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Zincate-type enolate for radical α-trifluoromethylation

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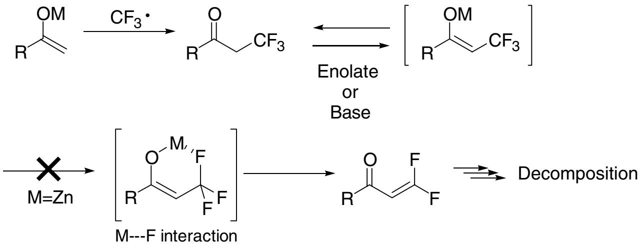
Abstract—Ketone zincate-type enolates can be applied to radical trifluoromethylation for the general synthesis of α-CF_3-ketones, cyclopentanones in particular. The addition of diethylzinc to lithium enolates is the key in the preparation of the zincate-type enolates for efficient radical trifluoromethylation.

Organofluorine compounds have attracted much interest in view of their important applications in material and biological sciences.[1] One of the most important organofluorine functionalities is trifluoromethyl (CF_3) one, which exhibits specific physical and biological properties. α-CF_3-carbonyl compounds are thus one of the most useful synthetic building blocks for CF_3-functionalization. However, the defluorination of α-CF_3-carbonyl compounds is problematic under basic conditions, in particular.[2] Defluorination is also encountered in their preparation via radical trifluoromethylation of metal enolates, because α-CF_3-carbonyl products could be easily deprotonated with the parent enolates and/or bases (Scheme 1). Therefore, it had long been recognized that highly basic conditions employing lithium enolates[3] could not be applied to trifluoromethylation.[4] Indeed only few examples had been reported especially for α-trifluoromethylation of ketones.[4–8] Recently, we have reported the radical trifluoromethylation of titanate enolates[9] with limited scope of ketonic substrates and lithium enolates[10] only applicable to cyclohexanone derivatives; Cyclopentanone and acyclic ketones gave only low-to-moderate yields.



Scheme 1.

On the basis of the longer bond length of soft late transition metal Zn and hard F[1d,2] in contrast to the shorter bond length of hard early transition metals Ti and F, we thought that zincate-type enolates might be more effective than the titanate counterpart for radical trifluoromethylation (Scheme 1). We report here that the zincate-type enolates can be applied to radical trifluoromethylation for the general synthesis of α-CF_3-ketones, particularly cyclopentanones.

First, several zinc enolates of cyclohexanone were examined for radical trifluoromethylation at −78 °C, using CF_3I (ca. 5 equiv), Et_3B (1.0 equiv), and O_2.[11] The yields were determined by ^{19}F NMR analysis using BTF (benzotrifluoride) as an internal standard (Fig. 1). In the case of zinc enolate generated by Et_2Zn and α-bromo cyclohexanone,[12] only a trace amount of α-CF_3-ketone was obtained (Eq. 1). The zincate-type enolate[13] could be easily formed just by adding Et_2Zn to the lithium enolate at low temperature. Upon treatment of the zincate-type enolate with CF_3 radical, the α-CF_3-ketone was obtained in an increased yield (Eq. 2). To increase the reactivity of the zincate-type enolate, the addition of 12-crown-4 was examined to trap the lithium counter cation, giving further increased yield up to 70% (Eq. 3).

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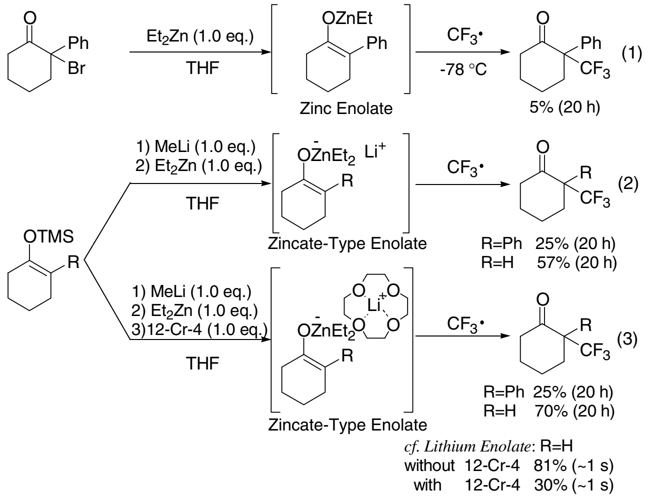


Figure 1. Trifluoromethylation of various zinc enolates.

Which is a reactive species, zincate-type enolate or separate lithium enolate associated with dialkylzinc? The question has been the subject of excellent but controversial mechanistic studies.[3,13,14] The increased yield in our case of the zincate-type enolate and 12-crown-4 is in sharp contrast to the significantly decreased yield in the case of lithium enolates with 12-crown-4. These results imply the zincate-type enolate as the reactive species at least in the radical trifluoromethylation of ketone metal enolates (Fig. 1).

Time dependence of yields was also investigated with zincate-type enolates in comparison with the lithium enolate (Fig. 2). Trifluoromethylation of the lithium enolate gave good yields of α-CF_3-ketone in much shorter reaction time because decomposition of the α-CF_3-ketone took place under the basic conditions for prolonged reaction time. In stark contrast, trifluoromethylation of the zincate-type enolate took longer reaction time to give the α-CF_3-ketone in good yield.

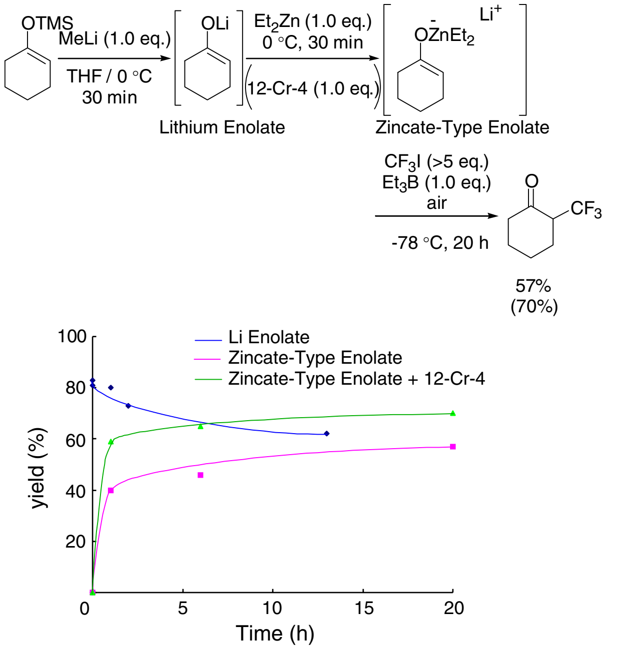


Figure 2. Time dependence of yields by zincate-type and lithium enolates.

On the basis of these results (Figs. 1 and 2), the zincate-type enolate is likely to be the active species in the present radical trifluoromethylation but not the lithium enolate associated with dialkylzinc.

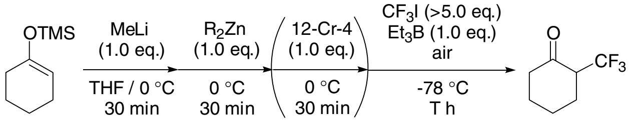
Therefore, radical trifluoromethylation of zincate-type enolates was further studied by changing the dialkylzinc species employed (Table 1). The use of Me_2Zn was also found to be effective in giving the good yield, after longer period of reaction time though (58% yield, 20 h).

The scope of the ketonic substrates was then investigated using silyl enol ethers as the enolate precursors, to exclude the effects of amines observed in the titanate case[9] (Table 2). Acyclic as well as cyclic substrates including cyclopentanone provided the α-CF_3-ketones in good yields. α-CF_3-α′-C_6H_5-cyclohexanone was obtained in an increased yield than that obtained by the lithium enolate (entries 3 and 4 vs 5). Starting from α-methylcyclohexanone,[15] the α-CF_3-ketone bearing all carbon quaternary center[16] was obtained in higher yields than that obtained by the titanate enolate (entries 6 and 7 vs 8). α-CF_3-cyclopentanone was also obtained in an increased yield than those obtained by the lithium and titanate enolates (entries 9 vs 10 and 11). An acyclic substrate also provided the α-CF_3-ketone in good yields (entries 12 and 13 vs 14 and 15).

These results show that α-trifluoromethylation of the zincate-type enolates was particularly effective not only for acyclic ketones but also for cyclic ketones including cyclopentanone as compared with the titanate and lithium enolates.

The synthesis of trifluoromethylated steroid D-ring analogue was thus investigated to highlight the significance of α-trifluoromethylation of carbonyl compounds, cyclopentanones in particular (Fig. 3). General treatment of zincate-type enolate of TMS-protected androsterone with $CF_3I/Et_3B/O_2$ provided the α-CF_3-androsterone in 45% yield ($\alpha:\beta = 3:1$).

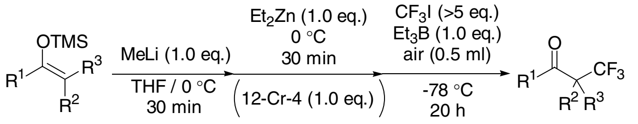
Table 1. Trifluoromethylation of zincate-type enolates with diethyl- and dimethylzincs

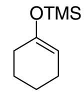
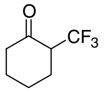
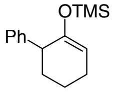
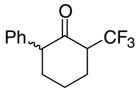
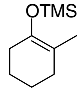
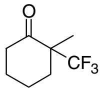
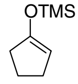
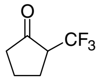
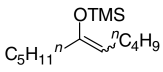
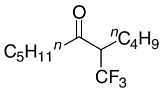


T (h)	Yield[a] (%)			
	R = Et no 12-Cr-4	R = Et 12-Cr-4	R = Me no 12-Cr-4	R = Me 12-Cr-4
1	40	59	—	—
6	46	65	—	—
20	57	70	36	58

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

Table 2. Trifluoromethylation of various substrates



Entry	*Si* enol ether	Product	Yield[a] (%)	de[b] (%)
1			57	
2			(70)[c]	
3			80	10
4			(86)[c]	14
5			43[d]	14
6			56	
7			(78)[c]	
8			42[e]	
9			50	
10			40[d]	
11			33[e]	
12			74	
13			(86)[c]	
14			35[d]	
15			64[e]	

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

[b] Determined by ^{19}F NMR analysis.

[c] With 12-crown-4 (1.0 equiv).

[d] With the lithium enolate.

[e] With the titanate enolate with $Ti(OPr^i)_4$ (1.6 equiv).

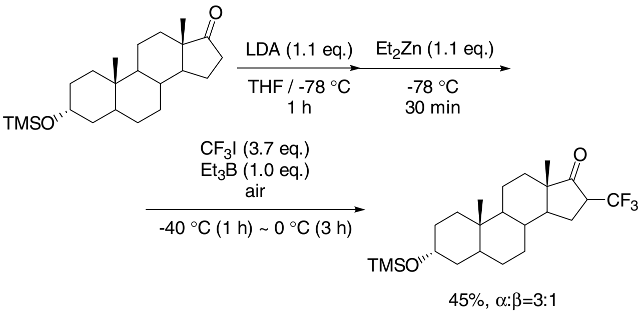


Figure 3. Trifluoromethylation of TMS-protected androsterone.

In conclusion, we have developed radical trifluoromethylation of zincate-type enolates, particularly cyclopentanones; CF_3 substituent can now be introduced into various ketones in higher yields.

References and notes

1. (a) Soloshonok, V. A.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J. F. *Current Fluoroorganic Chemistry*; ACS Symp. 949, 2006; (b) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006; (c) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214–231; (d) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119–6146; (e) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1–16; (f) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds*; Springer: Berlin, 2000; (g) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A., Ed.; Wiley: Chichester, 1999; (h) *Asymmetric Fluoroorganic Chemistry, Synthesis, Applications, and Future Directions*; Ramachandran, P. V., Ed.; American Chemical Society: Washington, DC, 2000; (i) *Organofluorine Chemistry*; Chambers, R. D., Ed.; Springer: Berlin, 1997; (j) Iseki, K. *Tetrahedron* **1998**, *54*, 13887–13914; (k) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996; (l) Smart, B. E., Ed. *Chem. Rev.* **1996**, *96*, 1555–1824 (Thematic issue of fluorine chemistry); (m) *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994; (n) *Synthetic Fluorine Chemistry*; Olah, G. A., Prakash, G. K. S., Chambers, R. D., Eds.; Wiley: New York, 1992.
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, and references cited therein.
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 bulky substitutent at 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; (c) Quite recently, we reported that the addition of diethylzinc to the ketone silyl enol ethers led to good yields even in the trifluoromethylation: Mikami, K.; Tomita, Y.; Ichikawa, Y.; Amikura, K.; Itoh, Y. *Org. Lett.* **2006**, *8*, 4671–4673.
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 on 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.
8. Also see: Yoshida, M.; Ohkoshi, M.; Iyoda, M. *Chem. Lett.* **2000**, 804–805, However, they reported the addition of perfluoroalkyl radical to α-chlorostyrenes giving eventually fluoroalkylated α,β-unsaturated ketones.
9. Titanate enolates: (a) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 649–651; (b) Itoh, Y.; Mikami, K. *J. Fluorine Chem.* **2006**, *127*, 539–544.
10. Lithium enolates: (a) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 4883–4885; (b) Itoh, Y.; Mikami, K. *Tetrahedron* **2006**, *62*, 7199–7203.

11. Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547–2549.
12. Hansen, M. M.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069–2074.
13. Reaction involving zincate-type enolates: McWilliams, J. C.; Armstrong, J. D., III; Bhupathy, N. M.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1996**, *118*, 11970–11971.
14. (a) Suzuki, M.; Koyama, H.; Noyori, R. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 259–268; (b) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785–1787.
15. The silyl enol ether of α-methylcyclohexanone consists of thermodynamic and kinetic enol ethers (87:13).
16. Reviews on the construction of quaternary carbon centers: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419–460; (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066; (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401; (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591–4597; (e) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146; (f) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A* **2004**, *101*, 5363–5367; (g) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396.