C–F Bond Activation

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Umpolung of Fluoroform by C–F Bond Activation: Direct Difluoromethylation of Lithium Enolates

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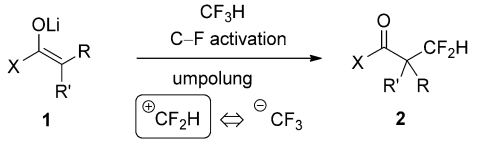
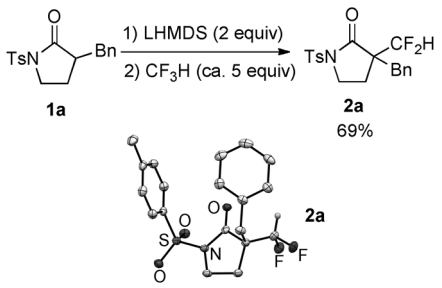
The synthesis of organofluorine compounds has flourished because of the wide scope of their applications in biological and material sciences in recent years.[1] Difluoromethyl fuctionalized compounds in particular are employed because of their significantly increased lipophilicity, membrane permeability, aqueous solubility, and metabolic stability, as exemplified by the anesthetic Desflurane, anticancer Gemcitabine, respiratory Roflumilast derivatives, antiulcer (−)-Pantoprazole, and antiviral difluoromethoxyquinolone Garenoxacin.[2] Generally, synthetic methods for the fluoromethylation reactions involve radical, electrophilic, or nucleophilic reactions.[1,3,4] In particular, the treatment of fluoroform with sodium or potassium alkoxide in DMF affords its trifluoromethyl adduct.[5] Fluoroform can thus be employed as the nucleophilic trifluoromethyl carbanion equivalent for non-enolizable carbonyl compounds. Herein we wish to report our polarity-inversion approach, namely the umpolung[6] of fluoroform by activation of an inert carbon–fluorine (C–F) bond to formally generate a difluoromethyl carbocation equivalent (Scheme 1).



Scheme 1. Umpolung of fluoroform with a lithium enolate.

C–F bond activation[7] has posed a challenge in transforming the inert C–F bond (490 kJ mol^{-1}; C–C bond: 350 kJ mol^{-1}; C–H bond: 420 kJ mol^{-1}). Actually, only limited types of reactions have thus far been reported for C–F bond activation in the transition metal catalyzed cross-coupling of C_{sp^2}-hybridized systems.[8,9] Amii and Uneyama have reviewed precedent reports on C–F bond activation including their own reductive C–F bond cleavage of trifluoromethyl ketones using a reducing metal.[10] In view of the environmental issues,[11] hydrodefluorination of perfluoroalkanes was recently developed by Douvris and Ozerov as an efficient strategy for chlorofluorocarbon (CFC) degradation through Si–F bond formation using silylium carborane catalysts and hydride sources.[12] Herein electrophilic difluoromethylation of lithium enolates with fluoroform by using a C–F bond activation is described. A direct C_{sp^2}–F bond activation and C–C bond formation sequence can be attained with lithium enolates, which take a central role in modern synthetic organic chemistry.[13] The difluoromethyl products are biologically and synthetically important, and therefore the introduction of the difluoromethyl group into organic compounds is of vital importance,[14] as shown for difluoromethyl ethers[2] or α-difluoromethyl α-amino acids.[15]

The direct and simple α-difluoromethylation was found to proceed with lithium enolates using fluoroform as the difluoromethylating reagent (Scheme 2). The α-difluoromethyl products were obtained with lithium enolates in particular, even in the absence of late-transition-metal complexes used to catalyze the Tamao–Kumada-type coupling of C_{sp^2}-aromatic and -vinylic fluorides.[8,9] Among the alkaline metal enolates (Li, Na, K) generated with the metal hexamethyldisilazide (MHMDS), only the lithium enolate (from LHMDS) gave the α-difluoromethyl product because of the strong Li–F interaction.[1] In contrast to LHMDS, lithium diisopropylamide (LDA) did not give the α-difluoromethyl product, presumably because of the less bulky and more coordinating secondary dialkylamine generated. The present synthetic method provides difluoromethyl-substituted all-carbon quaternary centers,[16] the congested structure of which was confirmed by the X-ray analysis of **2a** (Scheme 2).[17] The α-difluoromethyl product **2a** was thus obtained even at low temperature (−78 °C). The formation of difluorocyclopropane and the α-deuteriodifluoromethyl product was not observed from the generation of difluoromethylene (difluorocarbene)[18–20] in the presence of electron-rich olefins and upon quench with D_2O, respectively.



Scheme 2. Direct difluoromethylation of the lithium enolate with fluoroform. Bn = benzyl, Ts = 4-toluenesulfonyl.

The effect of the amount of the lithium amide base (LHMDS) on the difluoromethylation of the lithium enolate are shown in Table 1. An additional amount of LHMDS gave

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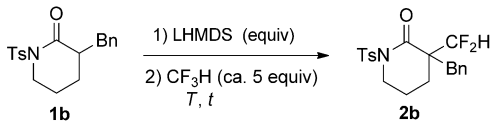
Table 1: The effects of the amount of the lithium amide.[a]



1b **2b**

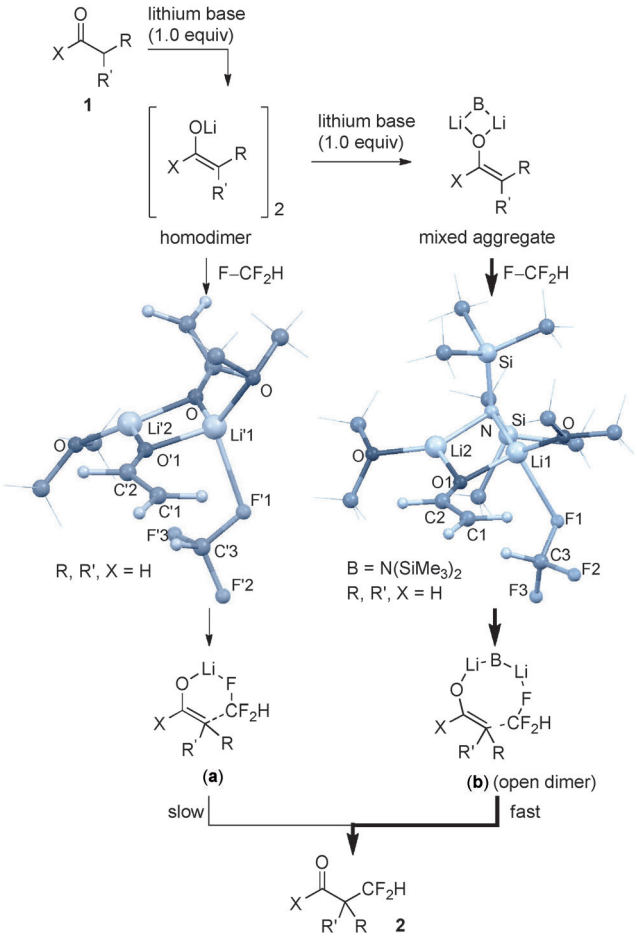
Entry	Equiv of base	*T* [°C]	*t* [h]	Yield [%][b]
1	1	−78	14	17
2	2	−78	14	45
3	3	−78	14	25
4	2	RT	6	64
5	3	RT	6	24

[a] The α-Benzyl-δ-lactam **1b** (0.1 mmol) was added to a solution of LHMDS at −78 °C under an argon atmosphere. The reaction mixture was then stirred at 0 °C for 30 min. CF_3H (ca. 5 equiv) was then added to the reaction mixture at −95 °C, warmed to the indicated temperature, and reacted for the specified time. [b] The yields were determined by ^{19}F NMR spectroscopy using BTF (benzotrifluoride) as an internal standard.

a higher yield by almost three times than obtained with only one equivalent of LHMDS (entries 1 versus 2). These results clearly show the critical dependence of the reaction rate on the amount of the base used. The lithium enolate with a second equivalent of LHMDS reacted with fluoroform to give **2b** in the highest (64%) yield at room temperature (entry 4). A further increase in the amount of LHMDS (up to 3 equiv) led to a decrease in the yield (entries 3 and 5).

Two equivalents of LHMDS could lead to a stable mixed aggregate (see below), which should be reactive for C–F activation but not for C–H deprotonation, thus affording the higher product yield relative to that obtained with one equivalent of LHMDS (Table 1, entries 1 versus 2). However, one more equivalent of free LHMDS (3 equiv) might deprotonate fluoroform and therefore give the lower yield of **2b** as actually observed (entries 3 and 5).

The possible reaction mechanisms can be viewed for the α difluoromethylation (Scheme 3). Lithium enolates could directly afford the α-difluoromethyl products by C–F bond activation through a Li–F interaction[21] upon addition of fluoroform, as pictured in the mixed aggregate and the open dimer of a lithium enolate with the lithium amide.[22,23] To obtain more information on the proposed reaction mechanism, DFT calculations on both complexes (homodimer and mixed aggregate) with fluoroform were performed at the wB97XD/6-31 + G(d) level of theory (Scheme 3). According to the predicted structures of the lithium enolates,[24] one solvent (Me_2O) molecule coordinates to each lithium atom. In the homodimer, one of the lithium ions (Li′1) interacts with the F′1 atom with distance of 2.281 Å, and the C′3–F′1 bond is slightly elongated (1.357 Å). Indeed, the characteristic Li–F interaction and possible C–C bond formation pathway were optimized (C′1···C′3 3.530 Å), but the acute C′1-C′3-F′1 angle of 86.20° implies a slow S_N2-type removal of the fluoride in the homodimer of lithium enolates.[24] In contrast, in the mixed aggregate,[24] the obtuse C1-C3-F1 angle of 105.94° suggests facile C–C bond formation via the putative open dimer (for DFT calculations, see the Supporting Information). Substantial interaction between Li1 and F1 (Li1···F1



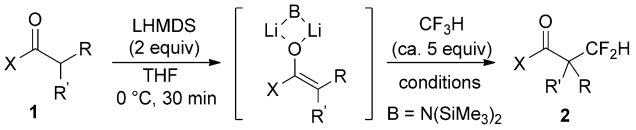
Scheme 3. Plausible mechanism of α-difluoromethylation.

2.280 Å), elongation of the F1–C3 bond (1.362 Å; F2-C3 1.338 Å, F3-C3 1.337 Å), the C1···C3 contact (3.510 Å), and the obtuse C1-C3-F1 angle indicate desirable geometries for the S_N2-type C–F activation. The F in HCF_3 could directly interact with the lithium cation, and the difluormethyl cation[25] could be formed only partially in HCF_3. Indeed, silyl enol ethers did not provide the captured difluoromethyl cation product under the reaction conditions.

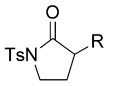
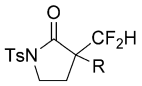
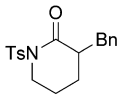
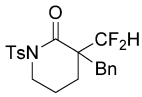
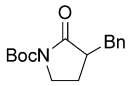
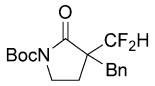
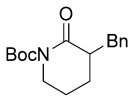
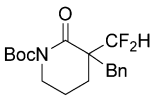
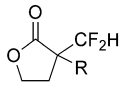
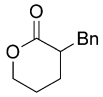
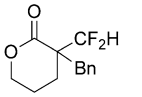
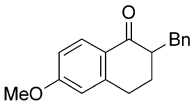
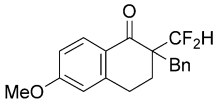
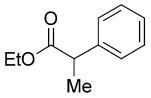
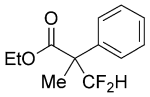
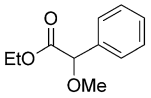
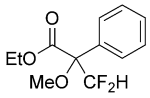
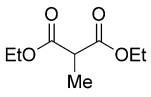
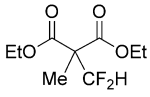
Both cyclic and acyclic substrates led to the α-difluoromethyl products **2** under the optimized reaction conditions (Table 2). Difluoromethylation of the lithium enolates of not only protected lactams **1a–c**,**e**,**f** with five- and six-membered rings but also the lactones **1g–i** and ketone **1j** was established to give the corresponding products (entries 1, 2, and 4–9). Unfortunately, the reaction of the α-nonsubstituted lactam **1d** did not provide any α-fluoromethyl(ene) product under the same reaction conditions as it proceeded with a greater than 99% substrate recovery (entry 3). In the case of acyclic substrates, the difluoromethylation also proceeded with the 2-phenylpropanate **1k** and α-methylmalonate (**1m**) to give the α-difluoromethyl products **2k** and **2m**, respectively, in yields of up to 80% upon isolation (82% yield as determined by NMR spectroscopy; entries 11 and 13). The difluoromethylated mandelate derivative (**2l**) was also obtained (entry 12).

The α-difluoromethylation reaction was used in the synthesis of the α-difluoromethyl analogue (**3**) of the anti-

Table 2: α-Difluoromethylation of various carbonyl compounds.



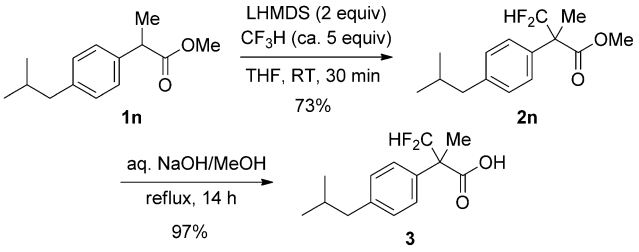
1 **2**

Entry	Substrate		Conditions	Product		Yield [%][a]
1		**1a** (R = Bn)	RT, 30 min		**2a**	69 (68[b])
2		**1c** (R = allyl)	RT, 2 h		**2c**	45
3		**1d** (R = H)	RT, 2 h		**2d**	0[c]
4		**1b**	RT, 6 h		**2b**	64
5		**1e**	0 °C, 2 d		**2e**	57
6		**1f**	0 °C, 2 d		**2f**	37
7		**1g** (R = Bn)	0 °C, 2 d		**2g**	47
8		**1h** (R = CO_2Et)	0 °C, 20 h		**2h**	47
9		**1i**	0 °C, 6 h		**2i**	33
10		**1j**	0 °C, 10 h		**2j**	36
11		**1k**	RT, 6 h		**2k**	78
12		**1l**	RT, 12 h		**2l**	35
13		**1m**	0 °C, 20 h		**2m**	82 (80[b])

[a] Yields were determined by ^{19}F NMR spectroscopy using BTF as an internal standard. [b] Yield of isolated product. [c] A greater than 99% substrate recovery. Boc = *tert*-butoxycarbonyl.

inflammatory and analgesic drug ibuprofen (Scheme 4).[26] Ibuprofen methyl ester was α-difluoromethylated with fluoroform in 73% yield upon isolation. It should be noted that the racemic ibuprofen analogue reserves the analgesic activity even with the non-epimerizable quaternary center.[22]

This report is the first on the direct α-difluoromethylation of lithium enolates for construction of the difluoromethyl-functionalized all-carbon quaternary centers using fluoroform as a simple difluoromethylating reagent. Lithium enolates lead to the α-difluoromethyl carbonyl compounds by C–F bond activation/C–C bond formation through the umpolung form of fluoroform.



1n **2n** **3**

Scheme 4. Synthesis of the α-difluoromethyl analogue of ibuprofen.

Experimental Section

General procedure of α-difluoromethylation of lithium enolate (Scheme 2): 3-Benzyl-1-tosylpyrrolidin-2-one (**1a**; 50 mg, 0.15 mmol, 1.0 equiv) in THF (0.3 mL) was added to a solution of lithium hexamethyldisilazide (LHMDS; 1.0 M in THF, 0.3 mL, 0.3 mmol, 2.0 equiv) at −78 °C under an argon atmosphere. The reaction mixture was then stirred at 0 °C for 30 min. CF_3H (ca. 5 equiv) was then added to the reaction mixture at −95 °C. After 30 min at room temperature, the reaction mixture was poured into a mixture of H_2O and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The yield (69%) was determined by ^{19}F NMR spectroscopy of the crude reaction mixture using BTF as an internal standard. The residue was purified by column chromatography on silica gel (5% ethyl acetate in *n*-hexane) to afford the difluoromethylated product in 68% yield.

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Communications

C–F Bond Activation

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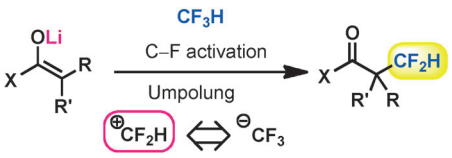
Umpolung of Fluoroform by C–F Bond Activation: Direct Difluoromethylation of Lithium Enolates



Double agent: The direct α-difluoromethylation of lithium enolates using an umpolung form of fluoroform as a difluoromethyl carbocation equivalent leads to an all-carbon quaternary center. Late transition metals are not necessary and the reaction involves activation of inert C–F bonds with subsequent C–C bond formation.