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Facile allylboration of ketones with β-benzyloxy-γ,γ-difluoroallylboronate: Preparation of *gem*-difluorinated homoallylic *tert*-alcohols

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ABSTRACT

The reaction of β-benzyloxy-γ,γ-difluoroallylboronate, at room temperature and in the absence of catalysts, with a variety of aromatic and aliphatic ketones of varying sterics and electronic requirements furnishes fluorinated homoallylic *tert*-alcohols in 62–82% yields. Representatives of these alcohols were converted to their corresponding α,α-difluoro-β-hydroxy ketones in 73–85% yields.

1. Introduction

Preparation of *gem*-difluoroalkyl containing molecules is important and challenging [1–7]. For example, the introduction of a difluoromethylene moiety into a bioactive peptide has led to the discovery of a potent competitive and reversible protease inhibitors mimicking HIV proteases (**1**) [8] and 2′-deoxy-2′,2′-difluorocytidine (**2**) (Fig. 1) has shown interesting anticancer activity [9]. 1,1′-Difluoroalkenyl functionality may be considered as a biostere of the carbonyl group [10]. By virtue of the C–F bond strength, fluorinated analogues, in most cases, are much more resistant to metabolic degradation. For example, the C-24 position of Vitamin D3 analogue (**3**) (Fig. 1) is blocked to the metabolic oxidation by difluorination [11]. Fluoro-organic molecules are generally synthesized either from fluorine containing starting materials or by using fluorinating reagents [12–14]. The lack of fluorine resources in nature demands sophisticated and efficient procedures for their introduction in complex molecules. Whereas considerable progress has been made in the area of fluoroaromatic or trifluoromethylated compounds, *gem*-difluorinated molecules have lagged behind and, due to their importance, demands considerable attention [15,16]. *Gem*-difluorinated homoallylic alcohols are generally prepared by the coupling of a *gem*-difluorinated allyl metal with a carbonyl [17–22].

We have been involved in the synthesis of fluoroorganic compounds *via* organoborones for nearly two decades [23–27]. Recently we reported the preparation of a novel β-benzyloxy-γ,γ-difluoroallylboronate (**4**) for the fluoro-allylboration of aldehydes [28]. Compared to the allylboration of aldehydes, the corresponding reaction of ketones has been studied only sparingly. In many cases, the reaction of ketones required an added catalyst and harsher conditions, particularly with allylboronates [29–32]. Introduction of fluorine on allylboronates have been shown to increase the rate of allylboration. Examples of these include the allylboronates derived from 3,3′-bis(trifluoromethyl)binaphthol (**5**) [33] and *N*,*N*′-bis(2,2,2-trifluoroethyl)-*N*,*N*′-ethylenetartramide (**6**) (Fig. 2) [34]. We were curious to examine the reactivity of our difluoroallylboronate with ketones. The results from our study follow.

2. Results and discussion

We began our study with the reaction of acetophenone with **4** in one pot. ((2,2-Difluorovinyloxy)methyl)benzene (**7**) was prepared in very good yield from trifluoroethanol. The protected enol ether was purified by distillation. Upon reaction with one equivalent of *n*-BuLi at −78 °C, compound **7** furnishes benzyloxydifluorovinyllithium (**8**) in almost quantitative yield. Addition of one equivalent of diisopropyl iodomethylboronate at that temperature provided the "ate" complex (**9**), which upon warming to room temperature displaced the iodide with the benzyloxydifluorovinyl group to furnish diisopropyl-2-(benzyloxy)-3,3-difluoroallylboronate (**4**). The *in situ* reaction of this allylboronate

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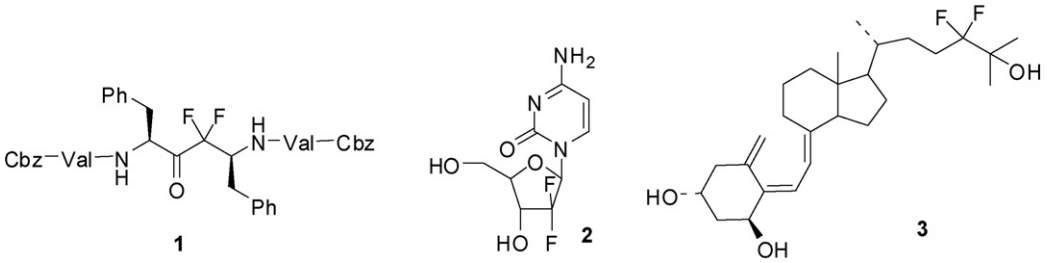


Fig. 1. Fluorinated bio-active molecules.

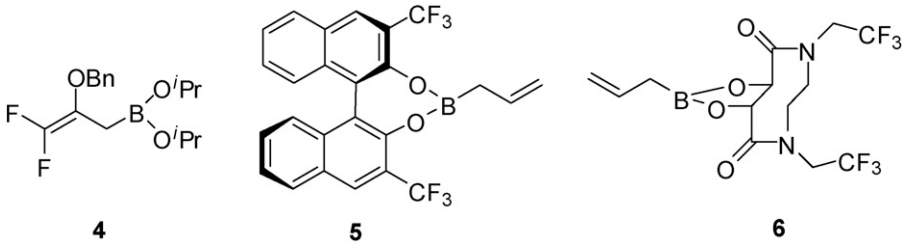


Fig. 2. Fluorine-containing allylboronates.

with acetophenone (**10a**) in THF under reflux was complete within 36 h and workup furnished the homoallylic *tert*-alcohol (**11a**) in 40% isolated yield (Scheme 1).

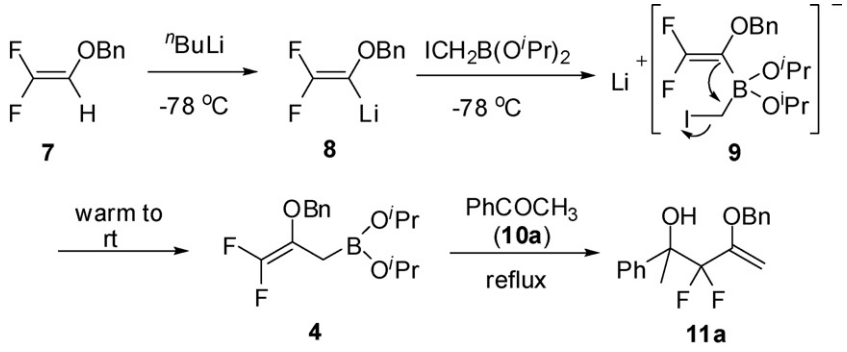
As described for the aldehydes [28], we examined the above reaction using purified allylboronate (**4**) to improve the yield of **11a**. The allylboronate (**4**) formed *via* the above reaction sequence (Scheme 1) can be purified readily by removing the solvent under vacuum and passing through a short bed of celite under nitrogen atmosphere. The reaction proceeded with a substantial improvement in the yield (62%) of the 3°-alcohol. Additionally, the reaction was complete within 6 h under reflux! The progress of the reaction was monitored by using ^{11}B NMR spectroscopy (δ shift from 28 ppm to 18 ppm upon completion).

A variety of solvents such as dichloromethane, toluene, pentane etc. were then screened for the reaction. In case of dichloromethane, the reaction was complete in 24 h at room temperature whereas it took 30 h in toluene. As in the case of aldehydes, the reaction was very facile in pentane. Indeed, the reaction of acetophenone with **4** in pentane was complete within 8 h at *room temperature*.

We then utilized the standardized protocol (rt, pentane) for the reaction of a variety of substituted acetophenones containing electron-withdrawing or -donating groups at the *para* position. Aliphatic ketones with variable sterics were also subjected to allyboration under this protocol. We included fluorinated ketones as well to prepare polyfluorinated homoallylic alcohols.

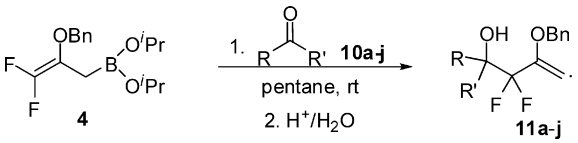
The aliphatic as well as aromatic ketones underwent allylboration within 8 h. An electron-withdrawing substituent, such as a nitro or a trifluoromethyl group increased the rate of the reaction, complete within 6 h at rt. The yield was mostly not influenced by the nature of the substituent on the aromatic ring (Table 1, entry 1–4), although the *p*-trifluoromethylacetophenone (**10c**) provided slightly improved yield (82%) of the homoallyl alcohol. Cyclohexanone (**10f**), a representative cyclic ketone provided the *tert*-alcohol in 69% yield (entry 6). A representative heteroaromatic ketone, 2-acetylthiophene (**10j**) reacted with the allylboronate in a similar fashion furnishing the *tert*-alcohol in 75% yield. In the case of aliphatic ketones, an increase in the bulk made the reaction little slower without much effect on the yield (entry 7, 8). The reactions of 2,2,2 trifluoroacetophenone (**10e**) as well as trifluoroacetone (**10i**) were relatively slow, probably due to the effective steric size of the trifluoromethyl group [35]. A moderate yield of the *tert*-alcohol was observed in these cases (entry 5, 9). The detailed results are summarized in Table 1.

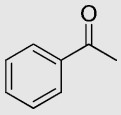
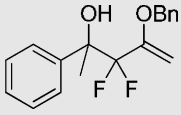
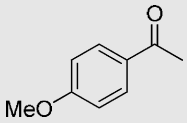
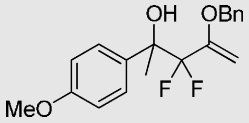
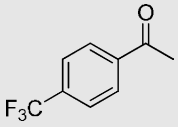
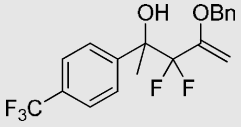
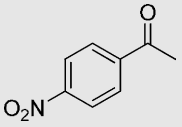
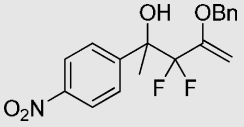
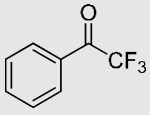
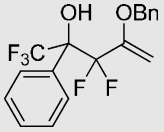
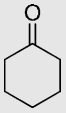
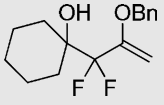
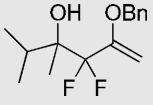
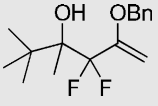
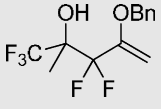
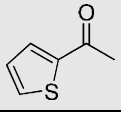
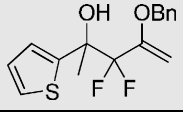
Having achieved a successful preparation of β,β-difluorinated functionalized 3°-alcohols, we converted the products to their corresponding β-hydroxy ketones *via* debenzylation of the vinyl ethers. Three products were chosen as representatives of both aliphatic and aromatic alcohols (**11a**, **11b** and **11f**) and were subjected to the debenzylaton using our earlier standardized conditions using sodium in liquid ammonia [28]. All of them



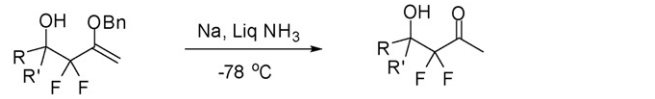
Scheme 1.

Table 1
Allylboration of ketones with β-benzyloxy-γ,γ-difluoroallylboronate.



Entry	Ketones[a]		Reaction time (h)	Homoallyl alcohol		
	#	Structure		#	Structure	Yield (%)[b]
1	**10a**		8	**11a**		70
2	**10b**		8	**11b**		72
3	**10c**		6	**11c**		82
4	**10d**		6	**11d**		70
5	**10e**		16	**11e**		57
6	**10f**		8	**11f**		69
7	**10g**		6	**11g**		72
8	**10h**		8	**11h**		74
9[c]	**10i**		16	**11i**		62
10	**10j**		6	**11j**		75

[a] Reagent: ketone = 1.2:1.
[b] Isolated yield of the purified product.
[c] Reagent: ketone = 1.5:1.



11a: R = Ph, R' = CH_3 **12a**: R = Ph, R' = CH_3, 73%

11b: R = 4-MeO-Ph, R' = CH_3 **12b**: R = 4-MeO-Ph, R' = CH_3, 85%

11f: R-R' = $(CH_2)_5$ **12f**: R-R' = $(CH_2)_5$, 75%

Scheme 2.

provided the desired hydroxyl ketones (**12a**, **12b** and **12f**) in 73–85% yield (Scheme 2).

3. Conclusions

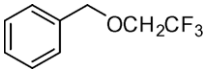
In Conclusion, we have developed a novel method for the preparation of *gem*-difluorinated homoallylic *tert*-alcohols *via* allylboration of a series of ketones using β-benzyloxy-γ,γ-difluoroallylboronate. Aliphatic, aromatic as well as fluorinated ketones reacted with the β-benzyloxy-γ,γ-difluoroallylboronate in pentane to furnish the desired homoallylic alcohols in very good yield within 8 h at room temperature. It is noteworthy that the reactions proceeded in the absence of any catalyst. Representatives of these alcohols were further converted to their corresponding α,α-difluoro-β-hydroxy ketones *via* the debenzylation of the vinylic ether.

4. Experimental

Unless otherwise noted, all manipulations were carried out under inert atmosphere in flame-dried glassware. Tetrahydrofuran (THF) was freshly distilled before use from sodium benzophenone ketyl; all other chemicals and solvents were purchased commercially and used without further purification, unless otherwise noted.

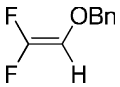
The ^{1}H, ^{11}B, ^{19}F and ^{13}C nuclear magnetic resonance (NMR) spectra were plotted on Varian Gemini-300 spectrometer and Varian Inova-300 spectrometer with Nalorac-quad probes using $CDCl_3$ as solvent at room temperature. The NMR chemical shifts (δ) are reported in ppm. Abbreviations for ^{1}H and ^{19}FNMR: s = singlet, d = doublet, m = multiplet, b = broad. The reactions were monitored by TLC using Merck silica gel 60 F_{254} precoated plates. Flash chromatography was performed using flash grade silica gel (Sorbant Technologies, particle size: 40–63 μm, 230 × 400 mesh).

4.1. Preparation of ((2,2,2-trifluoroethoxy)methyl)benzene



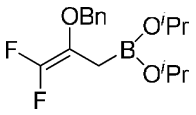
Trifluoroethanol (14.6 mL, 200 mmol) was added, slowly, to a suspension of NaH in THF (200 mL) (8.72 g, 55% dispersion in mineral oil, 200 mmol) at 0 °C and warmed to rt. Benzyl bromide (21.4 mL, 180 mmol) was added when the hydrogen evolution ceased, and refluxed for 3 h. The organic solvents were removed and the residue was washed with ether and the combined organics were washed with brine, dried (anhydrous $MgSO_4$), concentrated, and distilled to provide ((2,2,2-trifluoroethoxy)methyl)benzene as a colorless liquid (32 g, 94%). bp 80 °C/30 Torr. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45–7.32 (bs, 5H), 4.62 (s, 2H), 3.77 (q, J = 8.7 Hz, 2H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −75.3 (t, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.5, 128.6, 128.2, 127.8, 124.1 (d, J = 277.4 Hz), 74.0, 67.0 (q, J = 33.8 Hz). HRMS Found: 190.0600. HRMS Calc. for $C_9H_9F_3O$: 190.0605.

4.2. Preparation of ((2,2-difluorovinyloxy)methyl)benzene (7)



Under vigorous stirring, at −100 °C, the above ((2,2,2-trifluoroethoxy)methyl)benzene (7.6 g, 40 mmol) was added, slowly over a period of 20 min, to a solution of *n*-BuLi (40 mL, 2.5 M solution in hexane, 100 mmol) in THF (120 mL) and kept stirring for another 2 h. The dark red solution was quenched with methanol (12 mL) at this temperature, followed by the addition of aqueous saturated NH_4Cl solution (40 mL). The solution was warmed to rt and diluted with diethyl ether (200 mL). The ether layer was separated and the aqueous layer was washed with ether (3 mL × 20 mL). The combined ether layer was washed with brine, dried (anhydrous $MgSO_4$), and evaporated. The residue was distilled to yield ((2,2-difluorovinyloxy)methyl)benzene as a colorless viscous liquid (5.2 g, 76%). bp. 70 °C/30 Torr. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.34 (m, 5H), 5.66 (dd J = 2.9 Hz and 16.1 Hz, 1H), 4.72 (s, 2H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −101.4 (dd, J = 16.1 Hz and 77.5 Hz, 1F), −121.74 (d, J = 77.5 Hz, 1F). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.5 (dd, J = 274.2 Hz and 286.5 Hz), 136.3, 128.7, 128.5, 128.0, 107.6 (dd, 15.2 Hz and 52.6 Hz, 75.2. HRMS Found: 170.0539. HRMS Calc. for $C_9H_8F_2O$: 170.0543.

4.3. Preparation of diisopropyl 2-(benzyloxy)-3,3-difluoroallylboronate (4)

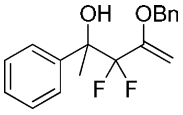


n-BuLi (12.2 mL, 2.5 M solution in hexane, 30.4 mmol) was added, slowly at −78 °C, to a solution of ((2,2-difluorovinyloxy)methyl)benzene (5.2 g, 30.4 mmol) in THF (60 mL) and stirred at that temperature for 20 min. Diisopropyl iodomethylboronate (8.2 g, 30.4 mmol) was added slowly, at −78 °C, to the resultant red solution, left stirred for 0.5 h, allowed to warm to rt and continued to stir for 2 h. The solvents were removed under vacuum and the residue was triturated with dry pentane (30 mL). The supernatant was filtered through a short bed of celite under inert atmosphere. The residue was washed with pentane (4 mL × 20 mL) and the combined organics was concentrated and distilled to yield β-benzyloxy-γ,γ-difluoroallylboronate (**4**) as a colorless liquid [36]. bp. 79–82 °C/0.2 Torr. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46–7.33 (m, 5H), 4.80 (s, 2H), 4.37 (septet, J = 6.2 Hz, 2H), 1.72 (t, J = 3.8 Hz, 2H), 1.15 (d, J = 6.2 Hz, 12H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −105.2 (d, J = 80.7 Hz, 1F), −116.2 (dt, J = 80.7 Hz and 3.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.9 (dd, J = 275.9 Hz and 282.1 Hz), 137.3, 128.3, 127.9, 115.8 (dd, J = 14.3 Hz and 42.1 Hz), 72.7, 65.8, 24.5.

4.4. Typical procedure of the allylboration of ketones

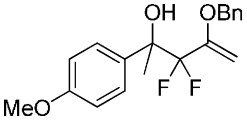
Allylboronate (**4**) (6 mL, 1 M solution in pentane, 6 mmol) was added to a solution of ketone (**10a–j**) (5 mmol) in pentane (2 mL). The reaction was allowed to stir at room temperature till the indicated time (Table 1). Upon completion (^{11}B NMR spectroscopy: δ 28 ppm to δ 18 ppm), the reaction was quenched with saturated ammonium chloride solution (5 mL). The product was extracted with ether (3 mL × 20 mL), dried over anhydrous Na_2SO_4, concentrated and purified by flash chromatography (hexane:ethylacetate = 9:1) to furnish the pure alcohol (**11a–j**) as a viscous colorless liquid.

*4.4.1. 4-(Benzyloxy)-3,3-difluoro-2-phenylpent-4-en-2-ol (**11a**)*



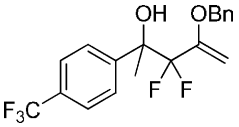
Liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59–7.56 (m, 2H), 7.27–7.45 (m, 8H), 4.79 (d, *J* = 11.4 Hz, 1H), 4.71 (d, *J* = 11.4 Hz, 1H), 4.64 (d, *J* = 3.3 Hz 1H), 4.40 (m, 1H), 3.37 (bs, 1H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −111.34 (d, *J* = 260.4 Hz, 1F), −112.32 (d, *J* = 260.4 Hz, 1F). ^{13}C NMR ($CDCl_3$, 75 Hz): δ 154.7 (t, *J* = 27.4 Hz), 141.3, 135.3, 128.7, 128.4, 127.9, 127.7, 127.6, 126.2, 117.3 (t, *J* = 257.7 Hz), 88.3, 76.7 (t, *J* = 26.3 Hz), 70.6, 24.0. HRMS Found: 304.1280. HRMS Calc. for $C_{18}H_{18}F_2O_2$: 304.1275.

*4.4.2. 4-(Benzyloxy)-3,3-difluoro-2-(4-methoxyphenyl)pent-4-en-2-ol (**11b**)*



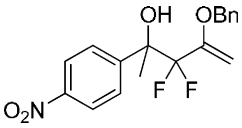
Liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51–7.41 (m, 5H), 7.29–7.31 (m, 2H), 6.90–6.93 (m, 2H), 4.79 (d, *J* = 11.1 Hz, 1H), 4.73 (d, *J* = 11.1 Hz, 1H), 4.66 (s, 1H), 4.43 (s, 1H), 3.87 (s, 3H), 3.35 (bs, 1H), 1.75 (s, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −111.46 (d, *J* = 256.6 Hz, 1F), −112.44 (d, *J* = 256.6 Hz, 1F). ^{13}C NMR ($CDCl_3$, 75 Hz): δ 159.1, 154.8 (t, *J* = 29.5 Hz), 135.4, 133.4, 128.7, 128.4, 127.7, 127.5, 117.5 (t, *J* = 252.6 Hz), 113.2, 88.3, 76.7 (t, *J* = 33.4 Hz), 70.6, 55.2, 24.1. HRMS Found: 334.1380. HRMS Calc. for $C_{19}H_{20}F_2O_3$: 334.1381.

*4.4.3. 4-(Benzyloxy)-3,3-difluoro-2-(4-(trifluoromethyl)phenyl)pent-4-en-2-ol (**11c**)*



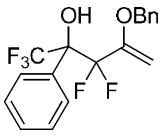
Liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.44–7.38 (m, 3H), 7.27–7.22 (m, 2H), 4.79–4.69 (m, 3H), 4.48–4.45 (m, 1H), 3.39 (s, 1H), 1.77 (s, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −111.71 (s, 2F), −62.44 (s, 3F). ^{13}C NMR ($CDCl_3$, 75 Hz): δ 154.3 (t, *J* = 29.5 Hz), 145.3, 135.0, 130.1, 129.7, 128.8, 128.6, 127.6, 126.8, 126.0, 124.8, 117.1 (t, *J* = 252.8 Hz), 88.7, 70.7, 24.2. HRMS Found: 372.1147. HRMS Calc. for $C_{19}H_{17}F_5O_2$: 372.1149.

*4.4.4. 4-(Benzyloxy)-3,3-difluoro-2-(4-nitrophenyl)pent-4-en-2-ol (**11d**)*



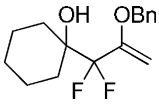
Liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.44–7.36 (m, 3H), 7.26–7.20 (m, 2H), 4.77–4.71 (m, 3H), 4.50–4.47 (m, 1H), 3.34 (bs, 1H), 1.78 (s, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −110.07 (d, *J* = 257.2 Hz, 1F), −112.52 (d, J = 257.2 Hz, 1F). ^{13}C NMR ($CDCl_3$, 75 Hz): δ 153.9 (t, *J* = 29.5 Hz), 148.4, 147.4, 134.9, 128.7, 128.6, 127.7, 127.4, 122.9, 116.9 (t, *J* = 252.7 Hz), 88.7, 76.7 (t, *J* = 25.2 Hz), 70.7, 24.2 HRMS Found: 349.1127. HRMS Calc. for $C_{18}H_{17}F_2NO_4$: 349.1126.

*4.4.5. 4-(Benzyloxy)-1,1,1,3,3-pentafluoro-2-phenylpent-4-en-2-ol (**11e**)*



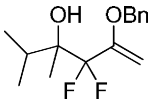
Liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.81–7.77 (m, 2H), 7.52–7.43 (m, 6H), 7.38–7.32 (m, 2H), 4.90 (d, *J* = 4.2 Hz, 1H), 4.86 (d, *J* = 10.8 Hz, 1H), 4.76 (d, *J* = 10.8 Hz, 1H), 4.61–4.57 (m, 1H), 4.47 (s, 1H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −73.89 (t, *J* = 9.9 Hz, 3F), −109.03 (qd, *J* = 9.9 Hz and 268.3 Hz, 1F), −110.46 (dq, *J* = 9.9 Hz and 268.3 Hz, 1F). ^{13}C NMR ($CDCl_3$, 75 Hz): δ 153.8 (t, *J* = 26.9 Hz), 134.7, 131.9, 129.5, 128.9, 128.8, 128.1, 128.0, 127.4, 117.5 (t, *J* = 254.7 Hz), 89.2, 71.4, 65.9. HRMS Found: 358.0997. HRMS Calc. for $C_{18}H_{15}F_5O_2$: 358.0992.

*4.4.6. 1-(2-(Benzyloxy)-1,1-difluoroallyl)cyclohexanol (**11f**)*



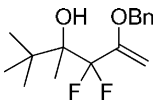
Liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46–7.38 (m, 5H), 4.90 (s, 2 H), 4.78 (m, 1H), 4.56 (m, 1H), 2.24 (bs, 1H), 1.82–1.58 (m, 10H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −116.9 (s) ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.9 (t, *J* = 29.5 Hz), 135.7, 128.7, 128.3, 127.5, 118.4 (t, *J* = 250.6 Hz), 88.0 (t, *J* = 6.3 Hz), 74.1 (t, *J* = 25.3 Hz), 70.4, 30.6, 25.5, 20.8. HRMS Found: 282.1435. HRMS Calc. for $C_{16}H_{20}F_2O_2$: 282.1431.

*4.4.7. 5-(Benzyloxy)-4,4-difluoro-2,3-dimethylhex-5-en-3-ol (**11g**)*



Liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.60–7.39 (m, 5H), 4.92 (s, 2H), 4.85 (d, *J* = 2.7 Hz, 1H), 4.58 (m, 1H), 2.46 (bs, 1H), 1.98 (septet, *J* = 6.8 Hz, 1H), 1.28 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.01 (dd, J = 2.1 Hz and 6.8 Hz, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −108.4 (d, *J* = 259.2 Hz, 1F), −110.2 (d, *J* = 259.2 Hz, 1F). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.5 (t, *J* = 29.5 Hz), 135.5, 128.8, 128.4, 127.6, 118.9 (t, *J* = 252.7 Hz), 87.8 (t, *J* = 6.3 Hz), 70.6, 33.7, 18.3, 17.3, 15.9. HRMS Found: 270.1439. HRMS Calc. for $C_{15}H_{20}F_2O_2$: 270.1431.

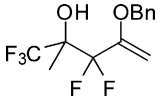
*4.4.8. 5-(Benzyloxy)-4,4-difluoro-2,2,3-trimethylhex-5-en-3-ol (**11h**)*



Liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45–7.40 (m, 5H), 4.89 (s, 2H), 4.86 (d, *J* = 3.6 Hz, 1H), 4.54 (m, 1H), 2.8 (bs, 1H), 1.37 (t, *J* = 2 Hz, 3H), 1.12 (s, 9H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −105.9 (s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7 (t, *J* = 29.5 Hz), 135.4, 128.8, 128.5, 127.7, 119.1 (t, *J* = 252.7 Hz), 87.2 (t, *J* = 6.2 Hz), 79.1 (t,

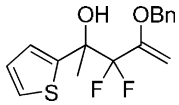
J = 24.8 Hz), 70.6, 37.8, 26.5, 19.4. HRMS Found: 284.1582. HRMS Calc. for $C_{16}H_{22}F_2O_2$: 284.1588.

*4.4.9. 4-(Benzyloxy)-1,1,1,3,3-pentafluoro-2-methylpent-4-en-2-ol (**11i**)*



Liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46–7.40 (m, 5H), 4.96–4.93 (m, 1H), 4.92 (s, 2H), 4.65 (t, J = 3.3 Hz, 1H), 3.8 (bs, 1H), 1.59 (s, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −111.4 (dq, J = 7.9 Hz and 269.3 Hz, 1F), −113.01 (dq, J = 7.9 Hz and 269.3 Hz, 1F), −78.7 (t, J = 7.9 Hz, 3F). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.9 (t, J = 26.3 Hz), 134.8, 128.9, 128.8, 127.9, 124.1 (dd, J = 4.5 Hz and 284.5 Hz), 113.8 (t, J = 251.2 Hz), 95.1, 88.5, 71.3, 15.9. HRMS Found: 296.0833. HRMS Calc. for $C_{13}H_{13}F_5O_2$: 296.0836.

*4.4.10. 4-(Benzyloxy)-3,3-difluoro-2-(thiophen-2-yl)pent-4-en-2-ol (**11j**)*

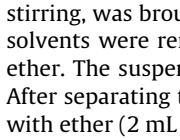


Liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47–7.30 (m, 6H), 7.09–7.03 (m, 2H), 4.84 (d, J = 11.7 Hz, 1H), 4.79 (d, J = 11.7 Hz, 1H), 4.48 (m, 1H), 3.76 (s, 1H), 1.81 (s, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −112.8 (s). ^{13}C NMR ($CDCl_3$, 75 Hz): δ 154.5 (t, J = 29.5 Hz), 146.0, 135.2, 128.8, 128.6, 127.8, 126.9, 125.1, 124.9, 116.5 (t, J = 252.7 Hz), 88.5 (t, J = 6.2 Hz), 70.8, 24.8. HRMS Found: 310.0840. HRMS Calc. for $C_{16}H_{16}F_2O_2S$: 310.0839.

*4.5. Typical procedure for the preparation of β-hydroxy ketones (**12**)*

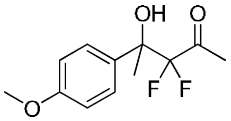
To a solution of **11** (10 mmol) in 30 mL THF was condensed liq. ammonia at −78 °C till the total volume of the solvent was 200 mL (marked previously). Sodium (∼0.4 g) was added to this homogeneous solution till the characteristic blue color became persistent. The dark solution was stirred for 10 min at that temperature and then the color was discharged by the careful addition methanol (1 mL). Solid ammonium chloride (2 g) was introduced inside the reaction flask in several batches over a period of 15 min. The cold bath was removed and the reaction, under stirring, was brought to room temperature overnight. The organic solvents were removed *in vacuo* and the solid was suspended in ether. The suspension was partitioned between ether and water. After separating the organic layer, the aqueous layer was washed with ether (2 mL × 20 mL). The combined ether layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified on flash silica gel chromatography (hexane/ethyl acetate = 9/1) to yield the hydroxyl ketone (**12**).

*4.5.1. 3,3-Difluoro-4-hydroxy-4-phenylpentan-2-one (**12a**)*



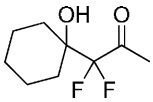
Liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.62–7.56 (m, 2H), 7.49–7.40 (m, 3H), 3.2 (bs, 1H), 2.17 (t, J = 1.8 Hz, 3H), 1.82 (t, J = 1.8 Hz, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −115.69 (d, J = 259.4 Hz, 1F), 116.67 (d, J = 259.4 Hz, 1F). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.5 (t, J = 31.6 Hz), 139.6, 128.4, 127.4, 126.2, 115.6 (t, J = 261.1 Hz), 75.8 (t, J = 25.3 Hz), 26.7, 23.4. HRMS Found: 214.0808. HRMS Calc. for $C_{11}H_{12}F_2O_2$: 214.0805.

*4.5.2. 3,3-Difluoro-4-hydroxy-4-(4-methoxyphenyl)pentan-2-one (**12b**)*



Solid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.49 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H), 3.2 (bs, 1H), 2.17 (t, J = 1.8 Hz, 3H), 1.79 (t, J = 1.8 Hz, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −115.91 (d, J = 257.2 Hz, 1F), −116.87 (d, J = 257.2 Hz, 1F). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.6 (t, J = 27.2 Hz), 159.5, 131.5, 127.6, 115.7 (t, J = 147.4 Hz), 113.7, 75.5 (t, J = 25.3 Hz), 55.3, 26.8, 23.5. HRMS Found: 244.0923. HRMS Calc. for $C_{12}H_{14}F_2O_3$: 244.0911.

*4.5.3. 1,1-Difluoro-1-(1-hydroxycyclohexyl)propan-2-one (**12f**)*



Liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.45 (t, J = 1.8 Hz, 3H), 2.36–2.30 (m, 1H), 1.80–1.56 (m, 10H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −120.57 (s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.8 (t, J = 26.9 Hz), 116.6 (t, J = 258.9 Hz), 73.7 (t, J = 25.3 Hz), 29.7, 27.0, 25.2, 20.4. HRMS Found: 192.0968. HRMS Calc. for $C_9H_{14}F_2O_2$: 192.0962.

Acknowledgement

Financial support from the Herbert C. Brown Center for Borane Research is gratefully acknowledged.

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