Direct Generation of Ti-Enolate of α-CF₃ Ketone: Theoretical Study and High-Yielding and Diastereoselective Aldol Reaction

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The synthesis of organofluorine compounds has recently attracted explosive interest in material and biological sciences. One of the most important fluorine-containing compounds is a CF_3 compound that exhibits specific physical and biological properties.[1] We have been interested in developing a synthetic method for the construction of CF_3-containing compounds because of its specific physical properties and lesser availabilities. α-CF_3 Enolate methodology is, in principle, one of the most effective ways for constructing CF_3-containing compounds. However, there is only one example in the generation of α-CF_3 enolate of ketone (Al), via DIBAL reduction of alkenyl phosphate.[2] Facile defluorination is always an obstacle in the generation of α-CF_3 enolate. We herein report our discovery of efficient generation of Ti-enolate directly from α-CF_3 ketone and highly diastereoselective aldol reaction.

Upon generation of an enolate of α-CF_3 ketone, we discovered that the enolate could be formed quantitatively by using $TiCl_4$ and Et_3N (Table 1).[3] α-Deuterated ketone (**2**) was obtained in quantitative yield using 35 wt % DCl/D_2O for quenching the enolate (entry 2).[4] This result clearly shows that $TiCl_3$-enolates can be directly generated quantitatively from α-CF_3 ketones. In sharp contrast, the Li-enolate was formed only in low yield using LDA, and the total recovery of **1** and **2** was only 35% (entry 3). This result indicates that defluorination took place in the case of Li-enolate.[5]

According to crystallographic data, Ti is of strong affinity to fluorine rather than Li.[1a,6] Therefore, it seems strange that the Ti-enolate of α-CF_3 ketone could be formed without defluorination. To clarify this anomaly, the structures of Ti- and Li-enolates of α-CF_3 ketone were optimized at B3LYP/631LAN (LANL2DZ for Ti, 6-31G* for others) level.[7,8] Optimized structures are shown in Figure 1. In the case of Li-enolate, strong interaction between Li and fluorine is clearly observed. It could be easily understood that defluorination readily occurs. On the contrary, in the case of Ti-enolate, the Ti−O−C angle is almost straight (170.2°) and Ti−F interaction could not be observed.[9] The stability of the $TiCl_3$-enolate of α-CF_3 ketone could be explained by the linearity of the Ti−O−C bond to suppress the Ti−F interaction. The linearity of Ti−O−C angle stems from the multiple bonding nature of the Ti−O bond. Donation of the lone electron pair of the oxygen to the empty d-orbital of Ti causes the multiple bonding nature. The multiple bonding is supported by the X-ray structure of Ti complexes and by computational study.[10,11]

Next, aldol reaction of the $TiCl_3$-enolate of α-CF_3 ketone was examined (Table 2). Upon addition of benzaldehyde to the *in situ*-generated $TiCl_3$-enolate of α-CF_3 ketone, the aldol product was obtained in high diastereoselectivity (anti:syn = >99:<1), although in moderate yield (46%). Several Lewis acids were examined as an additive, and $Ti(O^iPr)_4$ was extremely effective to produce the product in almost perfect yield and diastereoselectivity (97% yield, anti:syn = 99:1) (entry 1). In the case of aliphatic aldehydes, the product was obtained in good yield and excellent diastereoselectivity

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Table 1. Formation of the TiCl₃-Enolate of α-CF₃ Ketone

entry		% yield[a]	
		1	**2**
1	TiCl₄ (1.2)/Et₃N (1.4)	16	81
2[b]		trace	>99
3[c]	LDA (1.0)	31	4

[a] Determined by ^{19}F NMR. [b] 35 wt % DCl/D_2O was used. [c] THF was used as a solvent.
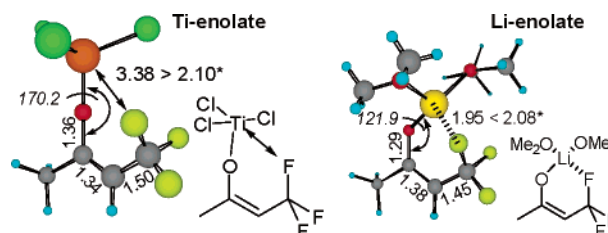

Figure 1. Three-dimensional structures of Ti- and Li-enolate optimized at the B3LYP/631LAN level, with the bond lengths in Å and bond angles (italics) in degrees. An asterisk (*) indicates the sum of vdW radii of F and ionic radii of the corresponding metal.

Table 2. Aldol Reaction of the TiCl₃-Enolate of α-CF₃ Ketone

entry		without Ti(O^iPr)₄	with Ti(O^iPr)₄
1	PhCHO	46% yield (>99:<1)	97% yield (99:1)
2	(CH₃)₂CHCHO	45% yield (98:2)	80% yield (99:1)
3	PhCH₂CH₂CHO	42% yield (98:2)	74% yield (97:3)

(entries 2, 3). All products showed *anti* diastereoselectivity confirmed by X-ray[12] and/or NMR analysis of the acetonide converted from the aldol product (see Supporting Information).

It is well-known that the aldol reaction of Ti-(*Z*)-enolate would produce *syn*-aldol via a cyclic transition state.[13] In the case of the aldol reaction of α-CF_3−Ti-enolate, all the reactions were found to give opposite *anti* selectivity. To shed light on the origin of the *anti*-selective aldol reaction of α-CF_3 ketone, two transition states

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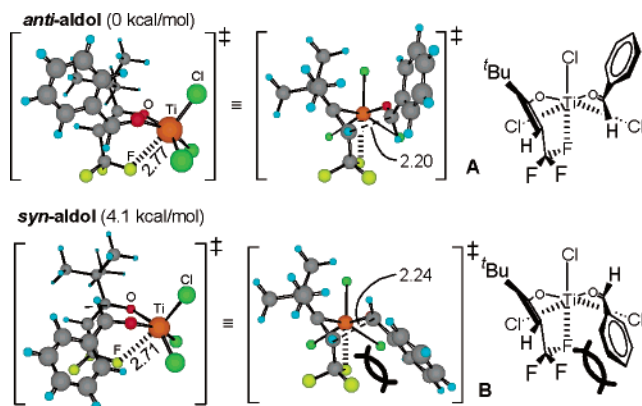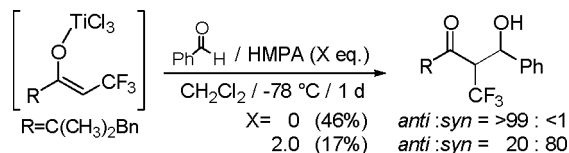
Figure 2. Three-dimensional structures of the TS of the aldol reaction of both *syn*- and *anti*-aldol optimized at the B3LYP/631LAN level, with the bond lengths in Å.

Scheme 1

(*syn* and *anti* transition states) of the aldol reaction[14] were optimized at the B3LYP/631LAN level[7,8,15] (Figure 2). Energy calculations of both transition states were in good agreement with the experimental result (syn transition state was 4.1 kcal/mol higher in energy than the anti transition state).

Surprisingly, interaction between Ti and CF_3 group was observed at both transition states (Figure 2), which was not observed at the starting Ti-enolate. The reason is that the donation of the lone electron pair of enolate oxygen to the empty d orbital of Ti would be weaker by carbonyl addition. Due to the Ti—F interaction, both transition structures (*syn* and *anti*) were fixed in the boat form; the CF_3 group in the enolate moiety would be attracted by Ti to enhance the steric repulsion with the equatorial substituent in the aldehyde moiety (benzene ring) (**B**). Along with this motion of the CF_3 group, the ^{t}Bu group in the enolate moiety would move away from the six-membered ring to reduce the steric repulsion with the axial substituent in the aldehyde moiety (**A**). Therefore, the transition state leading to *anti*-aldol would be stabilized. To confirm the effect of Ti—F interaction at the transition state, the reaction was carried out in the presence of HMPA to cleave Ti—F coordination leading to the usual *syn* selectivity. In fact, when HMPA was added in the reaction mixture, syn selectivity was obtained (anti:syn = 20:80) (Scheme 1). Therefore, it could be concluded that the anti-selective aldol reaction stems from Ti—F interaction at the aldol transition state, which was not observed in the Ti-enolate.[16]

In conclusion, we have discovered that the Ti-enolate of α-CF_3 ketone could be easily generated and that subsequent aldol reaction proceeds in up to quantitative yield and virtually perfect diastereoselectivity.

Ti—F interaction plays an important role in the course of the reaction. In the Ti-enolate of α-CF_3 ketone, there is no Ti—F interaction because of the multiple bonding nature of Ti—O bond, which retards F-elimination. On the other hand, at the transition state of the aldol reaction, there is a clear Ti—F interaction and, as a result, the aldol reaction shows *anti* diastereoselectivity. Further application of this aldol reaction to the asymmetric synthesis of organofluorine compounds (such as liquid crystalline molecules) is under investigation.

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(11) Orbital interaction could be observed by molecular orbital analysis. See Supporting Information.
(12) X-ray structure of the product with benzaldehyde was obtained. CCDC 240382 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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(14) Aldol reaction of $TiCl_3$-enolate of 1,1,1-trifluoro-4,4-dimethyl-pentan-3-one and benzaldehyde was adopted for the calculation model.
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(16) In sharp contrast, in the case with fluoral, the anti diastereoselectivity did not change (anti:syn = 62:38) even in the presence of HMPA. This could be the evidence for the dipole interaction-controlled diastereoselectivity in the case of fluoral. See ref 13.

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