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Radical Trifluoromethylation of Ketone Silyl Enol Ethers by Activation with Dialkylzinc

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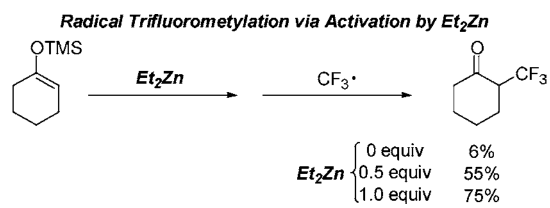
ABSTRACT



The radical trifluoromethylation of ketone silyl enol ethers gave α-CF_3 ketones in good yields with wide scope of the ketonic substrates including acyclic ketones and cyclopentanone. The use of dialkylzinc to activate the silyl enol ethers is the key to the efficient radical trifluoromethylation.

CF_3 compounds have attracted much attention because of their important applications as biologically active agents and liquid crystalline materials, which exhibit specific biological and physical properties.[1] α-CF_3 carbonyl compounds could be promising building blocks for the construction of CF_3 compounds. Radical trifluoromethylation of enolates is in principle one of the simplest ways to introduce a CF_3 unit at the α position of a carbonyl group because polarization of $CF_3^{\delta-}-X^{\delta+}$ is in contrast to $CH_3^{\delta+}-X^{\delta-}$ and because the reaction of CF_3I with enolates cannot give α-CF_3 ketones.[2] However, only limited examples are reported on radical trifluoromethylation, especially in the case of ketones.[3−6]

(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) (a) Huheey, J. E. *J. Phys. Chem.* **1965**, *69*, 3284−3291. (b) Yoshida, M.; Kamigata, N. *J. Fluorine Chem.* **1990**, *49*, 1−20.

(3) Perfluoroalkylation of silyl and germyl enolates of esters and ketones: (a) Miura, K.; Taniguchi, M.; Nozaki, K.; Oshima, K.; Utimto, 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 enolates proceeds in good yield.

(4) Trifluoromethylation of lithium enolate of imides: (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 bulky substituent at α position to suppress defluorination.

(5) 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.

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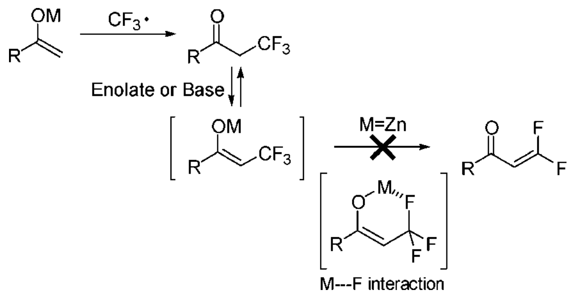
The synthetic difficulty has been reported to be due to defluorination of the α-CF_3 ketone product by the parent enolate or base during the reaction (Scheme 1).[4] Recently,

Scheme 1

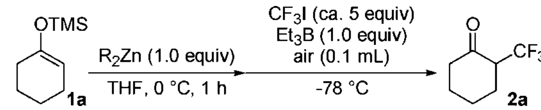


we reported that the use of titanium ate enolates[7] and lithium enolates[8] could avoid significant defluorination during radical trifluoromethylation. However, these methods work with limited scope of ketonic substrates. On the other hand, less reactive enolate equivalents such as silyl enol ethers have been used for radical trifluoromethylation to suppress defluorination of the α-CF_3 carbonyl compounds.[3] Due to its poor reactivity, this method could only be applied for ester silyl enol ethers (ketene silyl acetals), which is more nucleophilic than ketone silyl enol ethers. Thus, we focused our attention to zinc enolate, on the basis of the fact that the interaction between metals and the fluorine atom can be widely changed by the nature of the metals: the longer bond distance of soft late transition metal zinc with hard fluorine implies the negligible associative interaction.[1b,9] Therefore, metal enolates with zinc countercation might be employed for radical trifluoromethylation without decomposition of α-CF_3 ketonic products.

First, the generation of the zinc enolate of cyclohexanone was attempted starting from the silyl enol ether with dialkylzinc for radical trifluoromethylation using CF_3I (ca. 5 equiv), Et_3B (1.0 equiv), and O_2[10] at −78 °C. The yields were determined by ^{19}F NMR analysis using BTF (benzotrifluoride) as an internal standard. α-CF_3-cyclohexanone was obtained in good yield (75%) only after 1 h (Table 1).

The zinc enolate could not, however, be observed upon addition of dimethylzinc to the trimethylsilyl enol ether of cyclohexanone by TLC or NMR analyses. This observation implies the simple complexation of dialkylzinc with the silyl

Table 1. Trifluoromethylation of Silyl Enol Ether with Dialkylzinc



entry	time (h)	yield (%) R = Et	yield (%) R = Me
1	10 min	55	
2	0.5	65	45
3	1	75	50
4	6	76	63

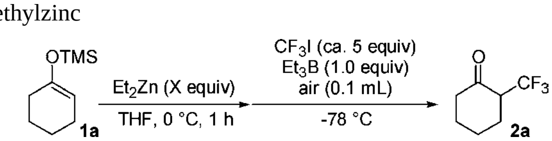
[a] Determined by ^{19}F NMR analysis using BTF as an internal standard.

enol ethers as d−π* complex **A** or Lewis acid/base complex **B** (Figure 1). The reactivity of the trimethylsilyl enol ether is significantly increased with or without formation of the zinc enolate under the reaction conditions. Quite recently, lithium cation complexation with an alkene was reported to accelerate radical addition reaction.[11]

Figure 1. Activation of silyl enol ethers with dialkylzinc.

On the basis of these results, dialkylzinc can be reduced in catalytic amounts (Table 2). As expected, even with a

Table 2. Trifluoromethylation with a Catalytic Amount of Diethylzinc



entry	Et_2Zn (equiv)	time (h)	yield[a] (%)
1	0	1	6
2	0	6	16
3	0	20	28
4	0.1	1	14
5	0.1	20	43
6	0.5	1	55
7	0.5	20	76
8	1.0	1	75

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

(6) There are some reports of trifluoromethylation using CF_3^+: (a) Yagupol'skii, L. M.; Kondratenko, N. V.; Timofeeva, G. N. *J. Org. Chem. USSR* **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.

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(9) (a) Plenio, H. *Chem. Rev.* **1997**, *97*, 3363−3384. (b) Murphy, E. F.; Murugavel, R.; Roesky, H. W. *Chem. Rev.* **1997**, *97*, 3425−3468 and references therein.

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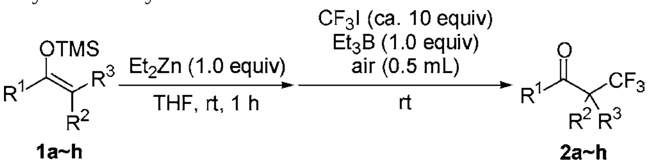
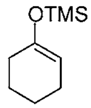
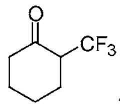
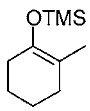
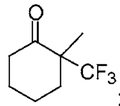
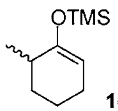
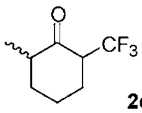
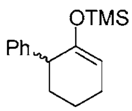
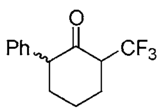
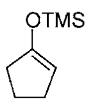
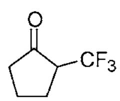
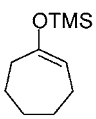
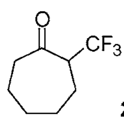
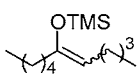
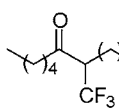
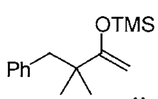
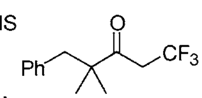
Table 3. Trifluoromethylation of Various Silyl Enol Ethers of Acyclic and Cyclic Ketones



entry	substrate	product	time (h)	yield (%)[a]
1	 **1a**	 **2a**	3	75
2	 **1b**	 **2b**	6	20
3			24	32
4	 **1c**	 **2c**	3	68[b]
5	 **1d**	 **2d**	(1 sec	43 (40)[d])[c]
6			24	60[e]
7	 **1e**	 **2e**	(1	33)[f]
8			24	50
9	 **1f**	 **2f**	12	34
10			24	51
11	 **1g**	 **2g**	(1 min	35)[c]
12			24	70
13	 **1h**	 **2h**	(5 min	17)[c]
14			24	54

[a] Determined by ^{19}F NMR analysis using BTF as an internal standard. [b] 16% de; trans major. [c] With lithium enolate. [d] Isolated yield. [e] 80% de. [f] With titanium ate enolate.

semicatalytic amount of diethylzinc (0.5 equiv), the trifluoromethylation product was obtained in good yield (55%, 1 h; 76%, 20 h) (entries 6 and 7). Without diethylzinc, the trifluoromethylation product was obtained in only low yields (entries 1−3).[3]

Several ketonic substrates were then investigated (Table 3). The present radical trifluoromethylation was found to give wide scope for the ketonic substrates applicable. The wide scope of applicable substrates is in sharp contrast to titanium ate enolate,[7] which is not applicable to cyclopentanone, and lithium enolate,[8] which is limited to cyclohexanone derivatives. Acyclic substrates as well as cyclic substrates including cyclopentanone provided the α-CF_3 ketone products in good yields via the silyl enol ethers activated with diethylzinc.

Since thermodynamic enolates could easily be prepared from the silyl enol ethers, the quaternary carbon center[12] with a CF_3 substituent could be produced from α-substituted ketone.[13] In the case of α-Me[14]-substituted cyclohexanone, the product with a CF_3-attached quaternary carbon was obtained in 32% yield for 24 h (entry 3).

In conclusion, we have thus developed the radical trifluoromethylation of ketone silyl enol ethers. Activation with dialkylzinc leads to the α-CF_3 ketones in increased yields with wide scope of the ketonic substrates including acyclic ketones and cyclopentanonone. The use of dialkylzinc to activate the silyl enol ethers is the key to the efficient radical trifluoromethylation, by which a CF_3 substituent can be introduced to give various α-CF_3 ketones, with or without formation of the zinc enolate intermediates.

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

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