Radical Trifluoromethylation of Titanium Ate Enolate

Yoshimitsu Itoh and Koichi Mikami*

Department of Applied Chemistry, Tokyo Institute of Technology, Tokyo 152-8552, Japan kmikami@o.cc.titech.ac.jp

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ABSTRACT



The radical trifluoromethylation of ketone titanium ate enolates gave α -CF₃ ketones in good yields. The use of excess amount of LDA and Ti(O'Pr)₄ in the preparation of titanium ate enolates is the key to the efficient radical trifluoromethylation.

Organofluorine compounds continue to attract much attention because of their important applications as biological active agents, liquid crystalline materials, and so on. One of the most important fluorine-containing compounds is a CF₃ compound, which exhibits specific physical and biological properties.¹ However, the synthesis of α -CF₃ carbonyl compounds has not been fully established. Radical trifluoromethylation of enolates is in principle one of the simplest ways to introduce a CF₃ unit at the α position of a carbonyl group; however, there are only limited examples, especially in the case of ketones.^{2–5} It has been reported that the

10.1021/ol047565a CCC: \$30.25 © 2005 American Chemical Society Published on Web 01/22/2005 synthetic difficulty is due to the defluorination of the α -CF₃ ketone product by the parent enolate or base during the reaction (Scheme 1).³ Recently we have reported the efficient



generation of titanium enolates of α -CF₃ ketones and high yielding aldol reactions.⁶ The stability of the titanium enolates of α -CF₃ ketones stems from the linearity of Ti–O–C bonds caused by the donation of the lone electron pair of the oxygen to the empty d-orbital of titanium to suppress Ti–F interac-

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⁽²⁾ Perfluoroalkylation of silyl and germyl enolates 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 enolates proceeds in good yield.

⁽³⁾ 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 a bulky substitutent at the α position to suppress defluorination.

tion⁷ and successive defluorination. On the basis of the fact that titanium enolates of α -CF₃ ketones are stable to defluorination, we report here that titanium ate enolates can be applied to radical trifluoromethylation for the synthesis of α -CF₃ ketones.

First, several titanium enolates of cyclohexanone were reacted with CF₃ radical, which was generated by CF₃I (ca. 5 equiv) and Et₃B (1.0 equiv).⁸ The reaction was carried out at -78 °C for 2 h. The yields were determined by ¹⁹F NMR using BTF as an internal standard (Figure 1). In the case of



Figure 1. Trifluoromethylation of various titanium enolates.

TiCl₃ enolate (formed by TiCl₄ and Et₃N in CH₂Cl₂ at -78 °C), no α -CF₃ ketone (**3a**) was obtained. In the case of Ti-(O²Pr)₃ enolate (formed by the addition of Ti(O²Pr)₃Cl to the corresponding lithium enolate in THF at -78 °C), the α -CF₃ ketone (**3a**) was formed, but in low yield (23%). To increase the reactivity of the enolate, the titanium ate^{9,10} enolate was examined. Titanium ate enolates could be easily formed just by adding Ti(O²Pr)₄ to lithium enolate at low temperature.⁹ Upon treatment of titanium ate enolate (**2a**) with CF₃ radical, the α -CF₃ ketone was obtained in an increased yield (56%).

Radical trifluoromethylation of titanium ate enolate (2a) was further investigated and the use of excess amount of

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M. T.; Wenderoth, B. *Tetrahedron Lett.* **1982**, *23*, 5259–5262. (b) Reetz,
M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek,
R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421–1440. (c) Reetz, M. T.; Steinbach,
R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441–
1454. (d) Takahashi, H.; Kawabata, A.; Niwa, H.; Higashiyama, K. *Chem. Pharm. Bull.* **1988**, *36*, 803–806. (e) Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Synthesis* **1988**, 238–240. (f) Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Chem. Pharm. Bull.* **1991**, *39*, 260–265. (g) Bernardi,
A.; Cavicchioli, M.; Scolastico, C. *Tetrahedron* **1993**, *49*, 10913–10916.
(h) Bernardi, A.; Marchionni, C.; Pilati, T.; Scolastico, C. *Tetrahedron Lett.* **1994**, *35*, 6357–6360. (i) Mahrwald, R. *Tetrahedron* **1995**, *51*, 9015–9022.

LDA and $Ti(O'Pr)_4$ was found to be important in increasing the yield (Table 1). When the enolate (2a) was formed by

Table 1. O Ia	Trifluorometh LDA THF / -78 °C 30 min	ylation of Titanium Ate E $Ti(O'Pr)_4$ $-78 ^{\circ}C$ 30 min $Ti(O'Pr)_4$ $-78 ^{\circ}C$ $-78 ^{\circ}C / 2 h$	O CF ₃ 3a
entry	LDA (equiv) $Ti(O^iPr)_4$ (equiv)	yield (%) ^a
1	1.0	1.0	56
2	1.3	1.3	72
3	1.6	1.6	81
4	2.0	2.0	80
5	1.0	1.6	52
^a Determ	nined by ¹⁹ F NM	R using BTF as an internal st	andard.

1.0 equiv of LDA and 1.0 equiv of $Ti(O^{i}Pr)_{4}$, the product (**3a**) was formed in 56% yield (entry 1). When 1.6 equiv of LDA and 1.6 equiv of $Ti(O^{i}Pr)_{4}$ were used, the yield increased up to 81% (entry 3). Using 1.0 equiv of LDA and 1.6 equiv of $Ti(O^{i}Pr)_{4}$ gave the α -CF₃ ketone (**3a**) in almost the same yield as in entry 1 (52%, entry 5). Therefore, both LDA and $Ti(O^{i}Pr)_{4}$ should be used in excess amounts.

The titanium ate enolate is prepared from the corresponding lithium enolate. When LDA was used for the preparation of lithium enolate, 1 equiv of ^{*i*}Pr₂NH was formed simultaneously. To investigate the effect of ^{*i*}Pr₂NH, ^{*n*}BuLi was added to silyl enol ether,¹¹ to generate the lithium enolates without formation of ^{*i*}Pr₂NH (Table 2) and the amount of ^{*i*}Pr₂NH could be controlled at will). When the reaction was carried

Table 2.	Trifluoromethylation of Titanium Ate Enolates	
Starting fr	om the Silyl Enol Ether	

OLV	IS			CF₀I (ca.	O 5.ea.) ∥	
	″BuLi	R ₂ NH	Ti(O [/] Pr) ₄	Et ₃ B (1.	0 eq.)	CF3
	THF / 0 °C 20~30 min	0 °C 20 min	-78 °C 30 min	-78 ° 2 h	°C	3a
	ⁿ BuLi		R_2NH		${\rm Ti}({\rm O}^i{\rm Pr})_4$	yield
entry	(equiv)		(equiv)		(equiv)	$(\%)^a$
1	1.0				1.0	63
2	1.0				1.6	62
3	1.6				1.6	68
4	1.0	$^{i}\mathrm{Pr}_{2}\mathrm{NH}$ (1.0)		1.0	49
5	1.6	$^{i}\mathrm{Pr}_{2}\mathrm{NH}$ (1.6)		1.6	74
6	1.0	2,2,6,6-M	le ₄ -piperidi	ne (1.0)	1.0	57
7	1.6	2,2,6,6-M	le4-piperidi	ne (1.6)	1.6	72
8	1.0	Et ₂ NH (1	.0)		1.0	6
9	1.6	Et_2NH (1	6)		1.6	11

^a Determined by ¹⁹F NMR using BTF as an internal standard.

out without addition of ${}^{i}Pr_{2}NH$, the yields did not change significantly even by increasing the amount of ${}^{n}BuLi$ and/or Ti(O ${}^{i}Pr_{4}$ (Table 2, entry 1–3). On the contrary, when three reagents (${}^{n}BuLi$, ${}^{i}Pr_{2}NH$, Ti(O ${}^{i}Pr_{4}$) were used in 1.0 equiv

⁽⁴⁾ 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.

⁽⁵⁾ 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.

each, the yield was decreased (entry 4 (vs entry 1)). In the case that the three reagents were used in 1.6 equiv each, the yield was increased (entry 5). Although the yield of entries 4 and 5 in Table 2 were slightly decreased compared to entries 1 and 3 in Table 1, a similar tendency was observed in the relationship of the yields and the amounts of the reagents.

From these results, the effect of ${}^{i}Pr_{2}NH$ could be proposed as follows (Scheme 2). ${}^{i}Pr_{2}NH$, which is formed by using



LDA in the preparation of titanium ate enolate (2a), would exchange with OPr ligand to give PrOH. PrOH could protonate the enolate to form ketone and titanium amide complex (LDA/Ti(OⁱPr)₄).¹² This mechanism rationalizes not only the decrease in yield upon addition of ^{*i*}Pr₂NH (Table 2, entry 4) (protonation of the enolate to reduce the amount of the reactive enolate species) but also the increase in yield using excess amount of LDA and Ti(O'Pr)₄ (the equilibrium shifts to titanium ate enolate). To support the mechanism, 2,2,6,6-tetramethylpiperidine and Et₂NH were investigated. 2.2.6.6-Tetramethylpiperidine is more bulky than ⁱPr₂NH and its coordinating ability is lower than that of Pr₂NH to shift the proposed equilibrium (Scheme 2) to titanium ate enolate (2a). In fact, when 2,2,6,6-tetramethylpiperidine was used in 1.0 equiv (entry 6), the decrease in the yield was not significant relative to ⁱPr₂NH (entry 4). When 2,2,6,6tetramethylpiperidine was used in 1.6 equiv (entry 7), the yield was increased as in the case of ^{*i*}Pr₂NH (entry 5). On the other hand, Et₂NH is less bulky than ^{*i*}Pr₂NH and, hence, its coordination ability is higher to shift the equilibrium (Scheme 2) to ketone (**1a**). In fact, when Et₂NH was used in 1.0 equiv (entry 8) and 1.6 equiv (entry 9), the yield was dramatically decreased. It should be noted that the LDA/Ti-(O'Pr)₄ complex, which might act as a base, works not for the decomposition of the α -CF₃ ketone products but for increasing the yield.

Several ketonic substrates were thus investigated (Figure 2). Acyclic substrates (**3c**,**d**) as well as cyclic substrates



Figure 2. Trifluoromethylation of various substrates: (*a*) yield determined by 19 F NMR, (*b*) isolated yield.

(3a,b) provided the α -CF₃ ketones in good yields. Although LDA could generate only kinetic lithium enolate, both kinetic and thermodynamic enolate could easily be prepared from silyl enol ethers. Therefore, thermodynamic titanium ate enolate of α -substituted ketone could be generated by silyl-to-lithium method to obtain quaternary carbon center attached with CF₃ substituent.^{13,14} In the case of α -Me¹⁵ and α -Ph¹⁶ substituted cyclohexanone, the products were obtained in reasonable yields (3e,f).

In conclusion, we have developed radical trifluoromethylation of titanium ate enolates. The key to the success is the use of an excess amount of ^{*n*}BuLi, ^{*i*}Pr₂NH, and Ti(O^{*i*}Pr)₄ to generate the titanium ate enolates. By this method, the CF₃ substituent can be introduced to give various ketones even with α -CF₃ quaternary carbon centers.

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

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⁽¹²⁾ NMR study of a titanium ate enolate^{9b} showed that the ketone was formed in the generation of the titanium ate enolate (although this is only mentioned in the foot note of Figure 2). This fact also supports the proposed mechanism.

⁽¹³⁾ Review of 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) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146.

⁽¹⁴⁾ Kimura, M.; Yamazaki, T.; Kitazume, T.; Kubota, T. Org. Lett. **2004**, 6, 4651–4654.

⁽¹⁵⁾ Silyl enol ether of α -Me cyclohexanone consists of thermodynamic enolate:kinetic enolate = 87:13.

⁽¹⁶⁾ Silyl enol ether of $\alpha\mbox{-}Ph$ cyclohexanone contains only thermodynamic enolate.