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Facile Radical Trifluoromethylation of Lithium Enolates

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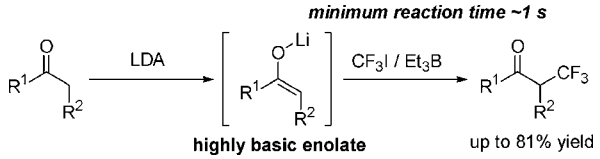
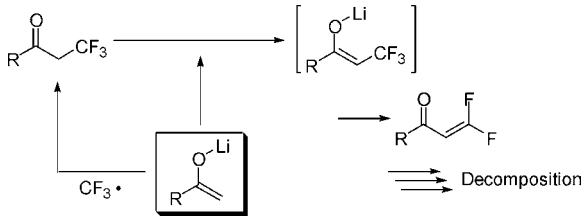
ABSTRACT



Highly basic lithium enolates are shown to be applicable to radical trifluoromethylation. The reaction is extremely fast, and the minimum reaction time is ~1 s.

The synthesis of fluorine-containing compounds continues to attract much attention because of their important applications in material and biological sciences. One of the most important organofluorine functionalities is CF_3, which exhibits specific physical and biological properties.[1] The α-CF_3 carbonyl compounds are some of the most useful synthetic intermediates for functionalization with CF_3. However, defluorination is problematic under basic conditions, in particular.[2] This difficulty could also be encountered in radical trifluoromethylation of metal enolates, which is, in principle, the most direct and efficient way to synthesize α-CF_3 carbonyl compounds. It has been widely recognized that highly basic conditions with lithium enolates[3] could not be applied to the trifluoromethylation (Scheme 1);[4] there are indeed only limited examples especially for ketones.[4−7] To avoid defluorination of α-CF_3 ketone products, less reactive enolate

Scheme 1



(1) (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119−6146. (b) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1−16. (c) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds*; Springer-Verlag: Berlin, Heidelberg, 2000. (d) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A., Ed.; Wiley: Chichester, 1999. (e) *Asymmetric Fluoroorganic Chemistry, Synthesis, Applications, and Future Directions*; Ramachandran, P. V., Ed.; American Chemical Society: Washington, DC, 2000. (f) *Organofluorine Chemistry*; Chambers, R. D., Ed.; Springer: Berlin, 1997. (g) Iseki, K. *Tetrahedron* **1998**, *54*, 13887−13914. (h) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996. (i) Smart, B. E., Ed. *Chem. Rev.* **1996**, *96*, 1555−1824 (Thematic issue of fluorine chemistry). (j) *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994. (k) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed; Ellis Horwood: Chichester, 1976.

(2) M−F interaction plays an important role in defluorination of α-CF_3 carbonyl compounds. (a) Schlosser, M. In *Organometallics in Synthesis−A Manual*; Schlosser, M., Ed.; John Wiley & Sons: Chichester, 1994; pp 1−166. (b) Murphy, E. F.; Murugavel, R.; Roesky, H. W. *Chem. Rev.* **1997**, *97*, 3425−3468. (c) Plenio, H. *Chem. Rev.* **1997**, *97*, 3363−3384.

(3) Seebach, D. *Angew. Chem,. Int. Ed. Engl.* **1988**, *27*, 1624−1654.

(4) Trifluoromethylation of lithium enolate of hindered imides (only exception for the use of lithium enolate): (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169−2170. (b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961−974. They have succeeded in trifluoromethylation by adopting Evans oxazolidinones with a bulky substitutent at the α position to suppress defluorination.

(5) Perfluoroalkylation of silyl and germyl enol ethers of esters and ketones: (a) Miura, K.; Taniguchi, M.; Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6391−6394. (b) Miura, K.; Takeyama, Y.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542−1553. Perfluoroalkylation of silyl enol ethers provided the products in good yields except for trifluoromethylation. Trifluoromethylation of ketone germyl enol ethers proceeds in good yield.

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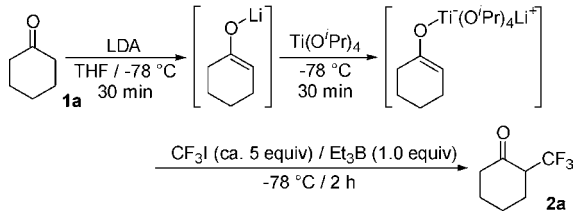
equivalents such as silyl or germyl enol ethers have been used for radical trifluoromethylation.[5] Therefore, it usually requires a long reaction time (more than 40 h in the case of ketone). During the course of our exploration of the radical trifluoromethylation of titanium ate enolates,[8] we discovered that lithium enolate could be, in fact, employed for radical trifluoromethylation and that the reaction proceeded extremely fast. We herein report the facile radical trifluoromethylation of lithium enolates.

Radical trifluoromethylation of the titanium ate enolate of cyclohexanone gave 81% yield of α-CF_3 cyclohexanone (Table 1, entry 1).[8] The yield greatly decreased without

Table 1. Radical Trifluoromethylation of Lithium Enolate



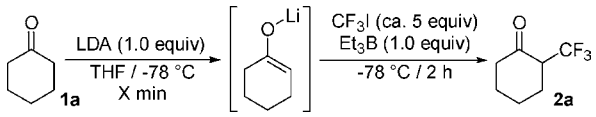
entry	LDS [equiv]	Ti(O^{i}Pr)$_4$ [equiv]	% yield[a]
1	1.6	1.6	81
2	1.6	0	41
3	1.0	0	63

[a] Determined by ^{19}F NMR using BTF as an internal standard.

Ti(O^{i}Pr)$_4$ (entry 2), presumably from decomposition of the α-CF_3 product due to an excess amount of LDA. Surprisingly, the use of just 1.0 equiv of LDA gave 63% yield of the α-CF_3 product. Therefore, we decided to further investigate the radical trifluoromethylation of lithium enolates.

First, preparation time of the lithium enolate was investigated (Table 2). In the case of titanium ate enolate, the preparation of the lithium enolate took only 30 min. It is speculated that the titanium ate enolate is in equilibrium with the parent ketone and ate complex (LDA/Ti(O^{i}Pr)$_4$). Therefore, even if the enolization by LDA was not completed in 30 min, enolization by titanium ate complex (LDA/Ti(O^{i}Pr)$_4$) would take place during the reaction.[8] There is no such equilibrium in the case of Li enolate. Therefore, 60 min of the preparation time was necessary to give sufficient yield of the α-CF_3 product (entry 3). However, longer preparation time was not necessary (entry 4). The reaction was carried out without radical initiator Et_3B (entry 2); no product was detected and a large amount of cyclohexanone was recovered, indicating that the reaction had proceeded by a radical mechanism.

Table 2. Preparation Time of the Lithium Enolate

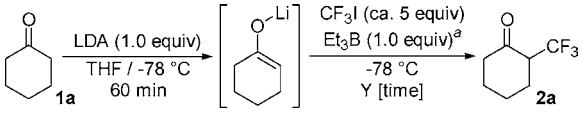


entry	X [min]	% yield[a]
1	30	63
2[b]	30	0
3	60	73
4	120	72

[a] Determined by ^{19}F NMR using BTF as an internal standard. [b] The reaction was carried out without Et_3B.

The radical reaction time was investigated using lithium enolate prepared over 60 min (Table 3). When the radical

Table 3. Investigation of the Trifluoromethylation Time



entry	reaction time Y	% yield[b]
1	13 h	62
2	2 h	73
3	1 h	80
4	1 min	83
5	~1 s	81

[a] Et_3B was added in 15 s. [b] Determined by ^{19}F NMR using BTF as an inernal standard.

trifluoromethylation was carried out for 1 h, the yield was 80% (entry 3). Longer reaction times decreased the yields; the α-CF_3 product was obtained in 62% yield when the reaction was quenched in 13 h (entry 1). This is probably due to the decomposition of the α-CF_3 product when exposed to basic conditions for prolonged periods of time. Shorter reaction times did not affect the yield. Finally, the ~1 s reaction gave the α-CF_3 product in 81% yield (entry 5).[9] Compared to the radical trifluoromethylation of titanium ate enolate, which took 2 h to give 81% yield, the reaction of lithium enolate is extremely fast.[10]

(6) Trifluoromethylation of enamines: (a) Cantacuzène, D.; Wakselman, C.; Dorme, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1365−1371. (b) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186−5191.

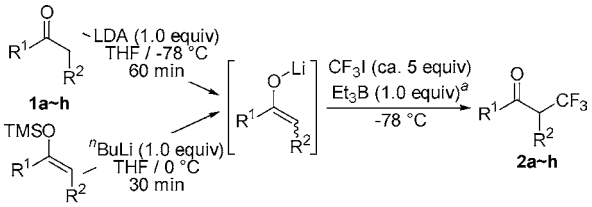
(7) There are some reports of trifluoromethylation using CF_3^+: (a) Yagupol'skii, L. M.; Kondratenko, N. V.; Timofeeva, G. N. *J. Org. Chem. U.S.S.R.* **1984**, *20*, 115−118. (b) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156−2164. (c) Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692−5699.

(8) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 649−651.

(9) For accuracy, Et_3B was added in 15 s and the reaction time was counted from the time when the addition of Et_3B was completed.

(10) **Typical Experimental Procedure.** To a solution of ^{i}Pr$_2$NH (28.0 μL, 0.20 mmol) in THF (2.0 mL) was added ^{n}BuLi (126.3 μL of 1.58 M solution in hexane, 0.20 mmol) at −78 °C. The reaction mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. To the solution was added cyclohexanone (20.7 μL, 0.2 mmol), and the mixture was stirred for 60 min at the temperature. Then, gaseous CF_3I (ca. 200 mg, ca. 1.0 mmol) was added with a cannula. Next, a syringe, which was filled with 0.12 mL of 5 M solution of acetic acid in THF, was set to the reaction vessel and kept untouching till quenching the reaction. Then Et_3B (0.2 mL of 1.0 M solution in hexane, 0.2 mmol) was added in 15 s to start the radical addition reaction. The reaction mixture was immediately quenched (in ~1 s) by acetic acid solution, which was set beforehand, at −78 °C. After warming to room temperature, BTF (10 μL, 0.082 mmol) was added as an internal standard. The yield was determined by ^{19}F NMR of the crude mixture (81%).

Table 4. Radical Trifluoromethylation of Various Carbonyl Compounds



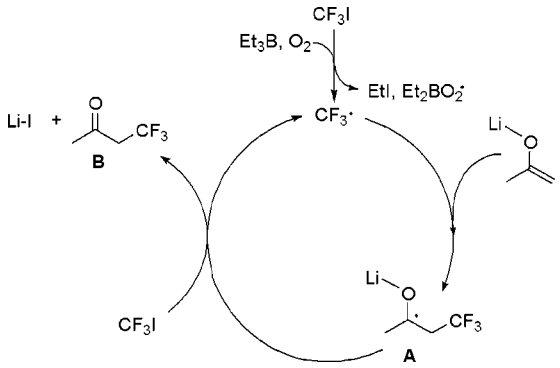
entry	substrate	product	reaction time	% yield[b]
1	1a	2a	~1 s	81
2	1a'	2a	2 h	77
3	1b	2b	~1 s	71 (67) [73:27]
4	1c	2c	~1 s	74 [57:43]
5[c]	1d	2d	2 h	58
6	1e	2e	~1 s	43 (40) [57:43]
7[d]	1f	2f	2 h	45 (45)
8	1g	2g	5 min	40
9	1h	2h	5 min	48

[a] Et_3B was added in 15 s. [b] Determined by ^{19}F NMR using BTF as an inernal standard. The values in ( ) refer to the yields of isolated products. The values in square brackets are the diastereomeric ratio. [c] Silyl enol ether of α-Me cyclohexanone consists of thermodynamic and kinetic enol ethers (87:13). [d] Silyl enol ether of α-Ph cyclohexanone contains only thermodynamic enol ether.

Several substrates were investigated (Table 4). In the case of 4-^{t}Bu (entry 3), 2-Me (entry 4), and 2-Ph (entry 6) substrates, the reactions proceeded with extremely fast reaction rates. By using LDA for the formation of lithium enolate, only kinetic enolate could be formed. However, thermodynamic lithium enolate could also be generated by treatment of the corresponding silyl enol ether with 1.0 equiv of ^{n}BuLi[11] to give the regioisomeric α-CF_3 product in reasonable yield after a 2 h reaction time (entries 2, 5, 7). The reaction rates of cyclopentanone (entry 8) and cycloheptanone (entry 9) were relatively slow (5 min).

Considering the facts that the reaction did not proceed without Et_3B (Table 2, entry 2) and CF_3I does not react in an S_N2-type trifluoromethylation,[12] we propose a radical reaction mechanism (Scheme 2).[4b] The CF_3 radical is

Scheme 2



generated by Et_3B and goes on to react with Li enolate. The radical intermediate (**A**) then reacts with another CF_3I to reproduce the CF_3 radial along with the α-CF_3 product (**B**).[13]

In summary, we have discovered that highly basic lithium enolates may be employed for radical trifluoromethylation. The reaction rate is extremely fast compared to the previous radical trifluoromethylation. The direct use of lithium enolate as a substrate is simpler and faster than that of titanium ate enolates or any other previous methods. The investigation of the detailed reaction mechanism and further applications of this methodology are now being pursued.

Supporting Information Available: Detailed experimental procedures and spectroscopic data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462−4464. (b) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464−4465.

(12) In sharp contrast to normal alkyl halides, perfluoroalkyl halides cannot undergo nucleophilic alkylation, because the electronegativities of perfluoroalkyl groups are higher than those of halogens. Thus the polarization of perfluoroalkyl halides is as $R_f^{\delta-}$-$I^{\delta+}$ and treatment with nucleophile could not produce R_f-Nu. (a) Yoshida, M.; Kamigata, N *J. Fluorine Chem.* **1990**, *49*, 1−20. (b) Huheey, J. E. *J. Phys. Chem.* **1965**, *69*, 3284−3291.

(13) When Et_3B was used in 20 mol %, the product was obtained in 75% yield. This indicates the involvement of chain-propagation step.