# Synthesis of 3,3-Difluoroazetidines

Willem Van Brabandt, Norbert De Kimpe*

Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, 9000 Ghent, Belgium
Fax +32(9)2646243; E-mail: norbert.dekimpe@UGent.be

*Received 19 April 2006*

**Abstract:** A high-yield synthesis of 3,3-difluoroazetidines was developed by a monochlorohydroalane reduction of 3,3-difluoroazetidin-2-ones. The latter compounds were conveniently synthesized by a Reformatsky-type reaction of aldimines with ethyl bromodifluoroacetate.

**Key words:** 3,3-difluoroazetidines, 3,3-difluoroazetidin-2-ones, aldimines, Reformatsky, monochlorohydroalane

Recently, fluorine chemistry has received a great deal of interest. Due to the peculiar properties of fluorine (high electronegativity; relatively small size; very low polarizability; tightly bound, three non-bonding electron pairs and excellent overlap between 2s an 2p orbitals of fluorine with the corresponding orbitals of other second period elements), its presence induces modifications to the physiological activity of bioactive compounds by introducing lipophilic, hydrogen bonding and steric effects.[1,2] At present, a rapidly growing interest in 3-fluorinated azetidines exists, as these compounds possess interesting biological activities. The medicinal importance of 3,3-difluoroazetidines is emphasized by recent patents which relate fluorinated azetidines to new therapeutically active and selective inhibitors of the enzyme dipeptidyl peptidase-IV (DPP-IV).[3–7] The inhibition of this enzyme is emerging as a new therapeutic approach for the treatment of type 2 diabetes.[8] In addition, the recent patents concerning fluorinated azetidines highlight the possibilities of these compounds as substituents to modulate the activity of different active compounds.[9–17] In the latter publications, 3,3-difluoroazetidines are mainly synthesised by treatment of 3-azetidinones with diethylaminosulphur trifluoride (DAST), but no examples of the synthesis of 2-functionalized 3,3-difluoroazetidines via this method are known. Furthermore, perfluoroazetidines have been prepared by thermolysis of the corresponding perfluoro-1,2-oxazines or by photolysis of perfluorinated triazines, but these perfluoroazetidines constitute a peculiar class of compounds.[18–21] In conclusion, no general pathway towards 3,3-difluoroazetidines is available, although the medicinal potential of this new class of compounds is very promising. As a result, new syntheses towards the highly attractive 3,3-difluoroazetidines are of considerable interest towards organic and medicinal chemists.

3,3-Difluoroazetidin-2-ones can be prepared by condensation of β,β-difluoro ester enolates with imines or oxazolidines and by ring-closure of 3-hydroxy-2,2-difluoropropionamides or α,α-difluoro-β-alaninates.[22] In the present report, 3,3-difluoro-4-phenylazetidin-2-ones **4**–**6** were synthesized in good yields (77–87%) via a Reformatsky-type reaction using ethyl bromodifluoroacetate and different benzaldimines **1**–**3**.[23,26] Therefore, ethyl bromodifluoroacetate was reacted with freshly activated Zn and an aldimine in THF under reflux during one hour. Performing the same reaction with *N*-(2-methylpropylidene)-2-propenyl-1-amine (**8**) afforded 3,3-difluoroazetidin-2-one (**9**) in 55% yield, next to a small amount (5%) of β-amino-α,α-difluoroester **10**. Debenzylation of 3,3-difluoro-1-(4-methoxybenzyl)azetidin-2-one (**4**) was achieved using three equivalents of ceric ammonium nitrate (CAN) in a mixture of acetonitrile and water in a 9:1 ratio. In this way, the deprotected 3,3-difluoroazetidin-2-one **7** was obtained in 83% yield (Scheme 1).

As an alternative pathway towards N-substituted 3,3-difluoroazetidin-2-ones, it was found that functionalization of 1-unsubstituted 3,3-difluoroazetidin-2-one **7** under phase-transfer conditions was possible. Therefore, different bromides were used in the presence of 0.1 equivalent of sodium iodide, 0.4 equivalent of tetrabutylammonium hydrogensulfate and 2 equivalents of potassium hydroxide in THF (Scheme 2).[24,27] In the case of allyl bromide, the reaction was complete after one hour of stirring at room temperature. Substitution of 3,3-difluoroazetidin-2-one **7** with 1-bromobutane turned out to be more difficult as one hour and a half of reflux in THF was required to complete the reaction.

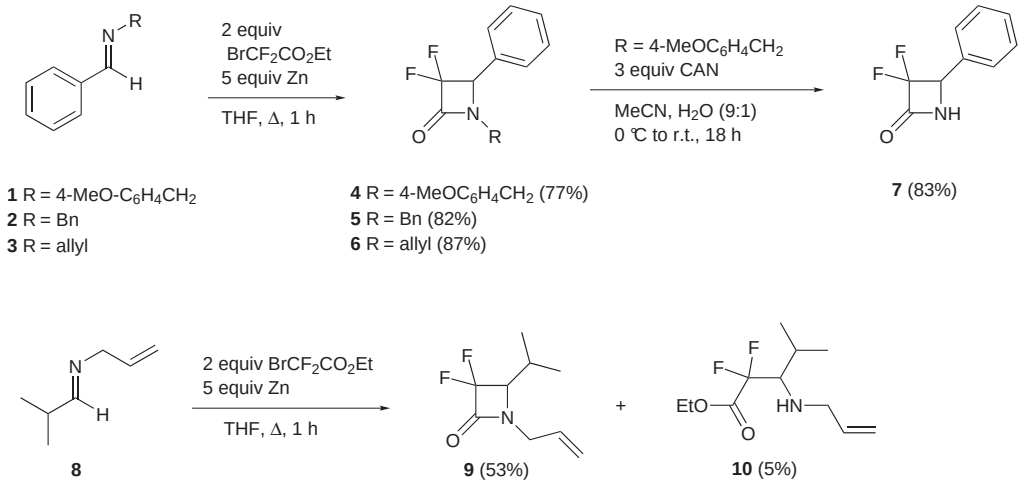
Finally, 3,3-difluoroazetidin-2-ones **4**–**7** and **9** were converted towards the corresponding new 3,3-difluoroazetidines **12**–**16** in high yields. An excess of six equivalents of monochlorohydroalane in diethyl ether at 0 °C for four hours proved to be an excellent reductive agent to perform these reactions (Scheme 3).[25,28] After work-up, no further purification was necessary, leading to high yields of 3,3-difluoroazetidines **12**–**16**.

In conclusion, a straightforward methodology toward new 3,3-difluoroazetidines was developed via reduction of 3,3-difluoroazetidin-2-ones with an excess of monochloroalane.

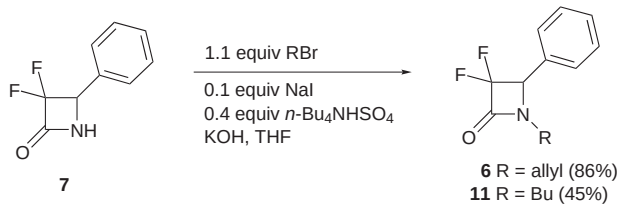
## Acknowledgment

The authors are indebted to Ghent University (GOA) for financial support.

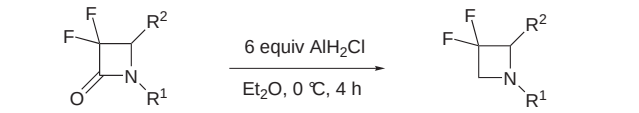
***SYNLETT*** 2006, No. 13, pp 2039–2042
Advanced online publication: 09.08.2006
DOI: 10.1055/s-2006-948186; Art ID: G14206ST




**Scheme 1**




**Scheme 2**




**4** $R^1$ = 4-MeO-Bn, $R^2$ = Ph
**5** $R^1$ = Bn, $R^2$ = Ph
**6** $R^1$ = allyl, $R^2$ = Ph
**7** $R^1$ = H, $R^2$ = Ph
**9** $R^1$ = allyl, $R^2$ = *i*-Pr

**12** $R^1$ = 4-MeOC$_6$H$_4$CH$_2$, $R^2$ = Ph (87%)
**13** $R^1$ = Bn, $R^2$ = Ph (84%)
**14** $R^1$ = allyl, $R^2$ = Ph (87%)
**15** $R^1$ = H, $R^2$ = Ph (82%)
**16** $R^1$ = allyl, $R^2$ = *i*-Pr (85%)

**Scheme 3**

## References and Notes


(1) Smart, B. *J. Fluorine Chem.* **2001**, *109*, 3.
(2) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.
(3) Parker, J. C.; Hulin, B. US 2005043292 A1, **2005**; *Chem. Abstr*. **2005**, *142*, 261783.
(4) Li, W.; Oliver, E. Jr.; Rojas, C.; Kalish, V.; Belyakov, S. WO 2004071454 A2, **2004**; *Chem. Abstr*. **2004**, *141*, 225299.
(5) Duffy, J. L.; Mathvink, R. J.; Weber, A. E.; Xu, J. WO 2004050022 A2, **2004**; *Chem. Abstr*. **2004**, *141*, 54612.
(6) Colandrea, V. J.; Edmondson, S. D.; Mathvink, R. J.; Mastracchio, A.; Weber, A. E.; Xu, J. WO 2004043940 A1, **2004**; *Chem. Abstr*. **2004**, *141*, 7438.
(7) Hulin, B.; Parker, J. C. WO 2003101958 A2, **2003**; *Chem. Abstr*. **2003**, *140*, 16965.
(8) Weber, A. *J. Med. Chem.* **2004**, *47*, 4135.
(9) Ge, P.; Horvath, R. F.; Zhang, L. Y.; Yamaguchi, Y.; Kaiser, B.; Zhang, X.; Zhang, S.; Zhao, H.; John, S.; Moorcroft, N.; Shutske, G. WO 2005023806 A2, **2005**; *Chem. Abstr*. **2005**, *142*, 261783.
(10) Brooks, D. P. WO 2005000311 A1, **2005**; *Chem. Abstr*. **2005**, *142*, 114098.
(11) Flohr, A.; Norcross, R. D. US 2004204584 A1, **2004**; *Chem. Abstr*. **2004**, *141*, 350158.
(12) Churcher, I.; Harrison, T.; Kerrad, S.; Oakley, P. J.; Shaw, D. E.; Teall, M. R.; Williams, S. WO 2004031137 A1, **2004**; *Chem. Abstr*. **2004**, *140*, 321108.
(13) Collins, I. J.; Cooper, L. C.; Harrison, T.; Keown, L. E.; Madin, A. R.; Mark, P. WO 2003093252 A1, **2003**; *Chem. Abstr*. **2003**, *139*, 16965.
(14) Provins, L.; Van Keulen, B. J.; Surtees, J.; Talaga, P.; Christophe, B. WO 2003087064 A1, **2003**; *Chem. Abstr*. **2003**, *139*, 337980.
(15) Borthwick, A. D.; Hatley, R. J.; Hickey, D. M. B.; Liddle, J.; Livermore, D. G. H.; Mason, A. M.; Miller, N. D.; Nerozzi, F.; Sollis, S. L.; Szardenings, A. K.; Wyatt, P. G. WO 2003053433A1, **2003**; *Chem. Abstr*. **2003**, *139*, 85377.
(16) Selnick, H. G.; Barrow, J. C.; Nantermet, P. G.; Williams, P. D.; Stauffer, K. J.; Sanderson, P. E.; Rittle, K. E.; Morissette, M. M.; Wiscount, C. M.; Tran, L. O.; Lyle, T. A.; Staas, D. D. WO 2002050056 A1, **2002**; *Chem. Abstr*. **2002**, *137*, 63475.
(17) Carling, W. R.; Mitchinson, A. R.; Michail, G. N.; Street, L. J. WO 2000047582 A1, **2000**; *Chem. Abstr*. **2000**, *133*, 177176.
(18) Banks, R. E.; Barlow, M. G.; Haszeldine, R. N. *J. Chem. Soc.* **1965**, 6149.
(19) Banks, R. E.; Haszeldine, R. N.; Matthews, V. *J. Chem. Soc.* **1967**, 2263.
(20) Yamamoto, T.; Yasuhara, A.; Shiraishi, F.; Kaya, K.; Abe, T. *Chemosphere* **1997**, *35*, 643.
(21) Chambers, R. D.; Shepherd, T.; Tamura, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 975.
(22) Lacroix, S.; Chequillaume, A.; Gérard, S.; Marchand-Brynaert, J. *Synthesis* **2003**, 2483; and references cited therein.
(23) Marcotte, S.; Pannecoucke, X.; Feasson, C.; Quirion, J.-C. *J. Org. Chem.* **1999**, *64*, 8461.
(24) Duboc, R.; Hénaut, C.; Savignac, M.; Genet, J.-P.; Bhatnagar, N. *Tetrahedron Lett.* **2001**, *42*, 2461.
(25) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K. *J. Org. Chem*. **1991**, *56*, 5263.

(26) **Synthesis of 3,3-Difluoroazetidines 4–6 and 9 via the Reformatsky-Type Reaction.**

As an example, the synthesis of 1-benzyl-3,3-difluoro-4-phenylazetidin-2-one(**5**) is described. To a refluxing suspension of freshly activated Zn dust (1.63 g, 25 mmol) in dry THF (10 mL) was added a solution of 2 (0.98 g, 5 mmol) and ethyl bromodifluoroacetate (1.52, 7.5 mmol) in THF at such a rate so as to maintain vigorous reflux. After 1 h of reflux, the reaction mixture was cooled and extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under vacuum. The residue was then purified by flash column chromatography over silica gel.

**Preparation of Activated Zn Dust.**

Nitrogen gas was bubbled through a mixture of 100 g (1.53 mol) of zinc and 250 mL of distilled $H_2O$. After 15 min of stirring, 7.5 g (46 mmol) of $CuSO_4$ was added, and the resulting mixture was stirred for 45 min under nitrogen atmosphere. At the same time, 500 mL of distilled $H_2O$ and 500 mL of acetone were degassed by stirring under a nitrogen atmosphere during 45 min. In order to remove the formed $ZnSO_4$, the Zn–Cu couple was filtered off and washed with 500 mL of degassed $H_2O$ and 500 mL of degassed acetone (to remove the water). After evaporation of the solvent in vacuo, the activated Zn thus obtained was used immediately in the cyclocondensation reaction above.

**1-Benzyl-3,3-difluoro-4-phenylazetidin-2-one (5)**: 82% yield; TLC: $R_f$ = 0.15 (PE–EtOAc, 10:1). $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.93 (1 H, dd, *J* = 14.6, 2.2 Hz, NCH), 4.72 [1 H, dd, *J* = 7.4, 2.2 Hz, NC(*H*)H], 4.95 [1 H, d, *J* = 14.6 Hz, NC(H)*H*], 7.09–7.45 (10 H, m, 2 × $C_6H_5$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 44.22 ($NCH_2$), 68.00 (dd, *J* = 26.5, 24.2 Hz, NCH), 120.59 (dd, *J* = 292.6, 290.2 Hz, $CF_2$), 128.08, 128.44, 128.60, 129.06, 129.09 and 129.84 (2 × $CC_5H_5$), 129.99 and 133.38 (2 × $CC_5H_5$), 160.94 (t, *J* = 30.6 Hz, C=O). $^{19}$F NMR (282 Hz, $CDCl_3$): δ = –114.18 (dd, *J* = 223.7, *J* = 7.0 Hz), –120.78 (d, *J* = 223.7 Hz). IR (NaCl): $\nu_{max}$ = 3034, 2926, 1789, 1496, 1457 cm$^{-1}$. MS (70 eV): *m/z* (%) = 274 (10) [$M^+$ + 1]. Anal. Calcd for $C_{16}H_{13}F_2NO$: C, 70.32; H, 4.79; N, 5.13. Found: C, 70.51; H, 4.91; N, 4.89.

**1-Allyl-3,3-difluoro-4-phenylazetidin-2-one (6)**: 87% yield; TLC: $R_f$ = 0.25 (PE–EtOAc, 10:1). $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.47–3.55 [1 H, m, NC(*H*)H], 4.29 [1 H, dd, *J* = 15.4, 5.2 Hz, NC(H)*H*], 4.94 (1 H, dd, *J* = 7.4, 2.2 Hz, NCH), 5.11–5.26 (2 H, m, CH=C$H_2$), 5.67–5.80 (1 H, m, C*H*=$CH_2$), 7.27–7.32 and 7.42–7.46 (5 H, 2 m, $C_6H_5$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 42.78 ($NCH_2$), 68.37 (t, *J* = 24.8 Hz, NCH), 120.31 (*C*$H_2$=CH), 120.62 (dd, *J* = 293.1, 289.6 Hz, $CF_2$), 128.02, 129.05 and 129.86 ($CC_5H_5$), 129.49 (*C*H=$CH_2$), 130.21 ($CC_5H_5$), 160.93 (t, *J* = 30.6 Hz, C=O). $^{19}$F NMR (282 Hz, $CDCl_3$): δ = –114.13 (dd, *J* = 223.7, 7.4 Hz), –121,43 (d, *J* = 223.7 Hz). IR (NaCl): $\nu_{C=O}$ = 1688, 1684 cm$^{-1}$. MS (70 eV): *m/z* (%) = 224 (100) [$M^+$ + 1]. Anal. Calcd for $C_{12}H_{11}F_2NO$: C, 64.57; H, 4.97; N, 6.27. Found: C, 64.40; H, 5.15; N, 6.41.

**1-Allyl-3,3-difluoro-4-isopropylazetidin-2-one (9)**: 53% yield; TLC: $R_f$ = 0.1 (PE–EtOAc, 10:1). $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.02 [3 H, dd, *J* = 6.9, 0.8 Hz, CH(C$H_3$)$CH_3$], 1.07 [3 H, d, *J* = 6.9 Hz, CH($CH_3$)C$H_3$], 2.03 [1 H, octet, *J* = 6.9 Hz, C*H*($CH_3$)$_2$], 3.66–3.77 [2 H, m, NC(*H*)H and NCH], 4.27 [1 H, ddt, *J* = 15.7, 5.0, 1.7 Hz, NC(H)*H*], 5.24–5.34 (2 H, m, CH=C$H_2$), 5.70–5.83 (1 H, m, C*H*=$CH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 18.21 and 18.25 (2 × $CH_3$), 18.84 [C*H*($CH_3$)$_2$], 44,34 ($NCH_2$), 70.87 (t, *J* = 22.5 Hz, NCH), 119.73 (*C*$H_2$=CH), 120.62 (dd, *J* = 290.8, 283.8 Hz, $CF_2$), 130.39 (*C*H=$CH_2$), 161.28 (t, *J* = 30.6 Hz, C=O). $^{19}$F NMR (282 Hz, $CDCl_3$): δ = –113.96 (dd, *J* = 223.4, 9.5 Hz), –124.56 (d, *J* = 223.4 Hz). IR (NaCl): $\nu_{C=O}$ = 1794, $\nu_{max}$ = 2971, 2938, 1645, 1473 cm$^{-1}$. MS (70 eV): *m/z* (%) = 190 (100) [$M^+$ + 1]. Anal. Calcd for $C_9H_{13}F_2NO$: C, 57.13; H, 6.93; N, 7.40. Found: C, 57.29; H, 7.14; N, 7.68.

**Ethyl 3-(Allylamino)-2,2-difluoro-4-methylpentanoate (10)**: 5% yield; TLC: $R_f$ = 0.25 (PE–EtOAc, 10:1). $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.98 and 1.06 [6 H, 2 d, *J* = 6.88 Hz, CH(C$H_3$)$_2$], 1.35 (3 H, t, *J* = 7.15 Hz, $CH_2CH_3$), 2.03 [1 H, septd, *J* = 6.9, 4.4 Hz, C*H*($CH_3$)$_2$], 3.01 (1 H, ddd, *J* = 20.6, 9.4, 4.4 Hz, NHC*H*), 3.32 [1 H, dd, *J* = 14.0, 5.8 Hz, NHC(*H*)H], 3.39 [1 H, dd, *J* = 14.0, 6.3 Hz, NHC(*H*)H], 4.31 (2 H, q, *J* = 7.2 Hz, OC$H_2$), 5.03–5.20 (2 H, m, C$H_2$=CH), 5.73 (1 H, m, $CH_2$=C*H*). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.99 ($CH_3CH_2O$), 17.62 and 21.10 [CH(*C*$H_3$)$_2$], 28.00 [*C*H($CH_3$)$_2$], 52.14 ($NHCH_2$), 62.51 ($OCH_2$), 63.32 (dd, *J* = 24.2, 20.8 Hz, NHCH), 115.88 (*C*$H_2$=CH), 117.66 (t, *J* = 257.29 Hz),136.82 ($CH_2$=*C*H), 164.77 (t, *J* = 32.31 Hz, C=O). $^{19}$F NMR (282 Hz, $CDCl_3$): δ = –107.19 (dd, *J* = 254.9, 9.5 Hz), –117.44 (dd, *J* = 254.9, 20.8 Hz). IR (NaCl): $\nu_{C=O}$ = 1773, 1758, $\nu_{max}$ = 2966, 1468 cm$^{-1}$. MS (70 eV): *m/z* (%) = 236 (100) [$M^+$ + 1]. Anal. Calcd for $C_{11}H_{19}F_2NO_2$: C, 56.16; H, 8.14; N, 5.95. Found: C, 55.82; H, 8.31; N, 5.75.

(27) **Synthesis of 3,3-Difluoroazetidines 6 and 11 via N-Alkylation of Difluoro-β-lactam (7).**

As an example, the synthesis of 1-allyl-3,3-difluoro-4-phenylazetidin-2-one(**6**) is described. 3,3-Difluoroazetidin-2-one **7** (0.18 g, 1 mmol) was added to a solution of allyl bromide (0.15 g, 1.1 mmol), NaI (0.013 g, 0.1 mmol), *n*-$Bu_4NHSO_4$ (0.14 g, 0.4 mmol) and KOH (0.11 g, 2 mmol) in THF (10 mL). In the case of 3,3-difluoroazetidine **6**, 1 h stirring at r.t. proved to be sufficient to complete the reaction. Then, 1.5 h of reflux was needed to complete the reaction in the case of azetidin-2-one **11**. Subsequently, the mixture was poured in $H_2O$ (20 mL), and the reaction mixture was extracted three times with $Et_2O$ (20 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated under vacuum. The residue was then purified by flash column chromatography.

**1-Butyl-3,3-difluoro-4-phenylazetidin-2-one (11)**: 45% yield; TLC: $R_f$ = 0.15 (PE–EtOAc, 20:1). $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.90 (3 H, t, *J* = 7.3 Hz, $CH_3$), 1.26–1.39 (2 H, m, $CH_3CH_2$), 1.52 (2 H, quint, *J* = 7.4 Hz, $NCH_2CH_2$), 2.94–3.03 [1 H, m, NC(*H*)H], 3.56–3.80 [1 H, m, NC(H)*H*], 4.91 (1 H, dd, *J* = 7.2, 2.2 Hz, NCH), 7.26–7.33 and 7.44–7.47 (5 H, 2 m, $C_6H_5$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.48 ($CH_3$), 20.08 ($CH_3CH_2$), 29.06 ($NCH_2CH_2$), 40.16 ($NCH_2$), 68.74 (t, *J* = 24.8 Hz, NCH), 120.50 (dd, *J* = 293.1, 289.6 Hz, $CF_2$), 128.01, 129.05 and 129.86 ($CC_5H_5$), 130.45 ($CC_5H_5$), 161.22 (t, *J* = 30.0 Hz, C=O). $^{19}$F NMR (282 Hz, $CDCl_3$): δ = –114.38 (dd, *J* = 223.7, 7.8 Hz), –121.77 (d, *J* = 223.7 Hz). IR (NaCl): $\nu_{C=O}$ = 1788 cm$^{-1}$. MS (70 eV): *m/z* (%) = 240 (100) [$M^+$ + 1]. Anal. Calcd for $C_{13}H_{15}F_2NO$: C, 65.26; H, 6.32; N, 5.85. Found: C, 65.04; H, 6.39; N, 5.68.

(28) **Synthesis of 3,3-Difluoroazetidines 12–16.**

As an example, the synthesis of 1-allyl-3,3-difluoro-4-phenylazetidine (**14**) is described. $LiAlH_4$ (0.57 g, 0.015 mmol) was added to $AlCl_3$ (2.01 g, 0.015 mmol) in $Et_2O$ (30 mL) at 0 °C. After 30 min stirring at r.t., 3,3-difluoro-azetidin-2-one **6** (1.12 g, 0.005 mmol) was added to the reaction mixture. After 4 h of stirring at r.t., $H_2O$ was added until all $LiAlH_4$ was neutralized. The solvent was decanted and the resulting suspension was extracted three times with $Et_2O$ (20 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum, yielding pure 1-allyl-3,3-difluoro-4-phenylazetidine (**14**).

**3,3-Difluoro-1-(4-methoxybenzyl)-4-phenylazetidine (12)**: 87% yield. $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.21 [1 H, ddd, *J* = 15.7, 13.5, 9.5 Hz, NC(*H*)HCF$_2$], 3.48 [1 H, dd, *J* = 12.8, 2.2 Hz, NC(*H*)HC$_6$H$_4$], 3.65–3.74 [1 H, m, NC(H)*H*CF$_2$], 3.78 (3 H, s, CH$_3$O), 3.95 [1 H, d, *J* = 12.9 Hz, NC(H)*H*C$_6$H$_4$], 4.44 (1 H, dd, *J* = 14.9, 10.5 Hz, NCH), 6.82–6.87 (2 H, m, 2 × MeOCC*H*), 7.21–7.49 (7 H, m, C$_6$H$_5$ and 2 × NCH$_2$CC*H*). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 55.26 (CH$_3$O), 60.32 (NCH$_2$C$_6$H$_4$), 61.42 (t, *J* = 22.6 Hz, *C*H$_2$CF$_2$), 76.68 (t, *J* = 32.3 Hz, NCH), 113.81 (2 × CH$_3$OC*C*H), 117.03 (t, *J* = 279.8 Hz, CF$_2$), 127.87, 128.33, 128.44 and 129.90 (C*C*$_5$H$_5$ and 2 × MeOCCH*C*H), 129.09 and 134.07 (NCH*C* and NCH$_2$*C*), 159.02 (MeO*C*). $^{19}$F NMR (282 Hz, $CDCl_3$): δ = –116.65 (ddt, *J* = 190.7, 15.6, 10.4 Hz), –91.78 (dtd, *J* = 190.7, 14.3, 6.5 Hz). IR (NaCl): $\nu_{max}$ = 2959, 2935, 2838, 1613, 1513, 1454, 1331 cm$^{-1}$. MS (70 eV): *m/z* (%) = 290 (10) [M$^+$ + 1], 121 (100). Anal. Calcd for $C_{17}H_{17}F_2NO$: C, 70.57; H, 5.92; N, 4.84. Found: C, 70.71; H, 5.78; N, 4.60.

**1-Benzyl-3,3-difluoro-4-phenylazetidine (13)**: 84% yield. $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.24 [1 H, ddd, *J* = 15.7, 13.5, 9.5 Hz, NC(*H*)HCF$_2$], 3.47 [1 H, dd, *J* = 13.1, 1.9 Hz, NC(*H*)HC$_6$H$_5$], 3.68 [1 H, tdd, *J* = 9.6, 6.6, 1.5 Hz, NC(H)*H*CF$_2$], 3.96 [1 H, d, *J* = 13.1 Hz, NCH(*H*)C$_6$H$_5$], 4.44 (1 H, dd, *J* = 14.9, 10.5 Hz NCH), 7.18–7.49 (10 H, m, 2 × C$_6$H$_5$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 60.94 (N*C*H$_2$C$_6$H$_5$), 61.65 (dd, *J* = 24.2, 20.8 Hz, *C*H$_2$CF$_2$), 76.87 (t, *J* = 22.5 Hz, NCH), 117.01 (t, *J* = 279.2 Hz, CF$_2$), 127.43, 127.87, 128.31, 128.39, 128.45 and 128.62 (2 × C*C*$_5$H$_5$), 133.96 (NCH*C*), 137.08 (NCH$_2$*C*). $^{19}$F NMR (282 Hz, $CDCl_3$): δ = –117.00 (ddt, *J* = 190.7, 15.6, 10.4 Hz), –91.82 (dtd, *J* = 190.7, 13.9, 6.9 Hz). IR (NaCl): $\nu_{max}$ = 3064, 3031, 2970, 2925, 2855, 2802, 1604, 1496, 1453 cm$^{-1}$. MS (70 eV): *m/z* (%) = 260 (20) [M$^+$ + 1], 120 (100), 91 (20). Anal. Calcd for $C_{16}H_{15}F_2N$: C, 74.11; H, 5.83; N, 5.40. Found: C, 74.01; H, 6.11; N, 5.27.

**1-Allyl-3,3-difluoro-4-phenylazetidine (14)**: 87% yield. $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.13 [1 H, ddd, *J* = 13.4, 9.5, 1.0 Hz, NC(*H*)HCH=CH$_2$], 3.31 [1 H, ddd, *J* = 15.6, 13.5, 9.5 Hz, NC(*H*)HCF$_2$], 3.42 [1 H, ddt, *J* = 13.4, 5.5, 1.4 Hz, NC(H)*H*CH=CH$_2$], 3.84 [1 H, tdd, *J* = 9.5, 6.9, 1.5 Hz, NC(H)*H*CF$_2$], 4.44 (1 H, ddd, *J* = 15.1, 10.2, 0.8 Hz, NCH), 5.08–5.26 (2 H, m, CH=C*H*$_2$), 5.72–5.85 (1 H, m, C*H*=CH$_2$), 7.25–7.46 (5 H, m, C$_6$H$_5$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 60.26 (N*C*H$_2$CH=CH$_2$), 61.80 (dd, *J* = 24.2, 20.8 Hz, *C*H$_2$CF$_2$), 77.03 (t, *J* = 22.5 Hz, NCH), 116.95 (t, *J* = 279.8 Hz, CF$_2$), 118.04 (CH=*C*H$_2$), 127.90, 128.31 and 128.44 (C*C*$_5$H$_5$), 133.79 (*C*H=CH$_2$), 134.21 (NCH*C*). $^{19}$F NMR (282 Hz, $CDCl_3$): δ = –116.33 (ddt, *J* = 190.7, 15.6, 10.4 Hz), –91.63 (dtd, *J* = 190.7, 14.7, 6.9 Hz). IR (NaCl): $\nu_{max}$ = 3067, 3031, 2977, 2925, 2857, 2807, 1644, 1497, 1459, 1452 cm$^{-1}$. MS (70 eV): *m/z* (%) = 210 (20) [M$^+$ + 1], 190 (80), 88 (100). Anal. Calcd for $C_{12}H_{13}F_2N$: C, 68.88; H, 6.26; N, 6.69. Found: C, 69.09; H, 6.10; N, 6.53.

**3,3-Difluoro-4-phenylazetidine (15)**: 82% yield. $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.79 [1 H, ddd, *J* = 22.0, 10.5, 1.7 Hz, NC(*H*)HCF$_2$], 4.04 [1 H, ddd, *J* = 14.9, 13.5, 10.5 Hz, NC(H)*H*CF$_2$], 5.14 (1 H, dd, *J* = 14.9, 10.5 Hz, NCH), 7.22–7.44 (5 H, m, C$_6$H$_5$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 56.08 (t, *J* = 24.2 Hz, NHCH$_2$), 71.04 (t, *J* = 23.7 Hz, NHCH), 119.21 (t, *J* = 282.1 Hz, CF$_2$), 127.29, 128.34 and 128.40 (C*C*$_5$H$_5$), 135.46 (NHCH*C*). $^{19}$F NMR (282 Hz, $CDCl_3$): δ = –91.22 (dq, *J* = 189.9, 12.9 Hz), –110.18 (ddt, *J* = 189.9, 14.7, 11.3 Hz). IR (NaCl): $\nu_{max}$ = 3347, 2948, 2879, 1514, 1497, 1459 cm$^{-1}$. MS (70 eV): *m/z* (%) = 170 (100) [M$^+$ + 1]. Anal. Calcd for $C_9H_9F_2N$: C, 63.90; H, 5.36; N, 8.28. Found: C, 64.14; H, 5.25; N, 8.43.

**1-Allyl-3,3-difluoro-4-isopropylazetidine (16)**: 53% yield. $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.92 and 0.95 (6 H, 2 d, *J* = 6.7 Hz, 2 × CH$_3$), 1.96–2.08 [1 H, m, CH(CH$_3$)$_2$], 2.89–3.01 [2 H, m, NC*H* and NC(*H*)HCH=CH$_2$], 3.10 [1 H, td, *J* = 15.4, 10.2 Hz, NC(*H*)HCF$_2$], 3.51 [1 H, ddt, *J* = 13.4, 5.1, 1.5 Hz, NC(H)*H*CH=CH$_2$], 3.70 [1 H, tdd, *J* = 10.5, 10.2, 1.5 Hz, NC(H)*H*CF$_2$], 5.12–5.24 (2 H, m, CH=C*H*$_2$), 5.74–5.87 (1 H, m, C*H*=CH$_2$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 18.54 and 18.76 (2 × CH$_3$), 28.83 [C*H*(CH$_3$)$_2$], 61.94 (dd, *J* = 25.4, 20.8 Hz, *C*H$_2$CF$_2$), 62.28 (N*C*H$_2$CH=CH$_2$), 80.37 (dd, *J* = 21.9, 19.6 Hz, NCH), 117.7 (t, *J* = 278.1 Hz, CF$_2$), 118.21 (CH=*C*H$_2$), 133.81 (*C*H=CH$_2$). $^{19}$F NMR (282 Hz, $CDCl_3$): δ = –117.80 (dtd, *J* = 197.7, 16.5, 8.7 Hz), –88.64 (ddt, *J* = 197.7, 14.7, 10.0 Hz). IR (NaCl): $\nu_{max}$ = 2964, 2931, 2875, 2803, 1645, 1472, 1458 cm$^{-1}$. MS (70 eV): *m/z* (%) = 176 (100) [M$^+$ + 1]. Anal. Calcd for $C_9H_{15}F_2N$: C, 61.69; H, 8.63; N, 7.99. Found: C, 61.53; H, 8.69; N, 7.89.