



Cite this: *Org. Biomol. Chem.*, 2018, **16**, 285

Intramolecular nucleophilic addition of carbanions generated from *N*-benzylamides to cyclopropenes†

Vladimir Maslivetc,^a Colby Barrett,^a Nicolai A. Aksenov,^b Marina Rubina^{a,c} and Michael Rubin^{id} *^{a,b}

Received 18th August 2017,
Accepted 8th December 2017

DOI: 10.1039/c7ob02068f

rsc.li/obc

An unusual reaction is described, involving a formal intramolecular nucleophilic substitution of bromocyclopropanes with nitrogen ylides generated *in situ* from *N*-benzyl carboxamides. It is shown that this reaction involves cyclopropene intermediates and allows for the facile and expeditious preparation of 3-azabicyclo[3.1.0]hexan-2-one scaffolds.

Introduction

The base-assisted additions of heteroatom nucleophiles to cyclopropenes **2** generated *in situ* from stable halocyclopropanes **1** have emerged as a convenient route towards complex cyclopropyl scaffolds,¹ complementary to existing transition metal-catalyzed methodologies^{2,3} (Scheme 1, eqn (1)). Oxygen-,⁴ nitrogen-,⁵ sulfur-,⁶ or halogen⁷-based entities have been successfully added, in either an inter- or an intramolecular fashion.⁸ The employment of carbon-based nucleophilic species in non-catalyzed transformations of these types has thus far been less abundant. The apparent challenges associated with a strong basicity of organometallic reagents on the one hand, and a lower reactivity of stabilized carbon nucleophiles, such as enolates, toward non-conjugate cyclopropenes on the other hand, have limited the application of this chemistry. Within this scope, the addition of strongly nucleophilic organometallic reagents to cyclopropenes has been known since the 1970s.⁹ A regioselective variant of these chemistry exploiting bis-metallated cyclopropyl intermediates was later shown by Marek.¹⁰ More recently, Gong demonstrated the Michael addition of enolates to highly activated conjugate cyclopropenylketone **4** generated *in situ*, which was accompanied by the cleavage of the three-membered ring

(Scheme 1, eqn (2)).¹¹ Herein, we wish to report an intramolecular, ring-retentive 5-*exo-trig* cyclization of non-conjugated cyclopropenes **6** with nitrogen ylides, generated from *N*-benzylcarboxamides **5** in the presence of relatively mild alkoxide bases (Scheme 1, eqn (3)). This process allowed for the straightforward and highly expeditious assembly of biologically relevant 3-azabicyclo[3.1.0]hexan-2-one scaffolds, although in only moderate yields and selectivity.

Results and discussion

One of the challenges we encountered while developing the formal nucleophilic substitution of bromocyclopropanes was limitations in the existing synthetic approaches to cyclopropenes. Accordingly, a large part of our efforts was focused on expanding the scope of well-established methods to broaden the range of available strained olefins.¹² Thus, we demonstrated that a very efficient 1,2-dehydrohalogenation of bromocyclopropanes could be carried out in THF in the presence of catalytic amounts of 18-crown-6 ether.¹³ This modification allowed for more convenient isolation and improved overall yields of cyclopropenes compared to the classical protocol in dry DMSO. This proved to be particularly beneficial for the synthesis of functionalized cyclopropenes, such as tertiary carboxamides **9** bearing an alkyl group and an electron rich aryl group.¹³ Recently, we probed this procedure for the preparation of *N,N*-benzyl substituted cyclopropene **9a** from the corresponding bromocyclopropane **8** ($R^1 = R^2 = \text{Bn}$) (Scheme 2). Surprisingly, instead of olefin **9a**, a mixture of diastereomeric lactams **7a** was produced in *ca.* 60% yield.¹⁴ This was a pleasant surprise, since this scaffold occurs in nature¹⁵ and has significant importance for medicinal chemistry¹⁶ and synthetic methodology.¹⁷ Employing excess freshly sublimed

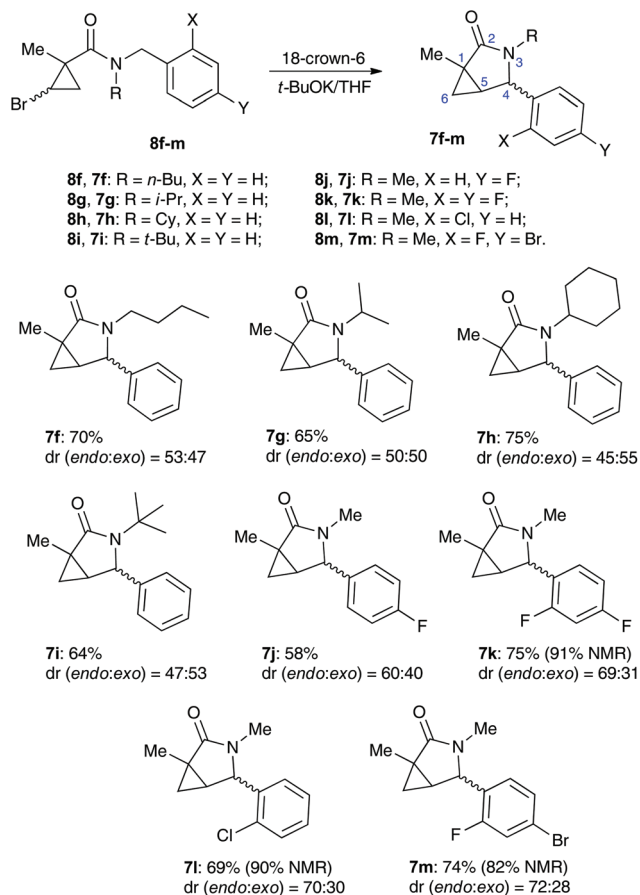
^aDepartment of Chemistry, University of Kansas, 1251 Wescoe Hall Dr., Lawrence, KS 66045-7582, USA. E-mail: mrubin@ku.edu; Tel: +1-785-864-5071

^bDepartment of Chemistry, North Caucasus Federal University, 1a Pushkin St., Stavropol 355009, Russian Federation

^cPeoples' Friendship University of Russia, 6 Miklukho-Maklaya st., Moscow 117198, Russian Federation

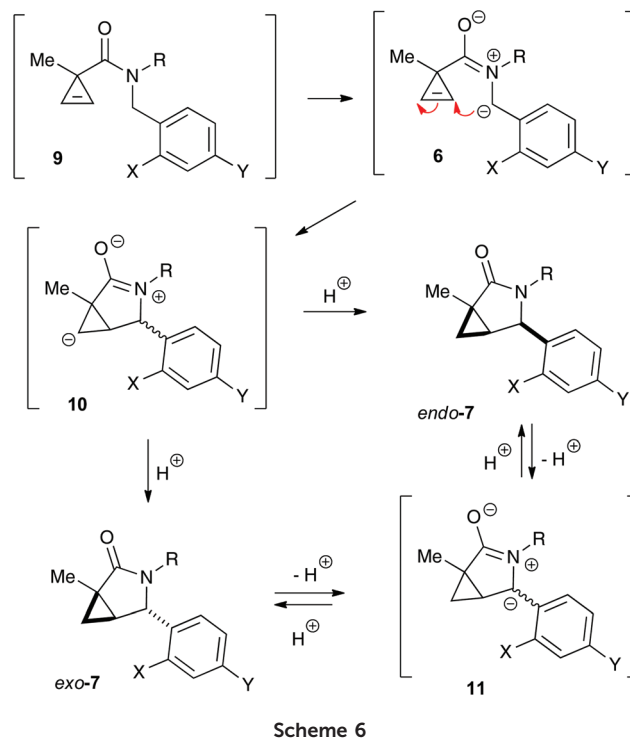
† Electronic supplementary information (ESI) available: ¹H and ¹³C spectral data, GC traces, optimized geometries, and X-ray spectral data. CCDC 1575277. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob02068f





reaction conditions (Scheme 4). All of the substrates possessing neutral or moderately electron-withdrawing substituents reacted smoothly affording the corresponding 3-azabicyclo [3.1.0]hexan-2-ones in moderate to high yields (Scheme 5). Remarkably, this reaction demonstrated high tolerance to steric hindrance at the nitrogen atom, as we were able to efficiently cyclize the substrates bearing (a) primary, Me (**8j–8m**) and *n*-Bu (**8f**), (b) secondary, *i*-Pr and Cy (**8h,g**, respectively), and (c) tertiary, *t*-Bu (**8i**) groups. Interestingly, steric hindrance on the nitrogen atom influences diastereoselectivity; however, this effect is quite weak.

It should be emphasized that all of the bicyclic products **7** were obtained as mixtures of *endo*- and *exo*-diastereomers. This was not surprising, taking into account the relatively high acidity of the tertiary C–H group at C-4, and the possibility of a facile base-assisted epimerization under the reaction conditions. The cyclization of ylide **6**, generated by the deprotonation of cyclopropenylamide **9**, should provide cyclopropyl anion **10** (Scheme 6). Subsequent protonation affords a mixture of *exo*-**7** and *endo*-**7** products, and their initial ratio depends on stereo-electronic factors at the cyclization step. However, the final product ratio is determined by a thermodynamic equilibrium that occurs *via* stabilized cyclic ylide **11**. The *exo/endo*-ratio change can be monitored in time by GC



(shown for compound **7m**, Fig. 1). In some cases, such as with *ortho*-chlorinated derivative **7l**, deprotonation at C-4 cannot be achieved efficiently due to steric hindrance, so the final diastereomeric ratio matches that for the initial kinetic distribution (Fig. 2).²¹

It should also be pointed out that the difference in the thermodynamic stabilities of *endo*- and *exo*-diastereomers in five-membered scaffold **7** is not large enough to warrant high degrees of diastereoselectivity. Our DFT modeling showed that *exo*-**7j** is more stable than *endo*-**7j** by only 2.386×10^{-3} amu ($1.50 \text{ kcal mol}^{-1}$), which corresponds to the best achievable dr of *ca.* 70:30.²² Also, this modeling helped to assign relative configurations of the diastereomeric bicyclic products. Indeed, calculation showed that dihedral angles between (C-4)–H and

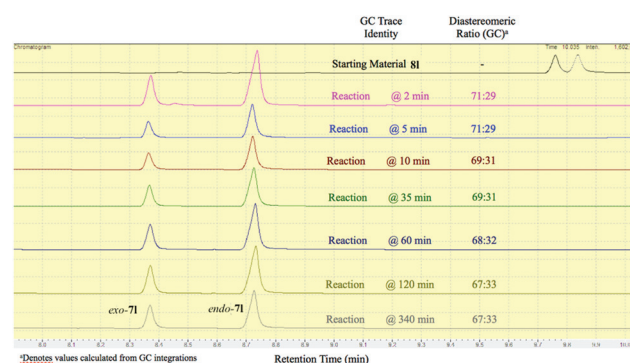


Fig. 1 Real-time GC monitoring of *endo*-**7m**:*exo*-**7m** equilibrium in the reaction mixture containing bromocyclopropane **8m** and *t*-BuOK in THF at 30 °C.



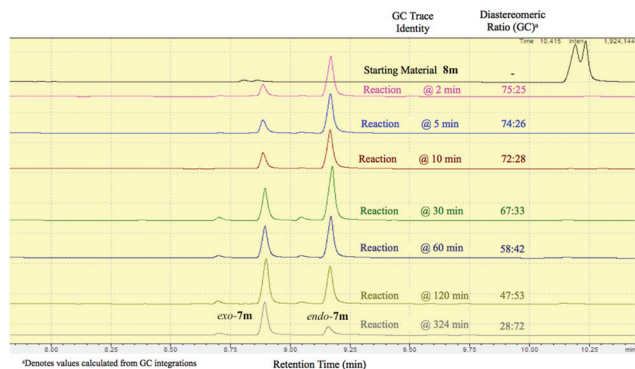


Fig. 2 Real-time GC monitoring of *endo*-7l : *exo*-7l equilibrium in the reaction mixture containing bromocyclopropane **8l** and *t*-BuOK in THF at 30 °C.

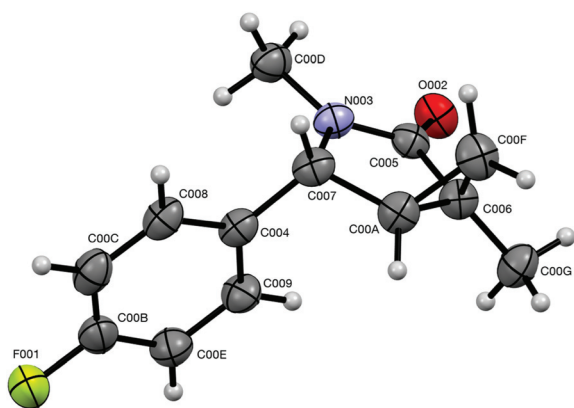


Fig. 3 ORTEP drawing of the crystal structure of compound *exo*-7j (CCDC 1575277†) showing atom numbering labels and 50% probability amplitude displacement ellipsoids.

(C-5)-H bonds in *endo*- and *exo*-isomers are 36.8° and 94.4°, respectively.²² This suggests that the value of the corresponding vicinal spin-spin coupling constants for *endo*-isomers should be larger. Indeed, the benzylic proton signals in the ¹H NMR spectra appeared as doublets for the isomers (*endo*) and as singlets for another one (*exo*). Also, the relative configuration of *exo*-7j was independently and unambiguously assigned by single-crystal X-ray diffraction (Fig. 3).

Conclusion

A cascade, base-assisted dehydrohalogenation/*5-exo-trig* nucleophilic cyclization of stabilized benzylic anions to cyclopropenes was discovered. This reaction represents the first example of the non-catalytic addition of carbon nucleophiles to unactivated cyclopropenes. The obtained results are valuable as a proof of concept and are being applied in design of the diastereoselective cyclization of carbon-based nucleophiles to obtain six- and seven-membered ring systems. The latter models are expected to allow for better stereo-electronic

control, due to a more substantial difference in the thermodynamic stabilities of the corresponding diastereomers. Synthetic and computational studies towards this goal are currently underway in our laboratories.

Experimental part

NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer (500 MHz) equipped with a dual carbon/proton cryoprobe (CPDUL) or with a BBO probe or on a Bruker Avance DPX-400 spectrometer (400 MHz) equipped with a quadruple-band gradient probe (H/C/P/F QNP). ¹³C NMR spectra were recorded with broadband decoupling. IR spectra were recorded on a ThermoFisher Nicolet™ iS™ 5 FT-IR spectrometer. HRMS was carried out on a LCT Premier (Micromass Technologies) instrument employing ESI TOF detection techniques. Glassware used in moisture-free syntheses was flame-dried under vacuum prior to use. Column chromatography was carried out on silica gel (Sorbent Technologies, 40–63 mm). Pre-coated silica gel plates (Sorbent Technologies Silica XG 200 mm) were used for TLC analyses. Anhydrous THF and dichloromethane (DCM) were obtained by the distillation of a degassed commercially available HPLC-grade inhibitor-free solvent over calcium hydride and stored over 4 Å molecular sieves under nitrogen. Commercial potassium *tert*-butoxide was sublimed under vacuum prior to use. The syntheses of bromocyclopropanes **8a–m** are described in the ESI.†²² All other reagents and solvents were purchased from commercial vendors and used as received.

(1*R**,5*S**)-3-Benzyl-1-methyl-4-phenyl-3-azabicyclo[3.1.0]hexan-2-one (**7a**)

Typical procedure I. An oven-dried Wheaton vial equipped with a Teflon septum cap was charged with freshly sublimed *t*-BuOK (315 mg, 2.80 mmol) and 18-crown-6 ether (18.5 mg, 0.07 mmol) in a nitrogen-filled glovebox. Anhydrous THF (2.22 mL) was then added to this vial and the solution was stirred to premix for 30 minutes. A solution of *N,N*-dibenzyl-2-bromo-1-methylcyclopropane-1-carboxamide (**8a**) (251 mg, 0.70 mmol) in anhydrous THF (1.48 mL) was added dropwise to the stirred reaction mixture, which was then stirred at 30 °C until starting materials were consumed (10 min for the reaction of **7a**). The reaction was then quenched by pouring the mixture into brine (35 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried with MgSO₄, gravity filtered, and concentrated *in vacuo*. The crude material contains a mixture of diastereomers 45 : 55 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (2 : 1) afforded the titled product as a pale yellow oil (*R*_f 0.38). Yield 156 mg (0.56 mmol, 80%). **endo**-**7a**: ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.32 (m, 3H), 7.31–7.21 (m, 3H), 7.20–7.14 (m, 2H), 7.09–7.01 (m, 2H), 5.06 (d, *J* = 15.0 Hz, 1H), 4.57 (d, *J* = 6.0 Hz, 1H), 3.50 (d, *J* = 14.5 Hz, 1H), 1.93–1.86 (m, 1H), 1.42 (s, 3H), 1.05 (t, *J* = 4.5 Hz,



1H), 0.64 (dd, $J = 7.8, 5.0$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.6, 138.5, 136.6, 128.9 (2C), 128.9 (2C), 128.7 (2C), 128.0, 127.6, 127.0 (2C), 59.6, 44.2, 27.1, 26.6, 16.4, 15.2. **exo-7a**: ^1H NMR (400 MHz, CDCl_3) δ 7.42–7.32 (m, 3H), 7.31–7.21 (m, 3H), 7.20–7.14 (m, 2H), 7.09–7.01 (m, 2H), 5.00 (d, $J = 14.9$ Hz, 1H), 4.12 (s, 1H), 3.36 (d, $J = 14.7$ Hz, 1H), 1.58 (dd, $J = 7.5, 3.9$ Hz, 1H), 1.48 (s, 3H), 0.72 (t, $J = 4.3$ Hz, 1H), 0.92 (dd, $J = 7.5, 4.6$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.5, 140.8, 137.2, 129.2 (2C), 128.8 (2C), 128.5, 128.5 (2C), 127.6, 127.0 (2C), 61.8, 43.9, 26.4, 25.6, 19.3, 15.1. FTIR (NaCl, cm^{-1}): 3063, 3030, 2961, 2928, 2869, 1694, 1495, 1454, 1414, 1357, 1301, 1200, 1151, 1078, 1029, 941, 747, 761, 701, 622; HRMS (TOF ES): found 300.1378, calculated for $\text{C}_{19}\text{H}_{19}\text{NONa}$ ($M + \text{Na}$) 300.1364 (4.7 ppm); EA found C 82.12, 82.00, H 6.76, 6.74, N 5.19, 5.12, calculated for $\text{C}_{19}\text{H}_{19}\text{NO}$: C 82.28, H 6.90, N 5.05.

(1R*,5S*)-3-Butyl-1-methyl-4-(4-(trifluoromethyl)phenyl)-3-azabicyclo[3.1.0]hexan-2-one (7d)

This compound was synthesized according to the Typical procedure I employing 2-bromo-*N*-butyl-1-methyl-*N*-(4-(trifluoromethyl)benzyl)cyclopropane-1-carboxamide (**8d**) (67 mg, 0.171 mmol), 18-crown-6 ether (4.5 mg, 0.017 mmol), and *t*-BuOK (77 mg, 0.68 mmol). The reaction mixture was stirred at rt for 5 min and then quenched with a saturated solution of ammonium chloride. The crude material contains an inseparable mixture of diastereomers 15 : 85 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (2 : 1) afforded the titled product as a colorless oil (R_f 0.33). Yield: 12.4 mg (0.046 mmol, 27%). **endo-7d**: ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, $J = 8.2$ Hz, 2H), 7.24 (d, $J = 8.1$ Hz, 2H), 4.90 (d, $J = 6.2$ Hz, 1H), 3.66 (ddd, $J = 13.9, 8.9, 7.1$ Hz, 1H), 2.50–2.43 (m, 1H), 1.96 (ddd, $J = 7.7, 6.1, 4.0$ Hz, 1H), 1.41 (s, 3H), 1.36–1.25 (m, 2H), 1.25–1.15 (m, 2H), 0.89 (t, $J = 4.5$ Hz, 1H), 0.85 (t, $J = 7.3$ Hz, 3H), 0.62 (dd, $J = 7.8, 5.0$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.2, 143.0, 130.0 (q, $^2J_{\text{CF}} = 40.0$ Hz), 126.9 (2C), 125.8 (q, $^3J_{\text{CF}} = 3.7$ Hz, 2C), 124.0 (q, $^1J_{\text{CF}} = 271.9$ Hz), 59.7, 40.2, 28.8, 28.2, 26.6, 20.1, 16.1, 15.0, 13.8. **exo-7d**: ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, $J = 8.2$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 4.43 (s, 1H), 3.59 (dt, $J = 14.0, 7.8$ Hz, 1H), 2.46 (ddd, $J = 13.8, 7.8, 5.5$ Hz, 1H), 1.57 (dd, $J = 7.5, 4.0$ Hz, 1H), 1.43 (s, 3H), 1.36–1.25 (m, 2H), 1.25–1.15 (m, 2H), 1.00 (dd, $J = 7.5, 4.7$ Hz, 1H), 0.85 (t, $J = 7.3$ Hz, 3H), 0.80 (t, $J = 4.3$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.5, 145.4, 130.6 (q, $^2J_{\text{CF}} = 32.7$ Hz), 126.9 (2C), 126.1 (q, $^3J_{\text{CF}} = 3.9$ Hz, 2C), 124.0 (q, $^1J_{\text{CF}} = 271.9$ Hz), 62.2, 40.0, 29.6, 26.4, 25.8, 19.9, 19.9, 14.9, 13.7. ^{19}F NMR (376 MHz, chloroform-*d*) δ –62.5, –62.6; FTIR (NaCl, cm^{-1}): 2961, 2933, 2873, 1676, 1645, 1459, 1414, 1326, 1294, 1246, 1166, 1125, 1067, 1018, 959, 846, 756, 608; HRMS (TOF ES): found 312.1578, calculated for $\text{C}_{17}\text{H}_{21}\text{NOF}_3$ ($M + \text{H}$) 312.1575 (1.0 ppm); EA found C 65.70, 65.45, H 6.38, 6.65, N 4.39, 4.78, calculated for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{NO}$: C 65.58, H 6.48, N 4.50.

(1R*,5S*)-3-Butyl-1-methyl-4-phenyl-3-azabicyclo[3.1.0]hexan-2-one (7f)

This compound was synthesized according to the Typical procedure I employing *N*-benzyl-2-bromo-*N*-butyl-1-methylcyclopropane-1-carboxamide (**8f**) (229 mg, 0.70 mmol), 18-crown-6 ether (18.5 mg, 0.07 mmol), and *t*-BuOK (314 mg, 2.80 mmol). The reaction mixture was stirred overnight at 30 °C. The crude material contains an inseparable mixture of diastereomers 53 : 47 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (3 : 1) afforded the titled product as a yellow oil (R_f 0.30). Yield 119.2 mg (0.49 mmol, 70%). **endo-7f**: ^1H NMR (400 MHz, CDCl_3) δ 7.41–7.29 (m, 3H), 7.15–7.09 (m, 2H), 4.85 (d, $J = 6.0$ Hz, 1H), 3.63 (ddd, $J = 13.8, 8.6, 7.3$ Hz, 1H), 2.50 (m, 1H), 1.93 (ddd, $J = 7.7, 6.0, 3.9$ Hz, 1H), 1.40 (s, 3H), 1.38–1.12 (m, 4H), 0.99–0.91 (m, 1H), 0.84 (t, $J = 7.3$ Hz, 3H), 0.59 (dd, $J = 7.7, 5.0$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.4, 138.8, 128.8 (2C), 127.9, 126.8 (2C), 60.2, 40.2, 29.0, 26.9, 26.7, 20.2, 16.2, 15.2, 13.9. **exo-7f**: ^1H NMR (400 MHz, CDCl_3) δ 7.41–7.29 (m, 3H), 7.22–7.17 (m, 2H), 4.35 (s, 1H), 3.55 (dt, $J = 13.9, 7.7$ Hz, 1H), 2.50 (m, 1H), 1.59 (dd, $J = 7.5, 3.9$ Hz, 1H), 1.42 (s, 3H), 1.38–1.12 (m, 4H), 0.99–0.91 (m, 1H), 0.84 (t, $J = 7.3$ Hz, 3H), 0.76 (t, $J = 4.2$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.6, 141.3, 129.1 (2C), 128.3, 126.7 (2C), 62.8, 39.9, 29.8, 26.7, 25.9, 20.0 (2C), 15.1, 13.8. FTIR (NaCl, cm^{-1}): 2960, 2931, 2872, 1692, 1457, 1417, 1372, 1219, 1051, 756, 701. HRMS (TOF ES): found 266.1514, calculated for $\text{C}_{16}\text{H}_{21}\text{NONa}$ ($M + \text{Na}$) 266.1521 (2.6 ppm); EA found C 78.81, 79.23, H 8.42, 8.50, N 5.92, 5.55, calculated for $\text{C}_{16}\text{H}_{21}\text{NO}$: C 78.97, H 8.70, N 5.76.

(1R*,5S*)-3-Isopropyl-1-methyl-4-phenyl-3-azabicyclo[3.1.0]hexan-2-one (7g)

This compound was synthesized according to the Typical procedure I employing *N*-benzyl-2-bromo-*N*-isopropyl-1-methylcyclopropane-1-carboxamide (**8g**) (217 mg, 0.70 mmol), 18-crown-6 ether (18.5 mg, 0.07 mmol), and *t*-BuOK (314 mg, 2.80 mmol). The reaction mixture was stirred at 30 °C for 3 h. The crude material contains a mixture of diastereomers 50 : 50 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (3 : 1) afforded the titled product as a pale yellow glass (R_f 0.36, 0.30). Yield 104.3 mg (0.455 mmol, 65%). Analytical samples of individual diastereomers were obtained by column chromatography on silica gel eluting with a $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ mixture (10 : 1). **endo-7g**: ^1H NMR (400 MHz, CDCl_3) δ 7.42–7.32 (m, 3H), 7.26–7.21 (m, 2H), 4.86 (d, $J = 5.8$ Hz, 1H), 3.47 (p, $J = 6.8$ Hz, 1H), 1.91 (ddd, $J = 7.7, 5.9, 3.9$ Hz, 1H), 1.38 (s, 3H), 1.32 (d, $J = 6.9$ Hz, 3H), 1.15 (d, $J = 6.8$ Hz, 3H), 1.08 (t, $J = 4.4$ Hz, 1H), 0.62 (dd, $J = 7.7, 4.8$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.2, 140.4, 128.7 (2C), 128.0, 126.9 (2C), 61.4, 46.1, 27.3, 26.8, 20.0, 19.6, 16.2, 15.1. **exo-7g**: ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.33 (m, 2H), 7.33–7.28 (m, 1H), 7.27–7.21 (m, 2H), 4.36 (s, 1H), 4.02 (p, $J = 6.9$ Hz, 1H), 1.49 (dd, $J = 7.3, 3.9$ Hz, 1H), 1.44 (s, 3H), 1.08 (d, $J = 6.8$ Hz, 3H), 0.91 (dd, $J = 7.3, 4.6$ Hz, 1H), 0.77 (d, $J = 6.9$ Hz, 3H), 0.66 (t, $J = 4.2$ Hz, 1H);



^{13}C NMR (126 MHz, CDCl_3) δ 176.8, 143.6, 128.9 (2C), 128.2, 126.7 (2C), 61.5, 44.7, 26.6, 26.2, 21.3, 20.4, 19.5, 15.0. FTIR (NaCl, cm^{-1}): 2970, 2931, 1685, 1456, 1412, 1380, 1345, 1223, 1028, 956, 763, 738, 702. HRMS (TOF ES): found 252.1353, calculated for $\text{C}_{15}\text{H}_{19}\text{NONa}$ ($\text{M} + \text{Na}$) 252.1364 (4.4 ppm); EA found C 78.47, 78.68, H 8.55, 8.18, N 6.07, 6.40, calculated for $\text{C}_{15}\text{H}_{19}\text{NO}$: C 78.56, H 8.35, N 6.11.

(1*R,5*S**)-3-Cyclohexyl-1-methyl-4-phenyl-3-azabicyclo[3.1.0]hexan-2-one (7h)**

This compound was synthesized according to the Typical procedure I employing *N*-benzyl-2-bromo-*N*-cyclohexyl-1-methylcyclopropane-1-carboxamide (**8h**) (245 mg, 0.70 mmol), 18-crown-6 ether (18.5 mg, 0.07 mmol), and *t*-BuOK (314 mg, 2.80 mmol). The reaction mixture was stirred overnight at 30 °C. The crude material contains an inseparable mixture of diastereomers 45:55 (*endo*:*exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (3:1) afforded the titled product as a colorless glass (R_f 0.38). Yield 141.3 mg (0.525 mmol, 75%). **endo-7h** ^1H NMR (400 MHz, CDCl_3) δ 7.41–7.27 (m, 3H), 7.25–7.18 (m, 2H), 4.85 (d, $J = 6.0$ Hz, 1H), 3.10 (tt, $J = 12.2, 3.5$ Hz, 1H), 2.04–1.90 (m, 1H), 1.87 (ddd, $J = 7.8, 6.0, 3.9$ Hz, 1H), 1.67 (dd, $J = 22.8, 11.2$ Hz, 4H), 1.57–1.44 (m, 2H), 1.35 (s, 3H), 1.17–0.92 (m, 4H), 0.57 (dd, $J = 7.8, 4.8$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.2, 140.6, 128.6 (2C), 127.9, 126.8 (2C), 61.2, 54.5, 30.1, 29.6, 27.5, 26.8, 26.3, 26.0, 25.5, 16.2, 15.1. **exo-7h**: ^1H NMR (400 MHz, CDCl_3) δ 7.41–7.27 (m, 3H), 7.25–7.18 (m, 2H), 4.37 (s, 1H), 3.65 (tt, $J = 12.1, 3.8$ Hz, 1H), 1.73–1.59 (m, 1H), 1.55–1.42 (m, 5H), 1.42 (s, 3H), 1.43–1.33 (m, 1H), 1.30–1.21 (m, 2H), 1.18–1.00 (m, 1H), 1.00–0.70 (m, 2H), 0.64 (t, $J = 4.2$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.9, 143.9, 128.9 (2C), 128.0, 126.6 (2C), 61.6, 52.7, 31.9, 30.9, 26.8, 26.3, 25.9, 25.9, 25.5, 19.6, 15.0. FTIR (NaCl, cm^{-1}): 2931, 2855, 1684, 1453, 1414, 1360, 1205, 1028, 894, 751, 736, 702, 624. HRMS (TOF ES): found 292.1664, calculated for $\text{C}_{18}\text{H}_{23}\text{NONa}$ ($\text{M} + \text{Na}$) 292.1677 (4.4 ppm); EA found C 80.31, 80.34, H 8.89, 8.86, N 4.95, 5.14, calculated for $\text{C}_{18}\text{H}_{23}\text{NO}$: C 80.26, H 8.61, N 5.20.

(1*R,5*S**)-3-(*tert*-Butyl)-1-methyl-4-phenyl-3-azabicyclo[3.1.0]hexan-2-one (7i)**

This compound was synthesized according to the Typical procedure I employing *N*-benzyl-2-bromo-*N*-(*tert*-butyl)-1-methylcyclopropane-1-carboxamide (**8i**) (227 mg, 0.70 mmol), 18-crown-6 ether (18.5 mg, 0.07 mmol), and *t*-BuOK (314 mg, 2.80 mmol). The reaction mixture was stirred overnight at 30 °C. The crude material contains an inseparable mixture of diastereomers 47:53 (*endo*:*exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (3:1) afforded the titled product as a colorless glass (R_f 0.44). Yield 109 mg (0.448 mmol, 64%). **endo-7i**: ^1H NMR (500 MHz, CDCl_3) δ 7.39–7.26 (m, 4H), 7.28–7.14 (m, 1H), 4.97 (d, $J = 6.5$ Hz, 1H), 1.88 (ddd, $J = 7.9, 6.5, 3.7$ Hz, 1H), 1.34 (s, 3H), 1.26 (s, 9H), 0.98 (t, $J = 4.3$ Hz, 1H), 0.49 (dd, $J = 7.9, 4.8$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.8, 144.7, 128.5 (2C), 127.1, 125.5 (2C), 61.1, 54.4, 28.3 (3C), 28.3, 28.3, 16.1, 15.7.

^1H NMR (500 MHz, CDCl_3) δ 7.39–7.26 (m, 4H), 7.28–7.14 (m, 1H), 4.57 (s, 1H), 1.40 (dd, $J = 7.2, 3.9$ Hz, 1H), 1.38 (s, 3H), 1.24 (s, 9H), 0.84 (dd, $J = 7.2, 4.3$ Hz, 1H), 0.66 (t, $J = 4.1$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.8, 143.7, 128.9 (2C), 127.7, 126.1 (2C), 62.7, 55.5, 28.1 (3C), 26.4, 26.0, 19.2, 14.9. FTIR (NaCl, cm^{-1}): 2963, 2929, 2869, 1664, 1493, 1455, 1396, 1383, 1359, 1343, 1221, 1198, 1141, 950, 762, 740, 705; HRMS (TOF ES): found 266.1528, calculated for $\text{C}_{16}\text{H}_{21}\text{NONa}$ ($\text{M} + \text{Na}$) 266.1521 (2.6 ppm); EA found C 79.05, 79.07, H 8.60, 8.95, N 5.92, 5.57, calculated for $\text{C}_{16}\text{H}_{21}\text{NO}$: C 78.97, H 8.70, N 5.76.

(1*R,5*S**)-4-(4-Fluorophenyl)-1,3-dimethyl-3-azabicyclo[3.1.0]hexan-2-one (7j)**

This compound was synthesized according to the Typical procedure I employing 2-bromo-*N*-(4-fluorobenzyl)-*N*,1-dimethylcyclopropane-1-carboxamide (**8j**) (51 mg, 0.171 mmol), 18-crown-6 ether (4.5 mg, 0.017 mmol), and *t*-BuOK (76 mg, 0.68 mmol). The reaction mixture was stirred at rt for 4 h. The crude material contains an inseparable mixture of diastereomers 60:40 (*endo*:*exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (3:1) afforded the titled product as a colorless glass (R_f 0.36). Yield 21.6 mg (0.099 mmol, 58%). **endo-7j**: ^1H NMR (400 MHz, CDCl_3) δ 7.11–7.02 (m, 4H), 4.68 (d, $J = 5.9$ Hz, 1H), 2.61 (s, 3H), 1.93 (ddd, $J = 7.7, 5.9, 4.0$ Hz, 1H), 1.40 (s, 3H), 0.90 (t, $J = 4.6$ Hz, 1H), 0.63 (dd, $J = 7.8, 5.0$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.4, 162.4 (d, $^1J_{\text{CF}} = 246.1$ Hz), 136.5 (d, $^4J_{\text{CF}} = 3.5$ Hz), 128.0 (d, $^3J_{\text{CF}} = 8.1$ Hz, 2C), 115.7 (d, $^2J_{\text{CF}} = 21.2$ Hz, 2C), 62.2, 28.1, 26.9, 25.7, 16.3, 14.9. **exo-7j**: ^1H NMR (400 MHz, CDCl_3) δ 7.21–7.13 (m, 2H), 7.11–7.02 (m, 2H), 4.23 (s, 1H), 2.57 (s, 3H), 1.57 (dd, $J = 7.6, 3.9$ Hz, 1H), 1.42 (s, 3H), 0.96 (dd, $J = 7.6, 4.7$ Hz, 1H), 0.81 (t, $J = 4.3$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.4, 162.6 (d, $^1J_{\text{CF}} = 247.0$ Hz), 136.5 (d, $^4J_{\text{CF}} = 3.5$ Hz), 128.1 (d, $^3J_{\text{CF}} = 8.2$ Hz, 2C), 116.0 (d, $^2J_{\text{CF}} = 21.7$ Hz, 2C), 64.5, 27.9, 26.6, 25.7, 20.0, 15.1. ^{19}F NMR (376 MHz, CDCl_3) δ -113.8, -114.6; FTIR (NaCl, cm^{-1}): 2929, 1683, 1509, 1481, 1398, 1223, 1158, 1007, 845, 819, 752, 668, 647. HRMS (TOF ES): found 242.0960, calculated for $\text{C}_{13}\text{H}_{14}\text{NOFNa}$ ($\text{M} + \text{Na}$) 242.0957 (1.2 ppm); EA found C 71.35, 71.27, H 6.18, 6.34, N 6.26, 6.33, calculated for $\text{C}_{13}\text{H}_{14}\text{FNO}$: C 71.21, H 6.44, N 6.39. Slow crystallization of the purified material from hexane afforded a crop of crystals of *exo-7j* suitable for X-ray analysis.

(1*R,5*S**)-4-(2,4-Difluorophenyl)-1,3-dimethyl-3-azabicyclo[3.1.0]hexan-2-one (7k)**

This compound was synthesized according to the Typical procedure I employing 2-bromo-*N*-(2,4-difluorobenzyl)-*N*,1-dimethylcyclopropane-1-carboxamide (**8k**) (54 mg, 0.171 mmol), 18-crown-6 ether (4.5 mg, 0.017 mmol), and *t*-BuOK (76 mg, 0.68 mmol). The reaction mixture was stirred at rt for 5 min and then quenched with a saturated solution of ammonium chloride. The crude material contains an inseparable mixture of diastereomers 69:31 (*endo*:*exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc



(2 : 3) afforded the titled product as a colorless oil (R_f 0.38). Yield 30.2 mg (0.127 mmol, 75%). **endo-7k**: ^1H NMR (500 MHz, CDCl_3) δ 6.93–6.79 (m, 3H), 4.95 (d, $J = 5.9$ Hz, 1H), 2.64 (s, 3H), 2.06 (ddd, $J = 7.8, 5.9, 4.0$ Hz, 1H), 1.38 (s, 3H), 0.77 (t, $J = 4.5$ Hz, 1H), 0.64 (dd, $J = 7.8, 5.0$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.9, 162.3 (dd, $^1J_{\text{CF}} = 249.2$ Hz, $^3J_{\text{CF}} = 13.2$ Hz), 160.7 (dd, $^1J_{\text{CF}} = 248.8$ Hz, $^3J_{\text{CF}} = 12.0$ Hz), 127.8 (dd, $^3J_{\text{CF}} = 9.4$ Hz, $^3J_{\text{CF}} = 5.8$ Hz), 122.1 (dd, $^2J_{\text{CF}} = 13.2$ Hz, $^4J_{\text{CF}} = 3.9$ Hz), 111.3 (dd, $^2J_{\text{CF}} = 21.0$ Hz, $^4J_{\text{CF}} = 3.6$ Hz), 104.3 (t, $^2J_{\text{CF}} = 25.5$ Hz), 56.0 (d, $^3J_{\text{CF}} = 4.5$ Hz), 28.5, 26.5, 25.6, 16.5, 14.9. **exo-7k**: ^1H NMR (500 MHz, CDCl_3) δ 7.14–7.07 (m, 1H), 6.93–6.79 (m, 2H), 4.57 (s, 1H), 2.59 (s, 3H), 1.60 (dd, $J = 7.6, 3.9$ Hz, 1H), 1.40 (s, 3H), 0.98 (dd, $J = 7.5, 4.7$ Hz, 1H), 0.82 (t, $J = 4.3$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.5, 162.7 (dd, $^1J_{\text{CF}} = 249.7$ Hz, $^3J_{\text{CF}} = 12.2$ Hz), 160.8 (dd, $^1J_{\text{CF}} = 249.7$ Hz, $^3J_{\text{CF}} = 12.2$ Hz), 128.8 (dd, $^3J_{\text{CF}} = 9.9$ Hz, $^3J_{\text{CF}} = 5.5$ Hz), 123.5 (dd, $^2J_{\text{CF}} = 13.2$ Hz, $^4J_{\text{CF}} = 3.9$ Hz), 112.0 (dd, $^2J_{\text{CF}} = 21.0$ Hz, $^4J_{\text{CF}} = 3.7$ Hz), 104.4 (t, $^2J_{\text{CF}} = 25.5$ Hz), 58.2 (d, $^3J_{\text{CF}} = 3.5$ Hz), 27.9, 25.7, 25.6, 20.0, 14.9. ^{19}F NMR (376 MHz, CDCl_3) δ -109.9 (d, $^4J_{\text{FF}} = 7.5$ Hz), -111.1 (d, $^4J_{\text{FF}} = 7.3$ Hz), -115.97 (d, $^4J_{\text{FF}} = 7.8$ Hz), -116.03 (d, $^4J_{\text{FF}} = 7.3$ Hz); FTIR (NaCl, cm^{-1}): 2932, 1694, 1617, 1503, 1430, 1397, 1269, 1234, 1140, 1092, 974, 961, 850, 765, 610. HRMS (TOF ES): found 260.0862, calculated for $\text{C}_{13}\text{H}_{13}\text{NOF}_2\text{Na}$ ($M + \text{Na}$) 260.0863 (0.4 ppm); EA found C 65.92, 65.51, H 5.60, 5.67, N 6.14, 5.82, calculated for $\text{C}_{13}\text{H}_{13}\text{F}_2\text{NO}$: C 65.81, H 5.52, N 5.90.

(1R*,5S*)-4-(2-Chlorophenyl)-1,3-dimethyl-3-azabicyclo[3.1.0]hexan-2-one (7l)

This compound was synthesized according to the Typical procedure I employing 2-bromo-*N*-(2-chlorobenzyl)-*N*,1-dimethylcyclopropane-1-carboxamide (**8l**) (54 mg, 0.171 mmol), 18-crown-6 ether (4.5 mg, 0.017 mmol), and *t*-BuOK (77 mg, 0.68 mmol). The reaction mixture was stirred at rt for 2 min and then quenched with a saturated solution of ammonium chloride. The crude material contains an inseparable mixture of diastereomers 70 : 30 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (2 : 3) afforded the titled product as a colorless oil (R_f 0.45). Yield 27.7 mg (0.118 mmol, 69%). **endo-7l**: ^1H NMR (400 MHz, CDCl_3) δ 7.47–7.39 (m, 1H), 7.33–7.22 (m, 2H), 6.86 (dd, $J = 6.9, 2.4$ Hz, 1H), 5.07 (d, $J = 5.9$ Hz, 1H), 2.67 (s, 3H), 2.24 (ddd, $J = 7.8, 5.9, 4.0$ Hz, 1H), 1.41 (s, 3H), 0.75 (t, $J = 4.5$ Hz, 1H), 0.60 (dd, $J = 7.8, 5.0$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.3, 136.4, 133.1, 130.2, 128.8, 127.1, 127.0, 59.9, 28.8, 26.6, 24.9, 16.5, 15.2. **exo-7l**: ^1H NMR (400 MHz, CDCl_3) δ 7.47–7.39 (m, 1H), 7.33–7.22 (m, 2H), 7.11 (dd, $J = 7.3, 2.1$ Hz, 1H), 4.80 (s, 1H), 2.64 (s, 3H), 1.60 (dd, $J = 7.5, 4.0$ Hz, 1H), 1.38 (s, 3H), 0.99 (dd, $J = 7.5, 4.7$ Hz, 1H), 0.86 (t, $J = 4.3$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.1, 138.0, 133.1, 130.2, 129.3, 127.7, 127.0, 61.3, 28.4, 25.2, 26.0, 20.1, 15.1. FTIR (NaCl, cm^{-1}): 2929, 1698, 1471, 1445, 1395, 1384, 1340, 1232, 1035, 972, 757, 698; HRMS (TOF ES): found 258.0660, calculated for $\text{C}_{13}\text{H}_{14}\text{NOClNa}$ ($M + \text{Na}$) 258.0662 (0.8 ppm); EA found C 66.21, 66.16, H 5.92, 6.10, N 5.64, 6.22, calculated for $\text{C}_{13}\text{H}_{14}\text{ClNO}$: C 66.24, H 5.99, N 5.94.

(1R*,5S*)-4-(4-Bromo-2-fluorophenyl)-1,3-dimethyl-3-azabicyclo[3.1.0]hexan-2-one (7m)

This compound was synthesized according to the Typical procedure I employing 2-bromo-*N*-(4-bromo-2-fluorobenzyl)-*N*,1-dimethylcyclopropane-1-carboxamide (**8m**) (65 mg, 0.171 mmol), 18-crown-6 ether (4.5 mg, 0.017 mmol), and *t*-BuOK (77 mg, 0.69 mmol). The reaction mixture was stirred at rt for 2 min and then quenched with a saturated solution of ammonium chloride. The crude material contains an inseparable mixture of diastereomers 72 : 28 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (1 : 1) afforded the titled product as a colorless oil (R_f 0.35). Yield 37.8 mg (0.127 mmol, 74%). **endo-7m**: ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.19 (m, 2H), 6.74 (t, $J = 8.2$ Hz, 1H), 4.89 (d, $J = 5.9$ Hz, 1H), 2.60 (s, 3H), 2.03 (ddd, $J = 8.0, 5.8, 3.9$ Hz, 1H), 1.34 (s, 3H), 0.71 (t, $J = 4.5$ Hz, 1H), 0.60 (dd, $J = 7.8, 5.0$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.0, 160.5 (d, $J = 250.9$ Hz), 128.2 (d, $J = 4.7$ Hz), 127.7 (d, $J = 3.6$ Hz), 125.6 (d, $J = 12.8$ Hz), 121.6 (d, $J = 9.9$ Hz), 119.6 (d, $J = 24.5$ Hz), 56.2 (d, $J = 4.4$ Hz), 28.6, 26.7, 25.5, 16.6, 15.0. **exo-7m**: ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.19 (m, 2H), 6.96 (t, $J = 8.0$ Hz, 1H), 4.52 (s, 1H), 2.56 (s, 3H), 1.55 (dd, $J = 7.5, 3.9$ Hz, 1H), 1.35 (s, 3H), 0.95 (dd, $J = 7.5, 4.8$ Hz, 1H), 0.78 (t, $J = 4.4$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.6, 160.6 (d, $J = 253.3$ Hz), 129.0 (d, $J = 5.1$ Hz), 128.3 (d, $J = 4.7$ Hz), 126.9 (d, $J = 13.0$ Hz), 122.3 (d, $J = 9.8$ Hz), 119.8 (d, $J = 23.9$ Hz), 58.3 (d, $J = 3.6$ Hz), 28.1, 25.8, 25.6, 20.1, 14.9. ^{19}F NMR (376 MHz, chloroform-*d*) δ -116.4, -117.3; FTIR (NaCl, cm^{-1}): 2961, 2930, 1695, 1605, 1574, 1483, 1396, 1220, 1077, 973, 883, 850, 757. HRMS (TOF ES): found 320.0056, calculated for $\text{C}_{13}\text{H}_{13}\text{NOFBrNa}$ ($M + \text{Na}$) 320.0062 (1.9 ppm); EA found 52.21, 52.44, H 4.29, 4.57, N 4.90, 4.64, calculated for $\text{C}_{13}\text{H}_{13}\text{BrFNO}$: C 52.37, H 4.40, N 4.70.

***N*-Butyl-*N*-(4-(*tert*-butyl)benzyl)-1-methylcycloprop-2-ene-1-carboxamide (9b)**

This compound was synthesized according to the Typical procedure I employing 2-bromo-*N*-butyl-*N*-(4-(*tert*-butyl)benzyl)-1-methylcyclopropane-1-carboxamide (**8b**) (266 mg, 0.70 mmol), 18-crown-6 ether (18.5 mg, 0.07 mmol), and *t*-BuOK (314 mg, 2.80 mmol). The reaction mixture was stirred at 25 °C for 47 h. The product was isolated by column chromatography eluting with a mixture of hexanes/EtOAc (3 : 2) as a yellow oil (R_f 0.39). Yield 72.2 mg (0.315 mmol, 45%). ^1H NMR (500 MHz, CDCl_3) δ 7.33 (br. s, 3H), 7.22 (br. s, 1H), 7.08 (br. s, 2H), 4.81–4.48 (m, 2H), 3.44–3.18 (m, 2H), [1.95 (br. s), 1.53–1.35 (m), $\Sigma 5\text{H}$], 1.37 (br. s, 11H), 1.31 (br. s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.3, (150.4, 149.9, 1C), (134.6, 134.2, 1C), (127.4, 126.5, 2C), 125.6 (2C), 115.8 (2C), (50.3, 44.0, 1C), 46.4, 34.5, 31.4 (3C), (30.6, 29.1, 1C), 24.1, 23.2, 20.1, 13.9; FTIR (NaCl, cm^{-1}): 2960, 2869, 1625, 1514, 1463, 1410, 1365, 1269, 1104, 1005, 927, 819, 732, 617; HRMS (TOF ES): found 322.2147, calculated for $\text{C}_{20}\text{H}_{29}\text{NONa}$ ($M + \text{Na}$) 322.2147 (0.0 ppm); EA found C 80.07, 80.50, H 9.75, 9.95, N 4.93, 4.97, calculated for $\text{C}_{20}\text{H}_{29}\text{NO}$: C 80.22, H 9.76, N 4.68.



***N*-Butyl-*N*-(4-methoxybenzyl)-1-methylcycloprop-2-ene-1-carboxamide (9c)**

This compound was synthesized according to the Typical procedure I employing 2-bromo-*N*-butyl-*N*-(4-methoxybenzyl)-1-methylcyclopropane-1-carboxamide (**8c**) (248 mg, 0.70 mmol), 18-crown-6 ether (18.5 mg, 0.07 mmol), and *t*-BuOK (314 mg, 2.80 mmol). The reaction mixture was stirred at 25 °C for 27 h. The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (1 : 1) as a yellow oil (R_f 0.39). Yield 105.3 mg (0.385 mmol, 55%). ^1H NMR (500 MHz, CDCl_3) δ [7.30 (br. s), 7.24 (br. s), 7.07 (br. s), Σ 4H], 6.86 (br. s, 2H), 4.75–4.46 (m, 2H), 3.79 (s, 3H), 3.41–3.16 (m, 2H), [1.47 (br. s), 1.37 (s), 1.26 (br. s), Σ 7H], 0.90 (br. s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.2, 158.9, 129.1, 128.0, 115.8, 114.04 (2C), 55.3, 50.1, 46.1, 43.8, 30.5, 29.0, 24.0, 23.2, 20.1, 13.9; FTIR (NaCl, cm^{-1}): 2958, 2933, 2872, 1615, 1513, 1464, 1417, 1302, 1247, 1175, 1104, 1033, 815, 621. HRMS (TOF ES): found 296.1637, calculated for $\text{C}_{17}\text{H}_{23}\text{NO}_2\text{Na}$ ($M + \text{Na}$) 296.1626 (3.7 ppm); EA found C 74.72, 74.89, H 8.75, 8.39, N 4.89, 5.19, calculated for $\text{C}_{17}\text{H}_{23}\text{NO}_2$: C 74.69, H 8.48, N 5.12.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financed by the Russian Foundation for Basic Research (grant #15-03-02661) and the Ministry of Education and Science of the Russian Federation (the project numbers 02.a03.21.0008 and #4.1196.2017/4.6). Support for NMR instruments used in this project was provided by the NIH Shared Instrumentation Grant #S10RR024664 and the NSF Major Research Instrumentation Grant #0329648.

References

- For reviews, see: (a) A. Edwards, M. Rubina and M. Rubin, *Curr. Org. Chem.*, 2016, **20**, 1862–1877; (b) R. Vicente, *Synthesis*, 2016, 2343–2360; (c) Z.-B. Zhu, Y. Wei and M. Shi, *Chem. Soc. Rev.*, 2011, **40**, 5534–5563; (d) M. Rubin, M. Rubina and V. Gevorgyan, *Synthesis*, 2006, 1221–1245; (e) J. M. Fox and N. Yan, *Curr. Org. Chem.*, 2005, **9**, 719–732.
- For hydrometallations, see: (a) M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2004, **126**, 3688–3689; (b) Y. Lou, M. Horikawa, R. A. Kloster, N. A. Hawryluk and E. J. Corey, *J. Am. Chem. Soc.*, 2004, **126**, 8916–8918; (c) A. Parra, L. Amenos, M. Guisan-Ceinos, A. Lopez, J. L. Garcia Ruano and M. Tortosa, *J. Am. Chem. Soc.*, 2014, **136**, 15833–15836; (d) M. Rubin and V. Gevorgyan, *Synthesis*, 2004, 796–800; (e) M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2003, **125**, 7198–7199. For carbometallations, see: (f) D. S. Muller and I. Marek, *J. Am. Chem. Soc.*, 2015, **137**, 15414–15417; (g) M. Simaan, P. O. Delaye, M. Shi and I. Marek, *Angew. Chem., Int. Ed.*, 2015, **54**, 12345–12348; (h) D. Didier, P.-O. Delaye, M. Simaan, B. Island, G. Eppe, H. Eijlsberg, A. Kleiner, P. Knochel and I. Marek, *Chem. – Eur. J.*, 2014, **20**, 1038–1048; (i) P.-O. Delaye, D. Didier and I. Marek, *Angew. Chem., Int. Ed.*, 2013, **52**, 5333–5337; (j) K. Kramer, P. Leong and M. Lautens, *Org. Lett.*, 2011, **13**, 819–821; (k) S. Simaan, A. Masarwa, E. Zohar, A. Stanger, P. Bertus and I. Marek, *Chem. – Eur. J.*, 2009, **15**, 8449–8464; (l) V. Tarwade, X. Liu, N. Yan and J. M. Fox, *J. Am. Chem. Soc.*, 2009, **131**, 5382–5383; (m) L. Dian, D. S. Müller and I. Marek, *Angew. Chem., Int. Ed.*, 2017, **56**, 6783–6787; (n) F.-G. Zhang, G. Eppe and I. Marek, *Angew. Chem., Int. Ed.*, 2016, **55**, 714–718; (o) D. S. Müller, V. Werner, S. Akyol, H.-G. Schmaltz and I. Marek, *Org. Lett.*, 2017, **19**, 3970–3973.
- For dimetallations, see: (a) M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2002, **124**, 11566–11567; (b) A. Trofimov, M. Rubina, M. Rubin and V. Gevorgyan, *J. Org. Chem.*, 2007, **72**, 8910–8920; (c) A. Parra, L. Amenos, M. Guisán-Ceinos, A. Lopez, R. Garcia, L. Jose and M. Tortosa, *J. Am. Chem. Soc.*, 2014, **136**, 15833–15836; (d) B. Tian, Q. Liu, X. Tong, P. Tian and G.-Q. Lin, *Org. Chem. Front.*, 2014, **1**, 1116–1122. For hydroformylation, see: (e) W. M. Sherrill and M. Rubin, *J. Am. Chem. Soc.*, 2008, **130**, 13804–13809. For hydroacylation, see: (f) D. H. T. Phan, K. G. M. Kou and V. M. Dong, *J. Am. Chem. Soc.*, 2010, **132**, 16354–16355. For hydrophosphorylation, see: (g) B. K. Alnasleh, W. M. Sherrill and M. Rubin, *Org. Lett.*, 2008, **10**, 3231–3234. For hydroamination, see: (h) H. L. Teng, Y. Luo, B. Wang, L. Zhang, M. Nishiura and Z. Hou, *Angew. Chem., Int. Ed.*, 2016, **55**, 15406–15410; (i) Z. Li, J. Zhao, B. Sun, T. Zhou, M. Liu, S. Liu, M. Zhang and Q. Zhang, *J. Am. Chem. Soc.*, 2017, **139**, 11702–11705. For hydroalkylation, see: (j) Y. Luo, H.-L. Teng, M. Nishiura and Z. Hou, *Angew. Chem., Int. Ed.*, 2017, **56**, 9207–9210. For carboamination, see: (k) H. L. Teng, Y. Luo, M. Nishiura and Z. Hou, *J. Am. Chem. Soc.*, 2017, **139**, 16506–16509.
- (a) K. B. Wiberg, R. K. Barnes and J. Albin, *J. Am. Chem. Soc.*, 1957, **79**, 4994–4999; (b) J. E. Banning, A. R. Prosser, B. K. Alnasleh, J. Smarker, M. Rubina and M. Rubin, *J. Org. Chem.*, 2011, **76**, 3968–3986; (c) B. K. Alnasleh, W. M. Sherrill, M. Rubina, J. Banning and M. Rubin, *J. Am. Chem. Soc.*, 2009, **131**, 6906–6907; (d) J. E. Banning, A. R. Prosser and M. Rubin, *Org. Lett.*, 2010, **12**, 1488–1491; (e) P. Ryabchuk, A. Edwards, N. Gerasimchuk, M. Rubina and M. Rubin, *Org. Lett.*, 2013, **15**, 6010–6013; (f) K. N. Sedenkova, E. B. Averina, I. S. Borisov, Y. K. Grishin, V. B. Rybakov, T. S. Kuznetsova and N. S. Zefirov, *Russ. J. Org. Chem.*, 2012, **48**, 1265–1271; (g) M. Zhang, J. Guo and Y. Gong, *Eur. J. Org. Chem.*, 2014, 1942–1950; (h) M. Zhang, F. Luo and Y. Gong, *J. Org. Chem.*, 2014, **79**, 1335–1343; (i) J. Hu, M. Zhang and Y. Gong, *Eur. J. Org. Chem.*, 2015, 1970–1978; (j) P. Yamanushkin,



- M. Lu-Diaz, A. Edwards, N. A. Aksenov, M. Rubina and M. Rubin, *Org. Biomol. Chem.*, 2017, **15**, 8153–8156.
- 5 (a) J. E. Banning, J. Gentillon, P. G. Ryabchuk, A. R. Prosser, A. Rogers, A. Edwards, A. Holtzen, I. A. Babkov, M. Rubina and M. Rubin, *J. Org. Chem.*, 2013, **78**, 7601–7616; (b) E. C. Taylor and B. Hu, *Synth. Commun.*, 1996, **26**, 1041–1049; (c) K. N. Shavrin, V. D. Gvozdev, D. V. Budanov, S. V. Yurov and O. M. Nefedov, *Mendeleev Commun.*, 2006, **16**, 73–76; (d) K. N. Shavrin, V. D. Gvozdev and O. M. Nefedov, *Russ. Chem. Bull.*, 2010, **59**, 396–404; (e) A. R. Prosser, J. E. Banning, M. Rubina and M. Rubin, *Org. Lett.*, 2010, **12**, 3968–3971; (f) P. Ryabchuk, M. Rubina, J. Xu and M. Rubin, *Org. Lett.*, 2012, **14**, 1752–1755; (g) Z. Huang, J. Hu and Y. Gong, *Org. Biomol. Chem.*, 2015, **13**, 8561–8566; (h) Y. Zhu and Y. Gong, *J. Org. Chem.*, 2015, **80**, 490–498; (i) K. N. Shavrin, V. D. Gvozdev and O. M. Nefedov, *Mendeleev Commun.*, 2008, **18**, 300–301; (j) K. N. Shavrin, V. D. Gvozdev and O. M. Nefedov, *Russ. Chem. Bull.*, 2010, **59**, 1451–1458.
- 6 K. N. Shavrin, V. D. Gvozdev and O. M. Nefedov, *Russ. Chem. Bull.*, 2009, **58**, 2432–2436.
- 7 M. Zhang, Y. Gong and W. Wang, *Eur. J. Org. Chem.*, 2013, 7372–7381.
- 8 (a) P. Ryabchuk, J. P. Matheny, M. Rubina and M. Rubin, *Org. Lett.*, 2016, **18**, 6272–6275; (b) B. K. Alnasleh, M. Rubina and M. Rubin, *Chem. Commun.*, 2016, **52**, 7494–7496; (c) A. Edwards, T. Bennin, M. Rubina and M. Rubin, *RSC Adv.*, 2015, **5**, 71849–71853.
- 9 (a) T. Y. Rudashevskaya and O. A. Nesmeyanova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1983, 1821–1824; (b) T. Y. Rudashevskaya and O. A. Nesmeyanova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1979, 669–671; (c) A. Padwa and M. W. Wannamaker, *Tetrahedron Lett.*, 1986, **27**, 5817–5820.
- 10 A. Levin and I. Marek, *Chem. Commun.*, 2008, **44**, 4300–4302.
- 11 (a) Y. Zhu, M. Zhang, H. Yuan and Y. Gong, *Org. Biomol. Chem.*, 2014, **12**, 8828–8831; (b) J. Hu, Y. Liu and Y. Gong, *Adv. Synth. Catal.*, 2015, **357**, 2781–2787.
- 12 (a) W. M. Sherrill, R. Kim and M. Rubin, *Tetrahedron*, 2008, **64**, 8610–8617; (b) R. Kim, W. M. Sherrill and M. Rubin, *Tetrahedron*, 2010, **66**, 4947–4953.
- 13 W. M. Sherrill, R. Kim and M. Rubin, *Synthesis*, 2009, 1477–1484.
- 14 In an attempt to improve the selectivity, we also carried out these transformations at a lower temperature or in the presence of a smaller amount of base, but this proved impossible, as the first step, involving the generation of cyclopropenes *via* a base-assisted 1,2-elimination of the HBr reaction, did not proceed under these conditions. It should also be mentioned that unactivated benzylic groups do not demonstrate this type of reactivity, as their C–H acidity is not sufficient for such an anion to be generated in the presence of such a relatively weak base as *t*-BuOK. This was demonstrated, for example, in Fox's report, who used the derivatives of cyclopropene-3-carboxylic acid with Evans chiral auxiliary, derived from phenylalanine: L. Liao, E. Zhang, N. Yan, J. A. Golen and J. M. Fox, *Tetrahedron*, 2004, **60**, 1803–1816. In our case, such deprotonation is only possible because benzylic anions are generated next to carboxamide functionality, which is known to stabilize alpha-anions greatly due to the significant contribution of the nitrogen ylide resonance form.
- 15 See, for example: (a) S. Tanaka, Y. Honmura, S. Uesugi, E. Fukushi, K. Tanaka, H. Maeda, K. Kimura, T. Nehira and M. Hashimoto, *J. Org. Chem.*, 2017, **82**, 5574–5582; (b) P. Paya, M. Anastasiades, D. Mack, I. Sigalova, B. Tasdelen, J. Oliva and A. Barba, *Anal. Bioanal. Chem.*, 2007, **389**, 1697–1714.
- 16 See, for example: (a) H. P. Cho, D. W. Engers, D. F. Venable, C. M. Niswender, C. W. Lindsley, P. J. Conn, K. A. Emmitte and A. L. Rodriguez, *ACS Chem. Neurosci.*, 2014, **5**, 597–610; (b) K. X. Chen, L. Nair, B. Vibulbhan, W. Yang, A. Arasappan, S. L. Bogen, S. Venkatraman, F. Bennett, W. Pan, M. L. Blackman, A. I. Padilla, A. Prongay, K.-C. Cheng, X. Tong, N.-Y. Shih and F. G. Njoroge, *J. Med. Chem.*, 2009, **52**, 1370–1379.
- 17 For recent examples on the synthesis of bicyclic lactam systems like **7** *via* inter- or intramolecular cyclopropanations see: (a) J. Tao, C. D. Estrada and G. K. Murphy, *Chem. Commun.*, 2017, **53**, 9004–9007. Concerted cycloadditions: (b) S. McCabe and P. Wipf, *Angew. Chem., Int. Ed.*, 2017, **56**, 324–327. Alkene or alkyne hydroaminations: (c) D. C. Miller, G. J. Choi, H. S. Orbe and R. R. Knowles, *J. Am. Chem. Soc.*, 2015, **137**, 13492–13495; (d) B. de Carne-Carnaulet, C. Meyer, J. Cossy, B. Folleas, J.-L. Brayer and J.-P. Demoute, *J. Org. Chem.*, 2013, **78**, 5794–5799. Radical cyclizations: (e) M. K. Nielsen, B. J. Shields, J. Liu, M. J. Williams, M. J. Zacuto and A. G. Doyle, *Angew. Chem., Int. Ed.*, 2017, **56**, 7191–7194. Cyclizations, involving C–H activations: (f) E. Hernando, J. Villalva, A. M. Martinez, I. Alonso, N. Rodriguez, R. Gomez Arrayas and J. C. Carretero, *ACS Catal.*, 2016, **6**, 6868–6882. See also ref. 3k for a novel approach involving the asymmetric carboamination of cyclopropenes.
- 18 (a) R. A. Bragg, J. Clayden and C. J. Menet, *Tetrahedron Lett.*, 2002, **43**, 1955–1959; (b) R. A. Bragg and J. Clayden, *Tetrahedron Lett.*, 1999, **40**, 8323–8326; (c) R. A. Bragg, J. Clayden, G. A. Morris and J. H. Pink, *Chem. – Eur. J.*, 2002, **8**, 1279–1289; (d) P. Beak and B. Lee, *J. Org. Chem.*, 1989, **54**, 458–464; (e) A. J. Burton, J. P. Graham and N. S. Simpkins, *Synlett*, 2000, 1640–1642; (f) D. Seebach, J. J. Lohmann, M. A. Syfrig and M. Yoshifuji, *Tetrahedron*, 1983, **39**, 1963–1974; (g) J. J. Lohmann, D. Seebach, M. A. Syfrig and M. Yoshifuji, *Angew. Chem.*, 1981, **93**, 125–126; (h) A. I. Meyers, K. B. Kunnen and W. C. Still, *J. Am. Chem. Soc.*, 1987, **109**, 4405–4407.
- 19 (a) A. Couture, E. Deniau, D. Ionescu and P. Grandclaudeon, *Tetrahedron Lett.*, 1998, **39**, 2319–2320; (b) B. S. Bhakuni, A. Yadav, S. Kumar, S. Patel, S. Sharma and S. Kumar, *J. Org. Chem.*, 2014, **79**, 2944–2954; (c) J. Clayden, S. D. Hamilton and R. T. Mohammed, *Org. Lett.*, 2005, **7**,



3673–3676; (d) J. Clayden and C. J. Menet, *Tetrahedron Lett.*, 2003, **44**, 3059–3062.

20 Since *exo*-products are somewhat more stable than *endo*-isomers, the selective formation of *exo*-7d might be a result of thermodynamically-driven epimerization proceeding *via* a base-assisted deprotonation at the benzylic position. Unfortunately, this reaction has to be quenched after 5 min to obtain at least some isolated yield. Longer exposure to

the base causes quick decomposition of both *exo*- and *endo*-products, which does not allow us to exploit this isomerization for achieving even better selectivity.

21 Results for the detailed GC-monitoring for all other cyclization reactions are included in the ESI.† These were used to choose the best reaction duration and the appropriate quenching time for each particular product.

22 See the ESI† for details.

