# A Convenient Route to Synthesize N-Protected α,α-Difluorohomoallylic Amines by *gem*-Difluoroallylation of α-Amido Sulfones

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**Abstract:** A simple, mild, and efficient synthesis of α,α-difluorohomoallylic amines was achieved by the *gem*-difluoroallylation of α-amido sulfones with zinc powder.

**Key words:** fluorine compounds, allylations, amines, amido sulfones, zinc, ring-closing metathesis

It is well known that the introduction of a fluorine atom may often lead to great changes in the physicochemical and biological properties of a molecule. The synthesis of fluorine-containing organic compounds constitutes an important field in organic synthesis and pharmaceutical chemistry.[1] The difluoromethylene moiety ($CF_2$), in particular, has been found to be a highly useful structural unit in a great number of fluorinated compounds with special bioactivity and medicinal potential, mainly due to its unique properties as an isopolar–isosteric substitute for oxygen to modify the bioactivities of some drug candidates.[2] Therefore, as a convenient way to introduce this useful unit into organic compounds, the *gem*-difluoroallylation of carbonyl compounds, which could produce synthetically and medicinally useful *gem*-difluorohomoallyl alcohols, has been one of the research focuses of organofluorochemistry.[3] In 1991, Burton et al. reported a simple procedure mediated by acid-washed zinc powder for the *gem*-difluoroallylation of aldehydes and ketones with 3-bromo-3,3-difluoropropene, which gave the corresponding *gem*-difluorohomoallyl alcohols in moderate yields.[4] Subsequently, the Kirihara group found that indium was also a highly efficient promoter for the *gem*-difluoroallylation of aldehydes under mild reaction conditions.[3j] However, compared to this well-developed *gem*-difluoroallylation of carbonyl compounds, to the best of our knowledge, the *gem*-difluoroallylation of imines is almost unknown despite the fact that the resulting *gem*-difluorohomoallylic amines are also very important compounds in organic synthesis and medicinal chemistry.[3f,i,5] This is probably partly because imines are often less reactive and more moisture-sensitive than the corresponding carbonyl compounds.

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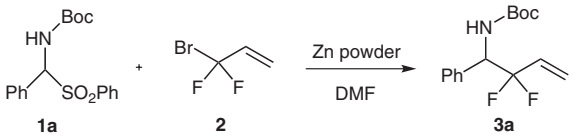
On the other hand, α-amidoalkyl phenyl sulfones, the precursors for the preparation of *N*-acylimines, are easily accessible and much less moisture-sensitive reagents than *N*-acylimines. Therefore, the use of α-amidoalkyl phenyl sulfones as substitutes for *N*-acyliminines has attracted much attention in organic synthesis recently.[6] Herein, we would like to describe the first preparation of *gem*-difluorohomoallyl amines directly from *gem*-difluoroallyl bromide and α-amido sulfones in the presence of activated zinc powder, in high yields and under mild conditions.

With α-amidoalkyl phenyl sulfone **1a** ($R^1$ = Ph; $R^2$ = Boc) as the model substrate and zinc powder as the promoter, the initial experiments were performed at room temperature (Table 1). Under these conditions, the effects of a variety of solvents were investigated first, and the results are shown in Table 1. When tetrahydrofuran, which had proved to be a suitable solvent for the *gem*-difluoroallylation of carbonyl compounds,[3] was used, the desired product **3a** was obtained in only 35% yield (Table 1, entry 1). The less polar solvent diethyl ether gave a much lower yield (Table 1, entry 5). Gratifyingly, when this reaction was run in *N*,*N*-dimethylformamide, the desired product **3a** could be obtained in almost quantitative yield (Table 1, entry 2). Other organic solvents such as ethanol and acetonitrile were also studied, but gave poor yields (Table 1,

**Table 1** Screening of Solvents[a]




**1a** **2** **3a**

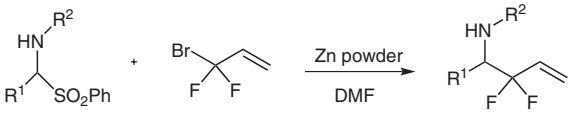
| Entry | Solvent | Yield[b] (%) |
|---|---|---|
| 1 | THF | 35 |
| 2 | DMF | 99 |
| 3 | EtOH | trace |
| 4 | MeCN | 18 |
| 5 | $Et_2O$ | 11 |
| 6 | $H_2O$ | trace |

[a] Reagents and conditions: **1a** (1 equiv), **2** (1.5 equiv), Zn (2.5 equiv), r.t., 3 h.
[b] Isolated yield after column chromatography.

entries 3 and 4). Additionally, the reaction was completely inhibited when performed in water (Table 1, entry 6).

With the optimal reaction conditions in hand, we tested the generality of this *gem*-difluoroallylation reaction with a series of α-amidoalkyl phenyl sulfones **1a–k** (Table 2). Generally, all the examined α-amidoalkyl phenyl sulfones **1** containing a phenyl $R^1$ group, with electron-donating groups (EDG) or electron-withdrawing groups (EWG) on the phenyl ring, gave the desired products in high yields (Table 2, entries 1–6). In addition, the heterocyclic 3-pyridyl sulfone **1g** also proved to be a suitable substrate for this transformation (Table 2, entry 7). Notably, the *gem*-difluoroallylation of the α-alkyl-α-amidoalkyl phenyl sulfone **1h** also provided a good yield (82%; Table 2, entry 8). Moreover, when the N-protecting group $R^2$ was changed to benzyloxycarbonyl, the reaction still proceeded smoothly to give the desired products, albeit with slightly lower yields (Table 2, entries 9–11). It is worth pointing out that this reaction can be scaled up to at least 2 mmol.

**Table 2** Scope of the Difluoroallylation of α-Amidoalkyl Phenyl Sulfones[a]




**1a–k** **2** **3a–k**

| Entry | $R^1$ | $R^2$ | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Ph | Boc | **3a** | 99 (97[c]) |
| 2 | 4-$BrC_6H_4$ | Boc | **3b** | 94 |
| 3 | Tol | Boc | **3c** | 87 |
| 4 | 2-$BrC_6H_4$ | Boc | **3d** | 85 |
| 5 | Tol | Boc | **3e** | 83 |
| 6 | 3-$O_2NC_6H_4$ | Boc | **3f** | 76 |
| 7 | 3-pyridyl | Boc | **3g** | 96 |
| 8 | Pr | Boc | **3h** | 82 |
| 9 | Ph | Cbz | **3i** | 94 |
| 10 | 4-$BrC_6H_4$ | Cbz | **3j** | 84 |
| 11 | Tol | Cbz | **3k** | 78 |

[a] Reagents and conditions: **1** (1 equiv), **2** (1.5 equiv), Zn (2.5 equiv), r.t., 3 h.
[b] Isolated yield after column chromatography.
[c] Yield on a 2 mmol scale.

Piperidine-derived heterocycles are ubiquitous substructures in many natural and synthetic products with important biological and pharmaceutical properties, and therefore many efforts have been directed towards the synthesis of these compounds.[7] Hence, as a demonstration of the utility of this *gem*-difluoroallylation reaction of α-amido sulfones and the accompanying products, **3a** was converted into **5**,[8] a fluorous counterpart of piperidine-derived heterocycles, in two steps involving a ring-closing-metathesis reaction;[9] **5** was obtained in moderate yield (Scheme 1).

In conclusion, a simple, mild, and efficient synthesis of α,α-difluorohomoallylic amines was achieved in good to high yields by the *gem*-difluoroallylation of α-amido sulfones mediated by zinc powder under mild reaction conditions. This method could be applied to the synthesis of natural-like products containing the difluoromethylene group. Efforts in this field are currently underway in our laboratory and will be reported in due course.

Zinc powder was purchased from Bodi Chemical Company (Tianjing) and activated by washing with dilute aqueous HCl solution. α-Amido sulfones were prepared according to known procedures.[6] DMF was purchased from Sinopharm Chemical Reagent Co. Ltd (Shanghai) and dried by distilling over $CaH_2$. Melting points were determined on a SGW X-4 apparatus and were uncorrected. $^1H$, $^{13}C$ and $^{19}F$ NMR were recorded on Varian EM-360A or Bruker DPX-300 instruments. TMS was used as the internal standard for $^1H$ and $^{13}C$ NMR. $CFCl_3$ was used as the external standard for $^{19}F$ NMR. ESI-MS was carried out on an Agilent LC/MSD and HRMS (ESI) was carried out on a Bruker ApeXIII 7.0 TESLA FTMS. IR spectra were determined on a Perkin-Elmer 983G instrument. Elemental analyses were carried out by the analytical center of Shanghai Institute of Organic Chemistry.

### *gem*-Difluoroallylation of α-Amido Sulfones; General Procedure

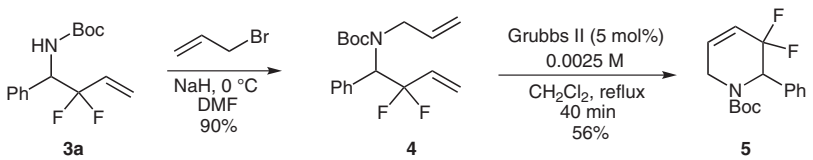
Prop-1-ene **2** (62.8 mg, 0.3 mmol) was added to a suspension of Zn dust (32 mg, 0.5 mmol) in anhyd DMF (2 mL) at r.t. After the mixture had stirred for 1 h, the appropriate α-amido sulfone **1** (0.2 mmol) in anhyd DMF (1 mL) was added dropwise. Stirring was continued for 2 h and then the mixture was quenched by the addition of sat. aq $NH_4Cl$ (0.8 mL) and extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to furnish the crude product, which was purified by column chromatography (silica gel, PE–EtOAc); this afforded pure products **3a–k**.

### Compound 3a

White solid; mp 77–79 °C.

IR (film): 3348, 3037, 2981, 1685, 1530, 1500, 1369, 704 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H), 5.89–5.62 (m, 2 H), 5.46–5.43 (d, *J* = 10.5 Hz, 1 H), 5.31–5.28 (m, 1 H), 5.09–4.98 (m, 1 H), 1.42 (s, 9 H).




**3a** **4** **5**

**Scheme 1**

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 154.9, 135.5, 130.7 (t, *J* = 26 Hz), 128.5 (2 C), 128.4, 128.3 (2 C), 121.2 (t, *J* = 9 Hz), 121.0 (q, *J* = 244 Hz), 80.3, 58.8 (t, *J* = 27 Hz), 28.3 (3 C).

$^{19}$F NMR (282 MHz, $CDCl_3$): δ = –106.87 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 20 Hz), –108.83 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 20 Hz).

ESI-MS: *m*/*z* = 306 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{19}F_2NO_2$: C, 63.59; H, 6.76; N, 4.94. Found: C, 63.50; H, 6.76; N, 5.02.

**Compound 3b**
White solid; mp 125–126 °C.

IR (film): 3344, 3030, 2980, 1710, 1688, 1526, 1368, 886, 801 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.48 (d, *J* = 8.4 Hz, 2 H), 7.23–7.20 (d, *J* = 8.4 Hz, 2 H), 5.90–5.65 (m, 2 H), 5.51–5.47 (d, *J* = 10.5 Hz, 1 H), 5.27 (br, 1 H), 5.03–4.99 (m, 1 H), 1.43 (s, 9 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 153.7, 133.4, 130.6 (2 C), 129.3, 128.9 (2 C), 121.5, 120.6 (t, *J* = 8 Hz), 118.0 (q, *J* = 244 Hz), 79.5, 57.3 (t, *J* = 27 Hz), 27.2 (3 C).

$^{19}$F NMR (282 MHz, $CDCl_3$): δ = –106.61 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12.6 Hz), –108.92 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12.6 Hz).

ESI-MS: *m*/*z* = 386 $[M + Na + 2]^+$, 384 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{18}BrF_2NO_2$: C, 49.74; H, 5.01; N, 3.87. Found: C, 49.85; H, 5.00; N, 3.73.

**Compound 3c**
White solid; mp 103–104 °C.

IR (film): 3343, 3005, 2982, 1688, 1515, 1369, 889, 807 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.22 (d, *J* = 10.2 Hz, 2 H), 6.89–6.85 (d, *J* = 10.2 Hz, 2 H), 5.89–5.62 (m, 2 H), 5.47–5.43 (d, *J* = 10.5 Hz, 1 H), 5.22 (br, 1 H), 5.05–4.96 (m, 1 H), 3.80 (s, 3 H), 1.42 (s, 9 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 158.5, 153.9, 129.7 (t, *J* = 28 Hz), 128.3 (2 C), 126.4, 120.0 (t, *J* = 9 Hz), 19.6 (q, *J* = 244 Hz), 112.8 (2 C), 79.2, 57.1 (t, *J* = 27 Hz), 54.2, 27.2 (3 C).

$^{19}$F NMR (282 MHz, $CDCl_3$): δ = –107.10 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12 Hz), –108.85 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12 Hz).

ESI-MS: *m*/*z* = 336 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{21}F_2NO_3$: C, 61.33; H, 6.76; N, 4.47. Found: C, 61.38; H, 6.75; N, 5.51.

**Compound 3d**
White solid; mp 75 °C.

IR (film): 3459, 3267, 2978, 2927, 1707, 1498, 1367, 753 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.56 (d, *J* = 7.8 Hz, 1 H), 7.36–7.30 (m, 2 H), 7.22–7.16 (m, 1 H), 5.99–5.62 (m, 3 H), 5.48–5.38 (m, 2 H), 1.43 (s, 9 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 154.7, 133.1, 130.3 (t, *J* = 26 Hz), 129.8 (2 C), 129.0, 127.7 (2 C), 127.4 (q, *J* = 244 Hz), 121.5 (t, *J* = 9 Hz), 80.5, 57.2 (t, *J* = 25 Hz), 28.3 (3 C).

$^{19}$F NMR (282 MHz, $CDCl_3$): δ = –107.36 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12 Hz), –108.27 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12 Hz).

ESI-MS: *m*/*z* = 386 $[M + Na + 2]^+$, 384 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{18}BrF_2NO_2$: C, 49.74; H, 5.01; N, 3.87. Found: C, 49.85; H, 5.06; N, 3.82.

**Compound 3e**
White solid; mp 95–97 °C.

IR (film): 3348, 3037, 2979, 2928, 1719, 1531, 1368, 889, 798 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.14 (dd, *J* = 7.8 Hz, 4 H), 5.86–5.63 (m, 2 H), 5.47–5.43 (d, *J* = 10.8 Hz, 1 H), 5.29–5.25 (m, 1 H), 5.08–4.94 (m, 1 H), 2.35 (s, 3 H), 1.42 (s, 9 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 153.8, 137.2, 131.4, 129.7 (t, *J* = 26 Hz), 128.1 (2 C), 127.1 (2 C), 120.3 (t, *J* = 9 Hz), 119.3 (q, *J* = 244 Hz), 79.2, 57.4 (t, *J* = 26 Hz), 28.3 (3 C), 20.1.

$^{19}$F NMR (282 MHz, $CDCl_3$): δ = –106.95 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12 Hz), –108.89 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12 Hz).

ESI-MS: *m*/*z* = 320 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{21}F_2NO_2$: C, 64.63; H, 7.12; N, 4.71. Found: C, 64.69; H, 7.18; N, 4.66.

**Compound 3f**
White solid; mp 89–91 °C.

IR (film): 3331, 3078, 2980, 1720, 1537, 1354, 871, 708 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.24–8.20 (m, 2 H), 7.71–7.68 (d, *J* = 10.8 Hz, 1 H), 7.59–7.53 (m, 1 H), 5.96–5.69 (m, 2 H), 5.58–5.54 (d, *J* = 10.5 Hz, 1 H), 5.42–5.39 (d, *J* = 8.4 Hz, 1 H), 5.23–5.12 (m, 1 H), 1.43 (s, 9 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 154.6, 137.5, 133.0 (t, *J* = 26 Hz), 129.5 (2 C), 128.8, 128.6 (2 C), 122.4 (t, *J* = 9 Hz), 119.1 (q, *J* = 244 Hz), 80.2, 59.0 (t, *J* = 27 Hz), 28.5 (3 C).

$^{19}$F NMR (282 MHz, $CDCl_3$): δ = –105.19 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 15 Hz), –109.53 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 15 Hz).

ESI-MS: *m*/*z* = 351 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{18}F_2N_2O_4$: C, 54.87; H, 5.53; N, 8.53. Found: C, 54.92; H, 5.54; N, 8.46.

**Compound 3g**
Colorless oil.

IR (film): 3345, 2964, 2933, 1709, 1507, 1174, 992 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 5.96–5.83 (m, 1 H), 5.70–5.64 (m, 1 H), 5.49–5.45 (d, *J* = 10.2 Hz, 1 H), 4.51–4.47 (d, *J* = 10.2 Hz, 1 H), 3.99–3.90 (m, 1 H), 1.42–1.20 (m, 13 H), 0.94–0.89 (t, *J* = 6.9 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 154.5, 129.9 (t, *J* = 26 Hz), 119.6 (t, *J* = 9 Hz), 120.6 (q, *J* = 244 Hz), 78.7, 58.8 (t, *J* = 25 Hz), 29.3, 27.2 (3 C), 17.7, 12.7.

$^{19}$F NMR (282 MHz, $CDCl_3$): δ = –108.17 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 10 Hz), –111.66 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 15 Hz).

ESI-MS: *m*/*z* = 272 $[M + Na]^+$.

Anal. Calcd for $C_{12}H_{21}F_2NO_2$: C, 57.81; H, 8.49; N, 5.61. Found: C, 57.92; H, 8.56; N, 5.55.

**Compound 3h**
Colorless oil.

IR (film): 3345, 2964, 2933, 1709, 1507, 1174, 992 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 5.96–5.83 (m, 1 H), 5.70–5.64 (m, 1 H), 5.49–5.45 (d, *J* = 10.2 Hz, 1 H), 4.51–4.47 (d, *J* = 10.2 Hz, 1 H), 3.99–3.90 (m, 1 H), 1.42–1.20 (m, 13 H), 0.94–0.89 (t, *J* = 6.9 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 154.5, 129.9 (t, *J* = 26 Hz), 119.6 (t, *J* = 9 Hz), 120.6 (q, *J* = 244 Hz), 78.7, 58.8 (t, *J* = 25 Hz), 29.3, 27.2 (3 C), 17.7, 12.7.

$^{19}$F NMR (282 MHz, $CDCl_3$): δ = –108.17 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 10 Hz), –111.66 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 15 Hz).

ESI-MS: *m*/*z* = 272 $[M + Na]^+$.

Anal. Calcd for $C_{12}H_{21}F_2NO_2$: C, 57.81; H, 8.49; N, 5.61. Found: C, 57.92; H, 8.56; N, 5.55.

**Compound 3i**
White solid; mp 99 °C.

IR (film): 3330, 3030, 2963, 1737, 1690, 1534, 1374, 1217, 703 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.32 (s, 5 H), 7.20–7.13 (m, 5 H), 5.83–5.57 (m, 3 H), 5.45–5.41 (d, *J* = 10.8 Hz, 1 H), 5.14–5.05 (m, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 155.7, 136.0, 135.1, 130.5 (t, *J* = 26 Hz), 129.0 (4 C), 128.6 (2 C), 128.5, 128.3 (3 C), 121.6 (t, *J* = 9 Hz), 120.9 (q, *J* = 244 Hz), 67.4, 59.4 (t, *J* = 27 Hz).

$^{19}F$ NMR (282 MHz, $CDCl_3$): δ = –106.17 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12 Hz), –107.24 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12 Hz).

ESI-MS: *m*/*z* = 340 $[M + Na]^+$.

Anal. Calcd for $C_{18}H_{17}F_2NO_2$: C, 68.13; H, 5.40; N, 4.41. Found: C, 68.15; H, 5.46; N, 4.32.

**Compound 3j**
White solid; mp 107–108 °C.

IR (film): 3318, 3037, 2961, 1716, 1539, 1491, 1259, 798, 697 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.51–7.47 (d, *J* = 8.1 Hz, 2 H), 7.35 (s, 5 H), 7.22–7.19 (d, *J* = 8.1 Hz, 2 H), 5.88–5.64 (m, 2 H), 5.56–5.53 (m, 1 H), 5.50–5.46 (d, *J* = 10.8 Hz, 1 H), 5.15–5.02 (m, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 154.6, 134.7, 133.0, 130.7 (3 C), 129.0 (t, *J* = 26 Hz), 128.9 (2 C), 127.5 (2 C), 127.3, 127.2, 121.8, 120.9 (t, *J* = 9 Hz), 119.5 (q, *J* = 244 Hz), 66.4, 57.9 (t, *J* = 27 Hz).

$^{19}F$ NMR (282 MHz, $CDCl_3$): δ = –106.40 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12 Hz), –107.85 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12 Hz).

ESI-MS: *m*/*z* = 420 $[M + Na + 2]^+$, 418 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{16}BrF_2NO_2Na$: 418.0231; found: 418.0225.

Anal. Calcd for $C_{18}H_{16}BrF_2NO_2$: C, 54.56; H, 4.07; N, 3.54. Found: C, 54.64; H, 4.16; N, 3.51.

**Compound 3k**
White solid; mp 102–104 °C.

IR (film): 3326, 3033, 2956, 1717, 1534, 1515, 1235, 796, 698 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.33 (s, 5 H), 7.22–7.13 (m, 4 H), 5.84–5.56 (m, 3 H), 5.44–5.40 (d, *J* = 10.8 Hz, 1 H), 5.13–5.03 (m, 3 H), 2.33 (m, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 154.6, 137.4, 134.9, 131.0, 129.5 (t, *J* = 26 Hz), 128.3 (4 C), 127.5, 127.2, 127.1, 126.9, 126.7, 120.4 (t, *J* = 9 Hz), 119.6 (q, *J* = 244 Hz), 66.3, 58.1 (t, *J* = 27 Hz), 20.1.

$^{19}F$ NMR (282 MHz, $CDCl_3$): δ = –107.17 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12 Hz), –108.24 (dd, $J_{F,F}$ = 260 Hz, $J_{F,H}$ = 12 Hz).

ESI-MS: *m*/*z* = 354 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{19}F_2NO_2$: C, 68.87; H, 5.78; N, 4.23. Found: C, 68.82; H, 5.97; N, 4.22.

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## References

(1) (a) Groß, U.; Rüdiger, S. In *Houben-Weyl*, Vol. E10a; Baasner, B.; Hagemann, H.; Tatlow, J. C., Eds.; Thieme: Stuttgart, **1999**, 18. (b) Hiyama, T. *Organofluorine Compounds: Chemistry and Properties*; Springer: Berlin, **2000**. (c) Welsch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, **1991**. (d) *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E.; Smart, B. E.; Tatlow, J. C., Eds.; Plenum Press: New York, **1994**.

(2) (a) Blackburn, G. M.; England, D. A.; Kolkmann, F. *J. Chem. Soc., Chem. Commun.* **1981**, 930. (b) Blackburn, G. M.; Kent, D. E.; Kolkmann, F. *J. Chem. Soc., Chem. Commun.* **1981**, 1188. (c) Blackburn, G. M.; Ivory, J. A.; Williamson, M. P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2573. (d) Chambers, R. D.; Jaouhari, R.; O'Hagan, D. *Tetrahedron* **1989**, *45*, 5101. (e) Burke, T. R. Jr.; Smyth, M. S.; Otaka, A.; Nomizu, M.; Roller, P. P.; Wolf, G.; Care, R.; Shoelson, S. E. *Biochemistry* **1994**, *33*, 6490. (f) Xu, X.-H.; Trunkfield, A. E.; Bugg, T. D. H.; Qing, F. L. *Org. Biomol. Chem.* **2008**, *6*, 157.

(3) For reviews, see: (a) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619. (b) Huang, X.-H.; Shi, G.-Q. *Youji Huaxue* **1997**, *17*, 394. (c) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921. For recent examples, see: (d) Ramachandran, P. V.; Chatterjee, A. *Org. Lett.* **2008**, *10*, 1195. (e) Wang, R.-W.; Qiu, X.-L.; Bols, M.; Ortega-Caballero, F.; Qing, F.-L. *J. Med. Chem.* **2006**, *49*, 2989. (f) Niida, A.; Tomita, K.; Mizumoto, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K.; Fujii, N. *Org. Lett.* **2006**, *8*, 613. (g) Wang, R.-W.; Qing, F.-L. *Org. Lett.* **2005**, *7*, 2189. (h) Wu, Y.-Y.; Zhang, X.-G.; Meng, W.-D.; Qing, F.-L. *Org. Lett.* **2004**, *6*, 3941. (i) Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634. (j) Kirihara, M.; Kawasaki, M.; Katsumata, H.; Kakuda, H.; Shiro, M.; Kawabata, S. *Tetrahedron: Asymmetry* **2002**, *13*, 2283. (k) Kirihara, M.; Takuwa, T.; Takizawa, S.; Momose, T.; Nemoto, H. *Tetrahedron* **2000**, *56*, 8275. (l) Jeong, I. H.; Kim, M. S.; Kim, B. T. *Synth. Commun.* **1999**, *29*, 235. (m) Qing, F.; Wan, D. *Tetrahedron* **1998**, *54*, 14189. (n) Kirihara, M.; Takuwa, T.; Takizawa, S.; Momose, T. *Tetrahedron Lett.* **1997**, *38*, 2853. (o) Arnone, A.; Bravo, P.; Viani, F.; Zanda, M.; Cavicchio, G.; Crucianelli, M. *J. Fluorine Chem.* **1996**, *76*, 169. (p) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *J. Org. Chem.* **1996**, *61*, 166. (q) Morikawa, T.; Uejima, M.; Kobayashi, Y. *Chem. Lett.* **1988**, 1407. (r) Hiyama, T.; Obayashi, M.; Sawahata, M. *Tetrahedron Lett.* **1983**, *24*, 4113. (s) Seyferth, D.; Simon, R. M.; Sepelak, D. J.; Klein, H. A. *J. Am. Chem. Soc.* **1983**, *105*, 4634.

(4) Yang, Z.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 1037.

(5) Ohba, T.; Ikeda, E.; Takei, H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1875.

(6) For a recent review, see: (a) Petrini, M. *Chem. Rev.* **2005**, *105*, 3949. For recent examples, see: (b) Lombardo, M.; Mosconi, E.; Pasi, F.; Petrini, M.; Trombini, C. *J. Org. Chem.* **2007**, *72*, 1834. (c) Mizuta, S.; Shibata, N.; Goto, Y.; Furukawa, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* **2007**, *129*, 6394. (d) Song, J.; Shih, H.-W.; Deng, L. *Org. Lett.* **2007**, *9*, 603. (e) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089. (f) Marques, M. M. B. *Angew. Chem. Int. Ed.* **2006**, *45*, 348. (g) Fini, F.; Bernardi, L.; Herrera, R. P.; Pettersen, D.; Ricci, A.; Sgarzania, V. *Adv. Synth. Catal.* **2006**, *348*, 2043. (h) Herrera, R. P.; Bernardi, L.; Fini, F.; Pettersen, D.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 9869.

(7) For reviews, see: (a) Enders, D.; Thiebes, T. *Pure Appl. Chem.* **2001**, *73*, 573. (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. For examples, see: (c) Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2000**, *11*, 4639. (d) De Matteis, V.; van Delft, F. L.; Tiebes, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2006**, 1166. (e) Petukhov, P. A.; Zhang, J.; Wang, C. Z.; Ye, Y. P.; Johnson, K. M.; Kozikowski, A. P. *J. Med. Chem.* **2004**, *47*, 3009. (f) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431; and references cited therein.

(8) Characterization data for **5**: colorless crystals; mp 96–97 °C. IR (film): 2925, 2855, 1707, 1456, 1408, 1393, 1168, 1092, 698 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 6.26 (m, 1 H), 6.09 (m, 1 H), 5.74 (m, 1 H), 4.48–4.38 (m, 1 H), 3.56–3.47 (m, 13 H), 1.49 (s, 9 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 154.1, 134.9, 133.6, 128.4, 128.2, 128.0, 122.1 (dd, $J$ = 17.3, 25.1 Hz), 115.9 (t, $J$ = 9 Hz), 120.6 (t, $J$ = 177.5 Hz), 81.2, 59.1, 40.6, 27.2 (3 C). $^{19}F$ NMR (282 MHz, $CDCl_3$): δ = –79.56 (d, $J_{F,F}$ = 279.2 Hz), –103.24 (d, $J_{F,F}$ = 297.2 Hz). MS (ESI): $m/z$ = 318 $[M + Na]^+$. HRMS (EI): $m/z$ calcd for $C_{11}H_{10}NF_2$ $[M^+–Boc]$: 194.0781; found: 194.0777.

(9) For recent examples of the application of RCM in olefins bearing fluorine substituents, see: (a) Fustero, S.; Fernández, B.; Sanz-Cervera, J. F.; Mateu, N.; Mosulén, S.; Carbajo, R. J.; Pineda-Lucena, A.; de Arellano, C. R. *J. Org. Chem.* **2007**, *72*, 8716. (b) Miles, J. A. L.; Mitchell, L.; Percy, J. M.; Singh, K.; Uneyama, E. *J. Org. Chem.* **2007**, *72*, 1575. (c) Yang, Y.-Y.; Xu, J.; You, Z.-W.; Xu, X.-H.; Qiu, X.-L.; Qing, F.-L. *Org. Lett.* **2007**, *9*, 5437. (d) You, Z.-W.; Wu, Y.-Y.; Qing, F. L. *Synthesis* **2006**, 2535.