 1H, $J = 7.3$ Hz), 3.58 (d from an AB system, 1H, $J = 12.8$ Hz), 3.50 (d from an AB system, 1H, $J = 12.8$ Hz), 3.21 (q, 1H, $J = 7.3$ Hz), 2.97 (q, 1H, $J = 7.3$ Hz), 2.25 (q, 2H, $J = 7.3$ Hz). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 136.2 (Cq), 128.8 (CH), 128.6 (CH), 127.7 (CH), 118.9 (Cq), 60.9 (CH$_2$), 52.5 (CH$_2$), 51.7 (CH), 25.7 (CH$_2$). IR (CHBr$_3$, cm$^{-1}$) v: 3053, 2945, 2837, 2238, 1664, 1598. HRMS (ESI, TOF MS) m/z: calcld for [MH$^+$] 173.1079, found 173.106.

General procedure for the azetidine alkylation:

The azetidine (1.2 mmol) was dissolved in 10 mL of dry dichloromethane. After cooling at 0°C, TfOMe (280 μL, 2.5 mmol, 2 eq) was added. The mixture was stirred for 1 hour and then all volatiles were removed to give the title compound.

Trifluoro-methanesulfonate-2-cyano-1,1-dimethyl-azetidinium (5)

Using 120 mg (1.2 mmol) of 1-methyl-azetidine-2-carbonitrile 11, 163.9 mg of a pink solid were obtained (46%). $^1$H NMR (300 MHz, Acetone-D$_6$) $\delta$: 6.00 (t, 1H, $J = 9.3$ Hz), 4.79 (q, 1H, $J = 9.3$ Hz), 4.62-4.53 (m, 1H), 3.66 (s, 3H), 3.62 (s, 3H), 3.32-3.19 (m, 2H). $^{13}$C NMR (75 MHz, Acetone-D$_6$) $\delta$: 113.5 (Cq), 66.7 (CH), 63.4 (CH$_2$), 54.0 (CH$_3$), 50.4 (CH$_3$), 21.0 (CH$_2$). IR (KBr, cm$^{-1}$) v: 2960, 2237, 1470. HRMS (ESI, TOF MS) m/z: calcld for [M$^+$] 111.0922, found 111.0919.

Trifluoro-methanesulfonate-1-benzyl-2-cyano-1-methyl-azetidinium (6)

500 mg (2.9 mmol) of 1-benzyl-azetidine-2-carbonitrile 12 were used to provide 870 mg of a white solid (83%). mp = 162°C. $^1$H NMR (300 MHz, Acetone-D$_6$) $\delta$: 7.78-7.56 (m, 5H), 6.32 (t, 1H, $J = 9.2$ Hz), 5.34-4.93 (m, 3H), 4.44-4.33 (m, 1H), 3.52 (s, 3H), 3.46-3.30 (m, 2H). $^{13}$C NMR (75 MHz, Acetone-D$_6$) $\delta$: 133.6 (Cq), 132.9 (CH), 131.9 (CH), 130.5 (CH),...
113.1 (Cq), 68.6 (CH), 64.8 (CH$_2$), 60.7 (CH$_2$), 46.6 (CH$_2$), 21.5 (CH$_2$). IR (KBr, cm$^{-1}$) ν: 3095, 3032, 3006, 2975, 2239, 1470, 1449. HRMS (ESI, TOF MS) m/z: calcd for [M$^+$] 187.1235, found 187.1245.

1-Benzyl-pyrrolidine-2-carboxylic acid amide (14)

To a suspension of benzylproline 488 mg (2.22 mmol) in 15 mL of dioxane, pyridine was added (109 μL, 1.33 mmol, 0.6 eq) followed by Boc$_2$O (0.63 g, 2.9 mmol, 1.3 eq) and finally (NH$_4$)$_2$CO$_3$ (0.28 g, 2.9 mmol, 1.3 eq). The mixture was stirred overnight. The solvent is removed and the crude product is partitioned between EtOAc and water. The organic layers were dried over MgSO$_4$, and evaporated to yield 398 mg of an off-white solid (88%). Spectroscopic data were identical to those previously reported.$^1$

1-Benzyl-pyrrolidine-2-carbonitrile (15)

To a solution of 1-Benzyl-pyrrolidine-2-carboxylic acid amide (14) (398 mg, 1.9 mmol) in 12 mL of dichloromethane, diisopropylethylamine (1.6 mL, 9.3 mmol, 4.8 eq) was added and the mixture was cooled to 0°C. Trifluoroacetic anhydride was added dropwise (553 μL, 3.9 mmol, 2 eq). After 40 min of stirring at room temperature, the reaction was poured in a saturated solution of Na$_2$(CO$_3$)$_2$, extraction with dichloromethane, drying of the organic phases over MgSO$_4$ and evaporation of the solvents, offered the crude product which was purified by flash chromatography (Et$_2$O/ PE, 2/8, Rf=0.68), to isolate 239 mg of a pale yellow oil (66%).$^1$ H NMR (300 MHz, CDCl$_3$) δ: 7.20-7.19 (m, 5H), 3.84 (d from an AB system, 1H, $J$ = 13.1 Hz), 3.63-3.57 (m, 2H), 2.90-2.82 (m, 1H), 2.54-2.46 (q, 1H, $J$ = 8.5 Hz), 2.08-2.02 (m, 2H), 1.91-1.81 (m, 2H).$^{13}$ C NMR (75 MHz, CDCl$_3$) δ: 137.6 (Cq), 128.9 (CH), 128.5 (CH), 127.5 (CH), 118.03 (Cq), 56.6 (CH$_2$), 53.2 (CH), 51.2 (CH$_2$), 29.6 (CH$_2$), 21.9 (CH$_2$). IR (CHBr$_3$, cm$^{-1}$) ν: 3137, 2960, 2873, 2811, 1669, 1557, data in accordance
with the previously reported characteristics. \textit{HRMS} (ESI, TOF MS) m/z: calcd for [MH$^+$ - HCN] 160.1126, found 160.1132.

1-benzyl-2-cyano-1-methyl-pyrrolidinium trifluoromethanesulfonate (13)

Cyanopyrrolidine (15) (112 mg, 6.01 mmol) was dissolved in 5 mL of dichloromethane and the resulting solution was cooled to 0°C. TfOMe (136 μL, 1.20 mmol, 2 eq) was added and the solution allowed to warm up to room temperature. The solvent was evaporated and the residue was triturated in Et$_2$O. The white solid was filtrated and dry under vacuum, 208 mg constituted of 2 diastereoisomers in a 55/45 ratio (93%) were obtained. \textit{\textsuperscript{1}H NMR} (300 MHz, Acetone-D$_6$) $\delta$: 7.66-7.42 (m, 10H), 5.27 (t, 1H, $J = 1$ Hz), 5.17 (t, 1H, $J = 9.4$ Hz), 4.85 (d, 2H, $J = 7.5$ Hz), 4.80 (d, 2H, $J = 8.8$ Hz), 3.95-3.75 (m, 3H), 3.65-3.5 (m, 1H), 3.26 (s, 3H), 3.23 (s, 3H), 2.90-2.65 (m, 2H), 2.55-2.45 (m, 2H), 2.45-2.27 (m, 4H). \textit{\textsuperscript{13}C NMR} (75 MHz, Acetone-D$_6$) $\delta$: 133.9 (CH), 133.8 (CH), 132.0 (CH), 131.9 (Cq), 130.9 (CH), 130.3 (CH), 130.2 (CH), 128.5 (Cq), 124.2 (Cq), 119.9 (Cq), 68.6 (CH$_2$), 66.1 (CH$_2$), 65.4 (CH), 65.3 (CH$_2$), 64.5 (CH$_2$), 62.6 (CH), 48.9 (CH$_3$), 46.1 (CH$_3$), 28.2 (CH$_2$), 28.0 (CH$_2$), 21.2 (CH$_2$), 20.9 (CH$_2$). \textit{IR} (KBr, cm$^{-1}$) v: 3064, 2967, 2845, 2805, 2189, 1622, 1596. \textit{HRMS} (ESI, TOF MS) m/z: calcd for [M$^+$] 201.1392, found 201.1388.

\textbf{General procedure for ammonium ylde cyclopropanation:}

A solution of azetidinium salt (0.80 mmol) in dry THF was cooled down to -78°C, Michael acceptor (0.97 mmol, 1.2 eq) was added, followed by lithium hexamethyldisilazane c = 2 mol.L$^{-1}$ in THF (1.70 mmol, 2 eq). The mixture was stirred while allowed to warm up to -30°C over a one hour period. The reaction was then stopped by addition of 10 mL of a saturated solution of ammonium chloride. Water was added and the aqueous layer was extracted three times with 15 mL of dichloromethane. After drying over magnesium sulfate.
and evaporation, the crude material was checked in proton NMR. Chromatographic purification using silica gel gave the cyclopropane.

2-Cyano-2-(2-dimethylamino-ethyl)-cyclopropanecarboxylic acid methyl ester (16)
Following the general procedure with 100 mg of Trifluoro-methanesulfonate-2-cyano-1,1-dimethyl-azetidinium (5) (0.80 mmol) and with methyl acrylate, after flash chromatography on silica gel using (Et₂O/Pentane: 3/7, Rf = 0.3) as eluent, 50 mg of a pale yellow oil were isolated (71%). ¹H NMR (300 MHz, CDCl₃) δ: 3.68 (s, 3H), 2.54-2.44 (m, 1H), 2.30-2.23 (m, 2H), 2.15 (s, 6H), 1.94-1.77 (m, 2H), 1.56 (dd, 1H, J = 5.2 Hz and 8.8 Hz), 1.40 (dd, 1H, J = 5.2 Hz et 6.0 Hz). ¹³C NMR (75 MHz, CDCl₃) δ: 169.3 (Cq), 121.5 (Cq), 57.3 (CH₂), 52.6 (CH₃), 45.6 (CH₃), 30.3 (Cq), 26.5 (CH₂), 25.4 (CH), 19.1 (CH₂). IR (CHBr₃, cm⁻¹) v: 2955, 2868, 2811, 2238, 1736, 1649, 1598. HRMS (ESI, TOF MS) m/z: calcd for [MH⁺] 197.1290, found 197.1282.

3-[2-(Benzyl-methyl-amino)-ethyl]-3-cyano-cyclopropane-1,2-dicarboxylic acid diethyl ester (21)
Following the general procedure with 939 mg of Trifluoro-methanesulfonate-1-benzyl-2-cyano-1-methyl-azetidinium (6) (2.62 mmol) and with diethylfumarate, after flash chromatography on silica gel using (Et₂O/PE: 1/1, Rf = 0.4) as eluent, 750 mg of a light yellow liquide were isolated (80%). This compound was also obtained using diethylmaleate as electrophile, 80 mg of an yellow oil (28%). ¹H NMR (300 MHz, CDCl₃) δ: 7.25-7.19 (m, 5H), 4.20-3.00 (m, 4H), 3.45 (s, 2H), 2.76 (d from an AB system, 1H, J = 6.4 Hz), 2.63- 2.50 (m, 2H), 2.43 (d from an AB system, 1H, J = 6.4 Hz), 2.09 (s, 3H), 2.02-1.91 (m, 2H), 1.26-1.17 (m, 6H). ¹³C NMR (75 MHz, CDCl₃) δ: 167.1 (Cq), 167.0 (Cq), 137.6 (Cq), 128.9 (CH), 128.3 (CH), 127.2 (CH), 117.7 (Cq), 62.8 (CH₂), 62.2 (CH₂), 62.1 (CH₂), 54.7 (CH₂),
41.9 (CH₃), 31.7 (CH), 31.2 (CH), 26.9 (CH₂), 24.0 (Cq), 14.15 (CH₃), 14.12 (CH₃). **IR** (CHBr₃, cm⁻¹) v: 3107, 2975, 2939, 2806, 2248, 1731, 1603. **HRMS** (ESI, TOF MS) m/z: calcd for [MH⁺] 359.1971, found 359.1947.

**3-[3-(Benzyl-methyl-amino)-propyl]-3-cyano-cyclopropane-1,2-dicarboxylic acid diethyl ester (25)**

Following the general procedure with Trifluoro-methanesulfonate-1-benzyl-2-cyano-1-methyl-pyrrolidinium (13) (127 mg, 0.34 mmol) and with diethylfumarate, after flash chromatography on silica gel using (Et₂O/PE: 1/1, Rf = 0.14) as eluent, 18.3 mg of a pale yellow oil were isolated (14 %). **¹H NMR** (300 MHz, CDCl₃) δ: 7.23-7.19 (m, 5H), 4.22-4.09 (m, 4H), 3.41 (s, 2H), 2.78 (d from an AB system, 1H, J = 6.5 Hz), 2.46 (d from an AB system, 1H, J = 6.5 Hz), 2.36-2.33 (m, 2H), 2.10 (s, 3H), 1.86-1.60 (m, 4H), 1.25-1.20 (m, 6H). **¹³C NMR** (75 MHz, CDCl₃) δ: 167.1 (Cq), 166.9 (Cq), 129.1 (CH), 128.3 (CH), 127.1 (CH), 125.6 (Cq), 117.9 (Cq), 62.3 (CH₂), 62.2 (CH₂), 62.18 (CH₂), 55.8 (CH₂), 41.8 (CH₃), 31.9 (CH), 31.4 (CH), 26.9 (CH₂), 24.9 (CH₂), 17.2 (CH₃), 17.1 (CH₃). **IR** (CHBr₃, cm⁻¹) v: 3043, 2975, 2929, 2878, 2248, 1721, 1639, 1588. **HRMS** (ESI, TOF MS) m/z: calcd for [MH⁺] 373.2127, found 373.2130.

**2-Cyano-2-(2-dimethylamino-1-phenyl-propyl)-cyclopropanecarboxylic acid methyl ester (27)**

Following the general procedure with 300 mg of Trifluoro-methanesulfonate-2-cyano-1,1,4-trimethyl-3-phenyl-azetidinium (26a) (0.80 mmol) and with methyl acrylate, after flash chromatography on silica gel using (Et₂O/Pentane: 3/7, Rf = 0.6) as eluent, 160 mg of a white solide (70%) were isolated. mp = 85°C, [α]₂⁰_D = +151.7 (c = 1.09, CHCl₃), **¹H NMR** (300 MHz, CDCl₃) δ: 7.29-7.27 (m, 5H), 3.30 (s, 3H), 3.14-3.05 (m, 1H), 2.64 (d, 1H, J =
11.2 Hz), 2.32 (s, 6H), 2.20 (dd, 1H, J = 7.1 Hz and 8.0 Hz), 1.84-1.75 (m, 2H), 0.65 (d, 3H, J = 6.6 Hz). ^13C NMR (75 MHz, CDCl₃) δ: 169.5 (Cq), 140.5 (Cq), 128.4 (CH), 128.3 (CH), 127.2 (CH), 122.5 (Cq), 62.7 (CH), 52.0 (CH₃), 49.5 (CH), 40.2 (CH₃), 24.9 (CH), 23.4 (Cq), 22.2 (CH₂), 8.6 (CH₃). IR (KBr, cm⁻¹) ν: 3104, 3078, 2960, 2919, 2863, 2837, 2781, 2238, 1721, 1605. HRMS (ESI, TOF MS) m/z: calcld for [MH⁺] 287.1760, found 287.1744.

7-(2-Dimethylamino-1-phenyl-propyl)-2-oxo-bicyclo [4.1.0]heptane-7-carbonitrile (31)

Following the general procedure with 300 mg of Trifluoro-methanesulfonate 2-cyano-1,1,4-trimethyl-3-phenyl-azetidinium (26a) (0.80 mmol) and with cyclohexenone, after flash chromatography on silica gel using (Et₂O/Pentane: 4/6, Rf = 0.48) as eluent, 312 mg of a white solid was obtained (90%). mp = 118°C, [α]_D^{28} = +88.9 (c = 1.0, CHCl₃), ^1H NMR (300 MHz, CDCl₃) δ: 7.40-7.25 (m, 5H), 3.30-3.20 (m, 1H), 2.53-2.42 (m, 1H), 2.35 (s, 6H), 2.32-2.25 (m, 2H), 2.07-2.02 (m, 4H), 2.00-1.71 (m, 2H), 0.70 (d, 3H, J = 6.4 Hz). ^13C NMR (75 MHz, CDCl₃) δ: 204.5 (Cq), 139.9 (Cq), 129.1 (CH), 128.7 (CH), 127.9 (CH), 120.0 (Cq), 62.0 (CH), 57.7 (CH), 40.5 (CH₃), 38.9 (CH₂), 34.0 (CH), 33.5 (CH), 32.0 (Cq), 24.6 (CH₂), 20.0 (CH₂), 9.0 (CH₃). IR (KBr, cm⁻¹) ν: 3032, 2970, 2939, 2852, 2827, 2770, 2217, 1700, 1608, 1597. HRMS (ESI, TOF MS) m/z: calcld for [MH⁺] 297.1967, found 297.1972.

2-Cyano-2-(2-dimethylamino-1-phenyl-propyl)-3-methyl-cyclopropanecarboxylic acid methyl ester (33)

The general procedure was followed with 456 mg of Trifluoro-methanesulfonate-2-cyano-1,1,4-trimethyl-3-phenyl-azetidinium (26a) (1.22 mmol) and with methylcrotonate. Two diastereoisomers were observed in proton NMR in a 75/25 ratio. After flash chromatography
on silica gel using (Et₂O/ Pentane, 3/7, Rf_major= 0.71, Rf_minor= 0.20). 264 mg of a colorless liquid (72%) 33a and 82 mg of a white solid (22%) 33b were isolated.

Major diastereoisomer (33a)

\[[\alpha]_D^{20} = +111.8 \ (c = 1.1, \text{CHCl}_3)\] 

$^1$H NMR (300 MHz, CDCl₃) \(\delta\): 7.29-7.22 (m, 5H), 3.29 (s, 3H), 3.13 (dq, 1H, \(J = 6.4\) Hz and 12.0 Hz), 2.59 (d, 1H, \(J = 12.0\) Hz), 2.24 (s, 6H), 1.94-1.83 (m, 1H), 1.74 (d, 1H, \(J = 6\) Hz), 1.30 (d, 3H, \(J = 9\) Hz), 0.58 (d, 3H, \(J = 6.4\) Hz). $^{13}$C NMR (75 MHz, CDCl₃) \(\delta\): 169.7 (Cq), 140.2 (Cq), 128.5 (CH), 128.2 (CH), 127.1 (CH), 120.6 (Cq), 62.3 (CH), 51.8 (CH₃), 50.5 (CH), 40.1 (CH₂), 31.8 (CH), 30.3 (Cq), 28.2 (CH), 14.2 (CH₃), 8.4 (CH₃). IR (CHBr₃, cm⁻¹) \(\nu\): 3011, 2919, 2858, 2832, 2228, 1721, 1608, 1597. HRMS (ESI, TOF MS) m/z: calcd for [MH⁺] 301.1916, found 301.1925.

Minor diastereoisomer (33b)

mp = 128°C, \[[\alpha]_D^{20} = -583.3 \ (c = 0.1, \text{CHCl}_3)\] 

$^1$H NMR (300 MHz, CDCl₃) \(\delta\): 7.25-7.15 (m, 5H), 3.53 (s, 3H), 3.34 (dq, 1H, \(J = 6.5\) Hz and 11.1 Hz), 2.40-2.29 (m, 7H), 1.24 (d, 3H, \(J = 9\) Hz), 1.21 (d, 1H, \(J = 6\) Hz), 0.58 (d, 3H, \(J = 6.5\) Hz). $^{13}$C NMR (75 MHz, CDCl₃) \(\delta\): 169.7 (Cq), 141.5 (Cq), 129.0 (CH), 127.9 (CH), 127.3 (CH), 120.4 (Cq), 62.3 (CH), 52.2 (CH₃), 49.0 (CH), 41.1 (CH), 33.1 (CH), 31.2 (CH), 31.0 (Cq), 12.8 (CH₃), 9.5 (CH₃). IR (KBr, cm⁻¹) \(\nu\): 3027, 2970, 2955, 2852, 2822, 2228, 1731, 1598, 1582. HRMS (ESI, TOF MS) m/z: calcd for [MH⁺] 301.1916, found 301.1892.

2-Cyano-2-(2-dimethylamino-1-phenyl-propyl)-3-phenyl-cyclopropanecarboxylic acid methyl ester (35)

The general procedure was followed with 306 mg of Trifluoro-methanesulfonate-2-cyano-1,1,4-trimethyl-3-phenyl-azetidinium (26a) (0.82 mmol) and with ethyl cinnamate. Two
diastereoisomers were observed in proton NMR in a 72/28 ratio. After flash chromatography on silica gel using (Et₂O/Pentane: 3/7, Rf<sub>major</sub> = 0.11, Rf<sub>minor</sub> = 0.51). 59 mg of a white solid (19%) 35b and 173 mg of an off-white solid (56%) 35a, were obtained.

**Major diastereoisomer (35a)**

mp = 80°C, [α]<sub>D</sub> = +28.8 (c = 1.1, CHCl₃), <sup>1</sup>H NMR (300 MHz, CDCl₃) δ: 7.19-7.11 (m, 10H), 4.14-3.95 (m, 2H), 3.50 (d, 1H, J = 5.1 Hz), 3.37-3.07 (m, 1H), 2.09 (d, 1H, J = 7.4 Hz), 2.01 (d, 1H, J = 5.1 Hz), 1.74 (s, 6H), 1.09 (t, 3H, J = 6.5 Hz), 0.34 (d, 3H, J = 6.5 Hz).<sup>13</sup>C NMR (75 MHz, CDCl₃) δ: 168.5 (Cq), 141.9 (Cq), 132.5 (Cq), 129.3 (CH), 129.1 (CH), 128.5 (CH), 128.0 (CH), 127.8 (CH), 127.4 (CH), 120.2 (Cq), 62.6 (CH), 61.4 (CH_<sub>2</sub>), 47.6 (CH), 40.7 (CH₃), 39.7 (CH), 31.7 (Cq), 30.4 (CH), 14.2 (CH₃), 9.3 (CH₃). IR (KBr, cm<sup>-1</sup>) v: 3111, 3086, 2975, 2925, 2859, 2233, 1749, 1603. HRMS (ESI, TOF MS) m/z: calcd for [MH<sup>+</sup>] 377.2229, found 377.2217.

**Minor diastereoisomer (35b)**

mp = 49°C, [α]<sub>D</sub> = +17.8 (c = 1.0, CHCl₃). <sup>1</sup>H NMR (300 MHz, CDCl₃) δ: 7.35-7.15 (m, 10H), 3.90-3.80 (m, 1H), 3.67-3.56 (m, 1H), 3.20-3.10 (m, 1H), 3.11 (d, 1H, J = 6.8 Hz), 2.83 (d, 1H, J = 11.4 Hz), 2.41 (d, 1H, J = 6.8 Hz), 2.30 (s, 6H), 0.90 (t, 3H, J = 7.1 Hz), 0.60 (d, 3H, J = 6.5 Hz). <sup>13</sup>C NMR (75 MHz, CDCl₃) δ: 169.7 (Cq), 134.7 (Cq), 134.5 (Cq), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.9 (CH), 127.2 (CH), 118.3 (Cq), 62.3 (CH), 61.4 (CH_<sub>2</sub>), 50.0 (CH), 40.2 (CH₃), 37.2 (CH), 31.7 (CH), 30.3 (Cq), 13.8 (CH₃), 8.9 (CH₃). IR (CHBr₃, cm<sup>-1</sup>) v: 3108, 3089, 2975, 2924, 2858, 2228, 1726, 1646, 1603.

2-Cyano-2-(2-dimethylamino-1-phenyl-propyl)-3-methyl-cyclopropanecarboxylic acid ethyl ester (37)
The general procedure was followed with 374 mg de Trifluoro-methanesulfonate-2-cyano-1,1,4-trimethyl-3-phenyl-azetidinium (26a) (1.0 mmol) and with ethyl methacrylate. Two diastereoisomers were observed in proton NMR in a 90/10 ratio. After flash chromatography on silica gel using (Et₂O/Pentane: 1/1), Rf_majo = 0.26, Rf_mino = 0.17) as eluent. 260 mg of a yellow oil (82%) 37a and 26 mg of a white solid (8%) 37b, were obtained.

Major diastereoisomer (37a):

[α]D²⁰ = +84.5 (c = 1.4, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ: 7.10-7.07 (m, 5H), 3.80-3.65 (m, 1H), 3.30-3.45 (m, 1H), 2.90-3.05 (m, 1H), 2.54 (d, 1H, J = 11.2 Hz), 2.19 (s, 6H), 1.85 (d, 1H, J = 5.6 Hz), 1.35 (s, 3H), 1.32 (d, 1H, J = 5.6 Hz). 0.79 (t, 3H, J = 7.2 Hz), 0.51 (d, 3H, J = 6.3 Hz). ¹³C NMR (75 MHz, CDCl₃) δ: 170.9 (Cq), 141.0 (Cq), 128.3 (CH), 128.2 (CH), 126.9 (CH), 121.2 (Cq), 63.1 (CH), 61.2 (CH₂), 50.1 (CH), 40.1 (CH₃), 29.2 (Cq), 28.9 (CH₂), 28.6 (Cq), 18.8 (CH₃), 13.5 (CH₃), 8.5 (CH₃). IR (CHBr₃, cm⁻¹) v: 3033, 2967, 2852, 2822, 2228, 1734, 1607, 1598. HRMS (ESI, TOF MS) m/z: calcd for [MH⁺] 315.2073, found 315.2058.

Minor diastereoisomer (37b):

mp = 76°C, ¹H NMR (300 MHz, CDCl₃) δ: 7.20-7.18 (m, 5H), 4.15-4.04 (m, 2H), 3.15-3.05 (m, 1H), 2.23 (d, 1H, J = 7.5 Hz), 2.23 (s, 6H), 2.18 (d, 1H, J = 5.8 Hz), 1.17 (t, 3H, J = 7.1 Hz), 1.01 (d, 1H, J = 5.8 Hz), 0.59 (d, 3H, J = 7.5 Hz). ¹³C NMR (75 MHz, CDCl₃) δ: 171.1 (Cq), 140.8 (Cq), 128.5 (CH), 128.1 (CH), 127.2 (CH), 121.3 (Cq), 63.3 (CH), 61.6 (CH₂), 53.2 (CH), 40.2 (CH₃), 30.6 (Cq), 28.0 (CH₂), 26.0 (Cq), 16.4 (CH₃), 14.1 (CH₃), 8.5 (CH₃). IR (KBr, cm⁻¹) v: 3027, 2942, 2864, 2832, 2228, 1731, 1607, 1599.
Crystal structures of compounds 27, 31, 33b and 35a
