Fluorine Chemistry

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Activation of C–F Bonds in Preference to C–I Bonds: Difluoromethylation of Lithium Enolates with Trifluoromethyl Iodide**

Koichi Mikami, Yuichi Tomita, and Yoshimitsu Itoh*

Perfluorocarbons are among the most inert and, hence, chemically stable functionalities, because of the large dissociation energy of a carbon–fluorine (C–F) bond.[1–5] Therefore, C–F bond activation has attracted current interest, because of the "challenge" in cleaving the inert C–F bonds[6] and degradation of chlorofluorocarbons (CFC or freons), which cause ozone depletion and global warming.[7] However, only a limited number of examples have been reported so far on C–F bond cleavage even by "oxidative addition" of transition metals in an aromatic sp^2-C–F system.[8–11] Herein, we report a conceptually different approach to the conversion of sp^3-C–F to C–C bonds with lithium enolates, which are widely employed in modern science and technology,[12,13] via cleavage of a C–F bond in preference to the weaker C–I bond[1–5] of trifluoromethyl iodide (Figure 1). The difluoromethyl compounds thus obtained are biologically and synthetically important and, therefore, the introduction of the difluoromethyl functionality into organic compounds is of vital importance,[14,15] as typically shown in difluoromethyl analogues of α-amino acids.[16,17] This conceptually new C–F activation/C–C formation and the mechanism are the subjects of this Communication.

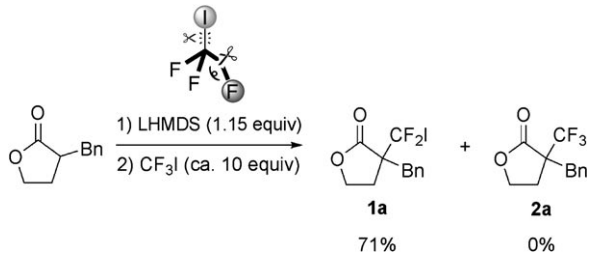

Figure 1. Conversion of a C–F bond to a C–C bond with lithium enolate.

During the course of our research on α-trifluoromethylation[18] of metal enolates catalyzed by late-transition-metal complexes, α-difluoromethyl products were obtained using lithium enolates (Figure 1), but without the need for any late-transition-metal catalyst such as nickel complexes.[8,9] The lithium enolate of 3-benzyldihydrofuran-2-one generated with lithium hexamethyldisilazide (LHMDS) gave the α-difluoromethyl product **1a** (72% ^{19}F NMR and 71% yield of isolated product). The present synthetic method provides difluoromethyl-attached all-carbon quaternary centers. Carbon centers bearing four carbon atom ligands pose a particular challenge because the creation of such all-carbon quaternary centers is rather difficult as a result of the steric repulsion between the four carbon ligands.[19]

To shed light on the reaction mechanism, the metal species in the enolate were scrutinized (Table S1 in the Supporting Information). Among the alkaline metal enolates (Na, K, Cs) employed, only the sodium enolate generated with sodium hexamethyldisilazide (NaHMDS), except for the lithium enolate (72% ^{19}F NMR yield), gave the α-difluoromethyl product **1a**, although in 12% yield. Potassium and "naked" enolates prepared from the trimethylsilyl enol ether and tetra-*n*-butylammonium fluoride (TBAF) did not give any α-difluoromethyl product at all. It is highly likely that this α-difluoromethylation takes place through the interaction of the Lewis acidic lithium center with fluoride in preference to iodide.[20] Indeed, the addition of [12]crown-4 to trap the Li cation from the Li enolate and to generate a "naked" enolate did not give the α-difluoromethyl product. In turn, the addition of the lithium salt of weakly coordinating bis(trifluoromethanesulfonyl)amide ($LiNTf_2$) to the potassium enolate led to the formation of the α-difluoromethyl product **1a**.[21]

In sharp contrast to LHMDS, lithium diisopropylamide (LDA) did not give the α-difluoromethyl product **1a** (Table 1, entries 7 and 8). Several lithium amides were then examined (Table 1). In the case of bis(silylamide)s such as LHMDS and lithium 1,1,3,3-tetramethyl-1,3-diphenyldisilazide (LTDDS), the amount of lithium amide did not affect the yields of **1a** (entries 1–4). The use of 1 and 2 equivalents of LHMDS was found to give approximately 70% yields constantly (entries 1 and 2). LTDDS gave relatively lower yield but in a similar range of 63–68% (entries 3 and 4). The use of dialkylamides such as lithium 2,2,6,6-tetramethylpiperidide (LTMP) gave comparably good yields, when 2 equiv of the lithium amide were used (entry 6 vs. entry 5). Amine-free lithium enolate prepared from the trimethylsilyl enol ether and *n*BuLi[22] was also investigated and found to give **1a** in 68% yield (Table 1,

[*] Prof. K. Mikami, Dr. Y. Tomita, Dr. Y. Itoh[+]
Department of Applied Chemistry, Tokyo Institute of Technology
Tokyo 152–8552 (Japan)
E-mail: mikami.k.ab@m.titech.ac.jp
[+] Present address: Department of Chemistry and Biotechnology
School of Engineering, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)

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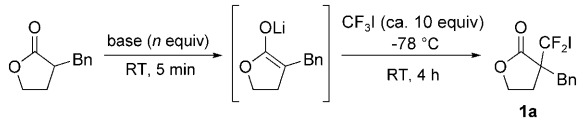
Table 1: Amine base effect.[a]



1a

Entry	*n*	Base	Yield [%]
1	1	LHMDS	72
2	2		68
3	1	LTDDS	68
4	2		63
5	1	LTMP	32
6	2		68
7	1	LDA	0
8	2		6[b]
9	1	*n*BuLi[c]	68

[a] To a solution of 3-benzyldihydrofuran-2-one in THF (0.5 mmol) was added the base at room temperature over 5 min and gaseous CF_3I at −78 °C. The reaction mixture was stirred for 4 h at room temperature and then quenched by acetic acid. The yield was determined by ^{19}F NMR spectroscopy using BTF (BTF = benzotrifluoride) as an internal standard. [b] 3% of trifluoromethyl product **2a** was observed. [c] Butyllithium was added to the reaction mixture of trimethylsilyl enol ether.

entry 9). The nature of the secondary amines derived from the lithium amide sources thus affects the reactivity of the lithium enolates in this α-difluoromethylation reaction.

The difference between the bis(silylamide) LHMDS and dialkylamide LDA was further examined (Table S2 in the Supporting Information). The corresponding secondary amines were added to the amine-free lithium enolate prepared from the trimethylsilyl enol ether and *n*BuLi (see Table 1, entry 9: 68% yield of **1a**). The addition of diisopropylamine significantly retarded the α-difluoromethylation; essentially, no difluoromethyl product was obtained. In contrast, hexamethyldisilazane did not affect the yield in this α-difluoromethylation at all (68% yield of **1a**).

Further investigation on the diisopropylamine-free lithium enolate, which was prepared by pumping off the amine from the enolate prepared with LDA, provided an increased yield of the α-difluoromethyl product **1a** of up to 53% (vs. 0%) These experiments clearly indicate that diisopropylamine inhibits the α-difluoromethylation reaction; relatively "less" bulky and more-coordinating secondary diisopropylamine, as compared with sterically more demanding but less-coordinating hexamethyldisilazane, could interact with lithium enolate to inhibit the difluoromethylation through Li–N and NH–π interactions (Figure 2). In fact, the NH–π interaction has been clarified by X-ray crystallographic analysis of the Li enolate of pinacolone crystallized in the presence of *N*,*N*,*N*′-trimethylethylenediamine (TriMEDA).[23]

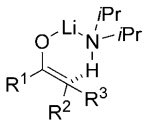


Figure 2. Li–N and NH–π interactions.

A plausible reaction mechanism for this α-difluoromethylation can be exemplified as shown in Figure 3, depending on the aggregation state of the lithium enolate.[24] Lithium bis(silylamide)s, even in 1 equivalent, afford the α-difluoromethyl product by a six-electron pericyclic process (a), by virtue of their sterically demanding and less-coordinating

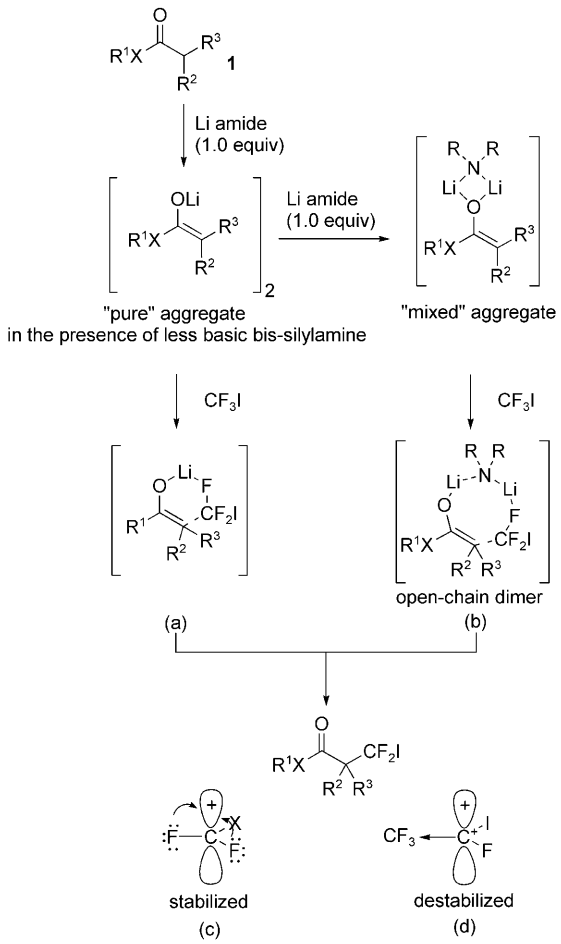
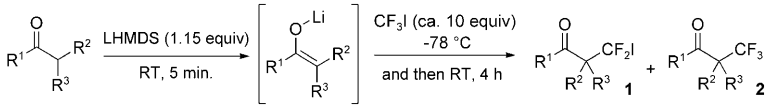


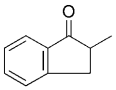
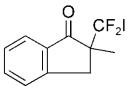
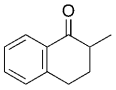
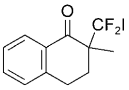
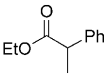
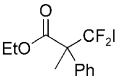
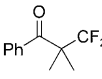
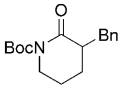
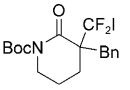
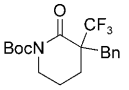
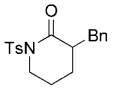
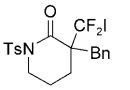
Figure 3. Plausible mechanism of the α-difluoromethylation.

nature.[25] Lithium amides in 2 equivalents, except for LDA,[26] lead to the formation of the α-difluoromethyl product, through mixed aggregates; upon addition of trifluoromethyl iodide, open-chain dimers with the lithium enolate (b) are involved to give the α-difluoromethyl product, wherein F in CF_3I interacts with the lithium cation. The positive charge as formulated in the "CF_2I^+" carbocation is even partially developed in CF_3I by the Li–F interaction and stabilized by the lone electron pairs of the α-F atoms (c)[15] to give the α-difluoromethyl products. In sharp contrast, pentafluoroethyl iodide gave the pentafluoroethylation product (**2a′**) (21% yield), and a defluoroethylation product was not observed at all; perfluoroalkyl iodide cannot provide even transiently the unstable carbocation (d), because of the strong electron-withdrawing effect of the trifluoromethyl (CF_3) group.[1–5]

Difluoromethylation of the Li enolates of several ketones, esters, and amides was then executed using LHMDS and CF_3I under the optimized reaction conditions (Table 2). Both acyclic and cyclic carbonyl substrates gave the α-difluoromethyl products **1** in good to moderate yields (entries 1–6). Boc-protected lactam was also investigated. It gave, in contrast, the α-trifluoromethyl product **2** (entries 7 and 8), even in the presence of [12]crown-4 (entry 8). Relatively electron-rich lactams lead to the α-trifluoromethyl prod-

Table 2: α-Difluoromethylation of carbonyl compounds.[a]



Entry	Substrate	Product				Yield [%][b] 1	2
1			**1a**			72 (71)	-
2			**1b**		**2b**	54	7
3			**1c**			52 (51)	–
4			**1d**			41 (43)	–
5			**1e**			56 (60)	–
6			**1f**			32	–
7			**1g**		**2g**	–	62 (63)
8[c]						–	51
9			**1h**			43 (41)	–

[a] A solution of the substrate in THF (0.5 mmol) was treated with LHMDS at room temperature (addition over 5 min) and gaseous CF_3I at −78 °C. The reaction mixture was stirred for 4 h at room temperature and then quenched by acetic acid. The yield was determined by ^{19}F NMR spectroscopy. [b] Yield of isolated product in brackets. [c] In the presence of [12]crown-4 (1 equiv).

ucts[27] without any radical initiator, presumably through single electron transfer from the lactam enolate.[28] Indeed, an electron-withdrawing tosyl-protected lactam led to the α-CF_2I product (entry 9). Five-membered lactams behaved similarly to the six-membered lactams.

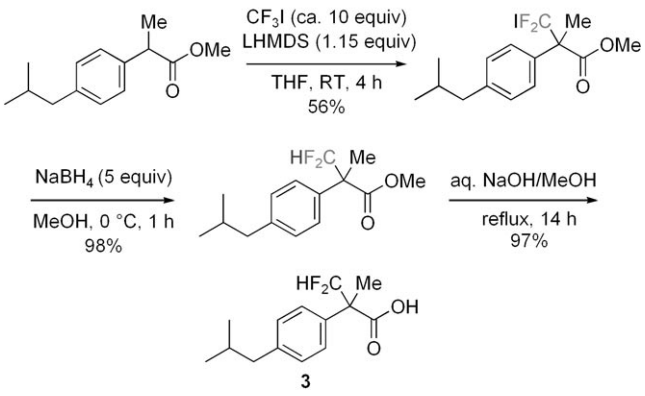


Figure 4. Synthesis of the α-difluoromethyl analogue of ibuprofen from ibuprofen through C–F bond activation, C–C bond formation, and hydrodeiodination in a total yield of 53%.

The α-difluoromethyl products can be used, through the iodide functionality, for further C–C bond forming reactions, such as radical and late-transition-metal-catalyzed alkylation, or geminal difluorocyclopropane cyclization and hydrodeiodination. In addition to the difluoromethyl analogues of α-amino acids,[16,17] the α-difluoromethylated analogue **3** of the anti-inflammatory and analgesic drug ibuprofen, which is known to exert its activity by inhibiting cyclooxygenase,[29] could be synthesized by hydrodeiodination under the optimized conditions (Figure 4). This racemic ibuprofen analogue with non-epimerizable quaternary center retains the analgesic activity in the 0.6% acetic acid writhing test,[30] which is intriguing on the basis of the results that (*S*)-ibuprofen is the active form both in vitro and in vivo and that in vivo 2-arylpropionyl-CoA epimerase converts (*R*)-ibuprofen into (*S*)-ibuprofen.[31]

This is an unprecedented route to construct difluoromethyl-attached all-carbon quaternary centers using lithium enolates and CF_3I, without any metal catalyst, through activation of a C–F bond in preference to the weaker C–I bond. The highlight of the present report is the synthesis of the α-difluoromethylated analogue of ibuprofen with retention of the analgesic activity even with non-epimerizable all-carbon quaternary centers.

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