ORGANIC LETTERS

2005
Vol. 7, No. 4
649−651

Radical Trifluoromethylation of Titanium Ate Enolate

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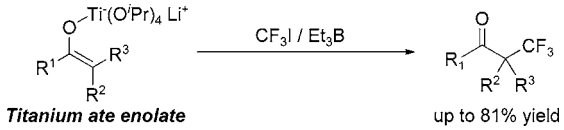
Received November 27, 2004

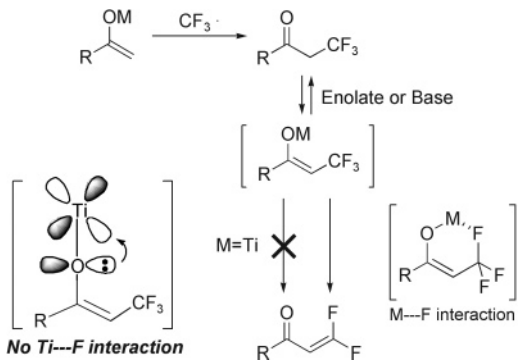
ABSTRACT



The radical trifluoromethylation of ketone titanium ate enolates gave α-CF_3 ketones in good yields. The use of excess amount of LDA and $Ti(O^iPr)_4$ 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 CF_3 compound, which exhibits specific physical and biological properties.[1] However, the synthesis of α-CF_3 carbonyl compounds has not been fully established. 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; however, there are only limited examples, especially in the case of ketones.[2−5] It has been reported that the synthetic difficulty is due to the defluorination of the α-CF_3 ketone product by the parent enolate or base during the reaction (Scheme 1).[3] Recently we have reported the efficient

Scheme 1



generation of titanium enolates of α-CF_3 ketones and high yielding aldol reactions.[6] The stability of the titanium enolates of α-CF_3 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-

(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) Soloshonok, V. A., Ed.; *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Wiley: Chichester, 1999. (e) Ramachandran, P. V., Ed.; *Asymmetric Fluoroorganic Chemistry, Synthesis, Applications, and Future Directions*; American Chemical Society: Washington, DC, 2000. (f) Chambers, R. D., Ed.; *Organofluorine Chemistry*; Springer: Berlin, 1997. (g) Iseki, K. *Tetrahedron* **1998**, *54*, 13887−13914. (h) Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; *Biomedical Frontiers of Fluorine Chemistry*; American Chemical Society: Washington, DC, 1996. (i) Smart, B. E., Ed.; *Chem. Rev.* **1996**, *96*, 1555−1824 (thematic issue of fluorine chemistry). (j) Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (k) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed; Ellis Horwood: Chichester, 1976.

(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.

10.1021/ol047565a CCC: $30.25
Published on Web 01/22/2005

tion[7] and successive defluorination. On the basis of the fact that titanium enolates of α-CF_3 ketones are stable to defluorination, we report here that titanium ate enolates can be applied to radical trifluoromethylation for the synthesis of α-CF_3 ketones.

First, several titanium enolates of cyclohexanone were reacted with CF_3 radical, which was generated by CF_3I (ca. 5 equiv) and Et_3B (1.0 equiv).[8] The reaction was carried out at −78 °C for 2 h. The yields were determined by ^{19}F NMR using BTF as an internal standard (Figure 1). In the case of

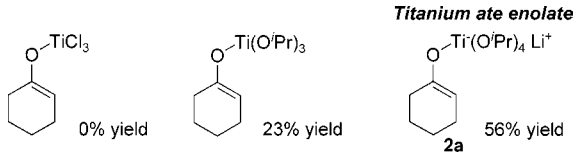
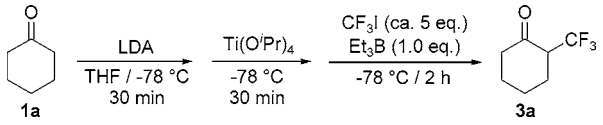


Figure 1. Trifluoromethylation of various titanium enolates.

$TiCl_3$ enolate (formed by $TiCl_4$ and Et_3N in CH_2Cl_2 at −78 °C), no α-CF_3 ketone (**3a**) was obtained. In the case of Ti(O^iPr)$_3$ enolate (formed by the addition of Ti(O^iPr)$_3$Cl to the corresponding lithium enolate in THF at −78 °C), the α-CF_3 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(O^iPr)$_4$ to lithium enolate at low temperature.[9] Upon treatment of titanium ate enolate (**2a**) with CF_3 radical, the α-CF_3 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 LDA and Ti(O^iPr)$_4$ was found to be important in increasing the yield (Table 1). When the enolate (**2a**) was formed by

Table 1. Trifluoromethylation of Titanium Ate Enolates



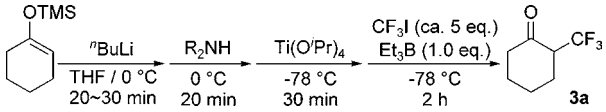
entry	LDA (equiv)	Ti(O^iPr)$_4$ (equiv)	yield (%)[a]
1	1.0	1.0	56
2	1.3	1.3	72
3	1.6	1.6	81
4	2.0	2.0	80
5	1.0	1.6	52

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

1.0 equiv of LDA and 1.0 equiv of Ti(O^iPr)$_4$, the product (**3a**) was formed in 56% yield (entry 1). When 1.6 equiv of LDA and 1.6 equiv of Ti(O^iPr)$_4$ were used, the yield increased up to 81% (entry 3). Using 1.0 equiv of LDA and 1.6 equiv of Ti(O^iPr)$_4$ gave the α-CF_3 ketone (**3a**) in almost the same yield as in entry 1 (52%, entry 5). Therefore, both LDA and Ti(O^iPr)$_4$ 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 $^iPr_2NH$ was formed simultaneously. To investigate the effect of $^iPr_2NH$, ^{n}BuLi was added to silyl enol ether,[11] to generate the lithium enolates without formation of $^iPr_2NH$ (Table 2) and the amount of $^iPr_2NH$ could be controlled at will). When the reaction was carried

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



entry	^{n}BuLi (equiv)	R_2NH (equiv)	Ti(O^iPr)$_4$ (equiv)	yield (%)[a]
1	1.0		1.0	63
2	1.0		1.6	62
3	1.6		1.6	68
4	1.0	$^iPr_2NH$ (1.0)	1.0	49
5	1.6	$^iPr_2NH$ (1.6)	1.6	74
6	1.0	2,2,6,6-Me_4-piperidine (1.0)	1.0	57
7	1.6	2,2,6,6-Me_4-piperidine (1.6)	1.6	72
8	1.0	Et_2NH (1.0)	1.0	6
9	1.6	Et_2NH (1.6)	1.6	11

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

out without addition of $^iPr_2NH$, the yields did not change significantly even by increasing the amount of ^{n}BuLi and/or Ti(O^iPr)$_4$ (Table 2, entry 1−3). On the contrary, when three reagents (^{n}BuLi, $^iPr_2NH$, Ti(O^iPr)$_4$) 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.

(6) Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Am. Chem. Soc.* **2004**, *126*, 13174−13175.

(7) (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.

(8) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547−2549.

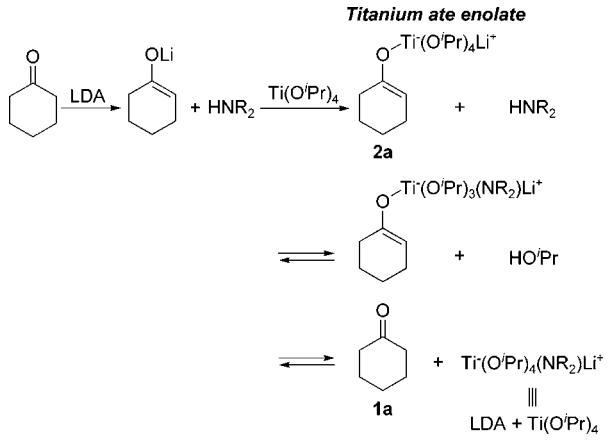
(9) Some reactions involving titanium ate enolates: (a) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722−5728. (b) Bernardi, A.; Cavicchioli, M.; Marchionni, C.; Potenza, D.; Scolastico, C. *J. Org. Chem.* **1994**, *59*, 3690−3694. (c) Yachi, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **1999**, *121*, 9465−9466. (d) Han, Z.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2000**, *41*, 4415−4418.

(10) Some reactions involving other titanium ate comlexes: (a) Reetz, 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.

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 $^{i}Pr_2NH$ could be proposed as follows (Scheme 2). $^{i}Pr_2NH$, which is formed by using

Scheme 2



LDA in the preparation of titanium ate enolate (**2a**), would exchange with $^{-}O^{i}Pr$ ligand to give $^{i}PrOH$. $^{i}PrOH$ could protonate the enolate to form ketone and titanium amide complex (LDA/Ti($O^{i}Pr$)$_4$).[12] This mechanism rationalizes not only the decrease in yield upon addition of $^{i}Pr_2NH$ (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($O^{i}Pr$)$_4$ (the equilibrium shifts to titanium ate enolate). To support the mechanism, 2,2,6,6-tetramethylpiperidine and Et_2NH were investigated. 2,2,6,6-Tetramethylpiperidine is more bulky than $^{i}Pr_2NH$ and its coordinating ability is lower than that of $^{i}Pr_2NH$ 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 $^{i}Pr_2NH$ (entry 4). When 2,2,6,6-tetramethylpiperidine was used in 1.6 equiv (entry 7), the yield was increased as in the case of $^{i}Pr_2NH$ (entry 5). On the other hand, Et_2NH is less bulky than $^{i}Pr_2NH$ and, hence, its coordination ability is higher to shift the equilibrium (Scheme 2) to ketone (**1a**). In fact, when Et_2NH 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($O^{i}Pr$)$_4$ complex, which might act as a base, works not for the decomposition of the α-CF_3 ketone products but for increasing the yield.

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

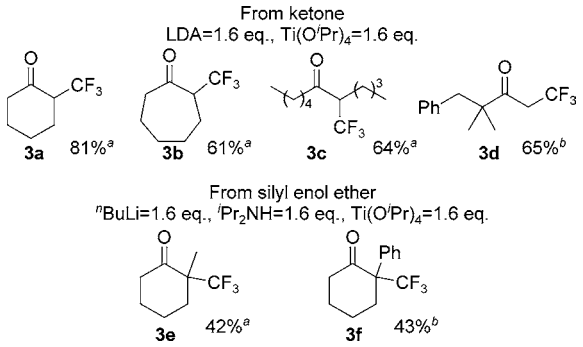


Figure 2. Trifluoromethylation of various substrates: (*a*) yield determined by ^{19}F NMR, (*b*) isolated yield.

(**3a**,**b**) provided the α-CF_3 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 CF_3 substituent.[13,14] In the case of α-Me[15] and α-Ph[16] 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 $^{n}BuLi$, $^{i}Pr_2NH$, and Ti($O^{i}Pr$)$_4$ to generate the titanium ate enolates. By this method, the CF_3 substituent can be introduced to give various ketones even with α-CF_3 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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(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) 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 α-Ph cyclohexanone contains only thermodynamic enolate.