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Coupling of *N*-acyliminium chlorides with *gem*-difluorinated organozinc reagents

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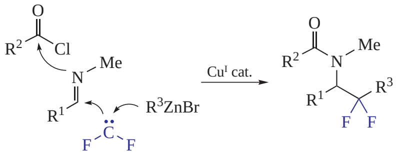
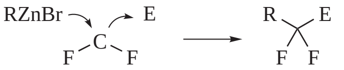
CuCl-catalyzed coupling of *N*-acyliminium chlorides (generated from imines and acyl chlorides) with *gem*-difluorinated organozincs affords *N*-(2,2-difluoroalkyl)carboxamides in moderate yield.



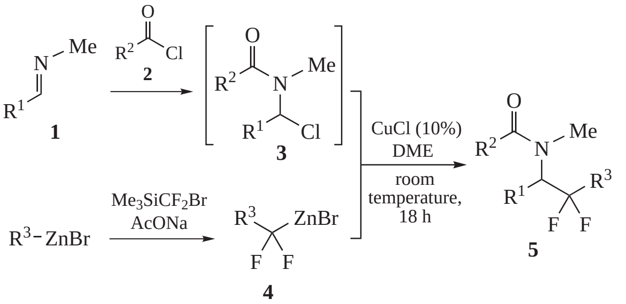
Organofluorine compounds play important role in medicinal chemistry.[1] In this regard, methods for assembling of fluorinated molecules from several building blocks would be very useful, since this would provide straightforward access to diverse structures.[2]

Recently we introduced a concept for the synthesis of *gem*-difluorinated compounds based on coupling of organozinc reagents, difluorocarbene, and electrophiles[3,4] (Scheme 1). As electrophilic component, heteroatom electrophiles (halogens,[3] nitrosonium cation,[4(a)] disulfides[4(b)]) and carbon electrophiles (allyl bromides,[4(c)] 1-bromoalkynes,[4(d)] nitrostyrenes[4(e)]) were employed.



Scheme 1

Herein, we report that *N*-acyliminium chlorides **3**, generated *in situ* from imines **1** and acyl chlorides **2**, can serve as electrophiles in the coupling with *gem*-difluorinated organozinc reagents (Scheme 2). *N*-Acyliminium chlorides constitute a class of reactive electrophiles, which have found widespread applications in reactions with π-electrophiles,[5] acetylenides,[6] and transition metal catalyzed processes.[7] However, reactions with fluorinated organometallics have not been described.



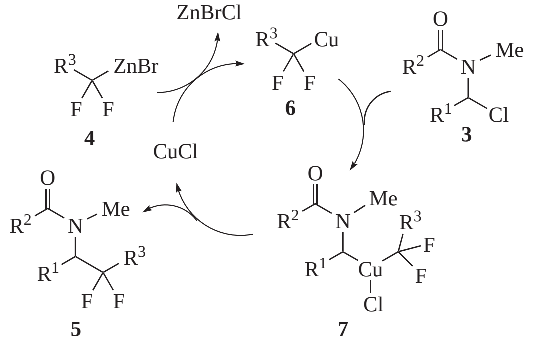
	R¹	R²	R³	Isolated yield (%)
5a	Ph	Bu^t	PhCH$_2$	55
5b	Ph	Pr^i	PhCH$_2$	30
5c	Ph	MeO	PhCH$_2$	53
5d	Ph	Pr^i	Pr^i	37
5e	4-MeOC$_6$H$_4$	MeO	PhCH$_2$	54

Scheme 2

N-Acyliminium chlorides **3** were generated simply by mixing equimolar amounts of imines **1** and acyl chlorides **2** and were treated with *gem*-difluorinated organozinc reagents (RCF$_2$ZnBr, **4**), which were prepared separately from organozinc bromides[8] and (bromodifluoromethyl)trimethylsilane[3(a),9,10] (see Scheme 2). In the absence of catalyst, no product was formed while organozinc reagent **4** underwent decomposition after 18 h at room temperature. At the same time, addition of 10 mol% of copper(I) chloride provided formation of coupling products **5**.[†]

Concerning the mechanism, we believe that the reaction starts from the zinc-copper transmetallation to generate organocopper species **6** (Scheme 3). Subsequent oxidative addition upon interaction of **6** with *N*-acyliminium chloride **3** can lead to copper(III) intermediate **7**, which rapidly undergoes reductive elimination affording product **5** along with regeneration of copper catalyst.

In summary, a coupling of imines, acyl chlorides, and *gem*-difluorinated organozinc reagents has been developed. Though



Scheme 3

[†] *Coupling of* N*-acyliminium chlorides with reagents* **4**. A mixture of acid chloride **2** (1.1 mmol), imine **1** (1.0 mmol) and CuCl (10 mg, 0.1 mmol) in DME (1 ml) was stirred at room temperature for 10 min and then immersed in an ice–water bath. A cold (about 0 °C) solution of RCF$_2$ZnBr **4** was added dropwise. After stirring at 0 °C for 30 min, the cooling bath was removed, and a homogeneous solution was stirred for 18 h. For the work-up, water (7 ml) was added, the mixture was extracted with methyl *tert*-butyl ether–hexane (1 : 1, 3×5 ml). The combined organic layers were filtered through Na$_2$SO$_4$, concentrated *in vacuo*, and the residue was purified by column chromatography.

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the reaction proceeds with moderate yield, it provides rapid assembly of valuable organofluorine compounds from three independently variable and readily available components.

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Online Supplementary Materials

Supplementary data associated with this article (experimental procedures, product characterization, NMR spectra) can be found in the online version at doi: 10.1016/j.mencom.2017.03.010.

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N-*(2,2-Difluoro-1,3-diphenylpropyl)*-N-*methylpivalamide* **5a**. Yield 190 mg (55%). Colorless crystals, mp 100–101 °C, R_f 0.32 (hexanes–EtOAc, 8 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (s, 9 H), 3.02 (s, 3 H), 3.08–3.39 (m, 2 H), 6.51 (t, 1H, J 15.6 Hz), 7.20–7.58 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.3, 33.2 (t, J 3.4 Hz), 39.4, 41.9 (t, J 24.3 Hz), 59.3 (dd, J 27.0, 22.4 Hz), 123.9 (t, J 250.1 Hz), 127.5, 128.2, 128.4, 128.8, 129.9 (t, J 2.3 Hz), 132.3 (dd, J 4.0, 1.7 Hz), 134.5, 178.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –102.1 (dm, 1F, J 250.1 Hz), –99.9 (dm, 1F, J 250.1 Hz). HRMS (ESI), m/z: 346.1971 $[M+H]^+$ (calc. for $C_{21}H_{26}F_2NO$, m/z: 346.1977).

For characteristics of products **5b**–**e**, see Online Supplementary Materials.