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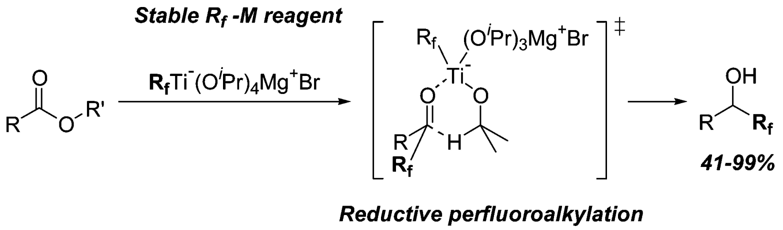

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Tandem Reductive Perfluoroalkylation of Esters with Perfluoroalkyl Titanate-Type Reagents

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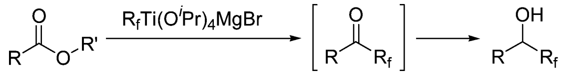
Organofluorine compounds have attracted current interest because of late but rich blooming in biological and material science.[1] However, perfluoroalkyl metal reagents have generally been recognized unstable and difficult to prepare because of the facile α- or β-metal fluoride (M−F) elimination.[2] Herein, we report the generation of *stable* perfluoroalkyl (R_f-) titanate-type reagents and their new type of reaction, namely tandem (domino)[3] reductive[4] perfluoroalkylation of esters (eq 1). The present report can thus be recognized as a significant advance toward the common use of *stable* perfluoroalkyl metal reagents with new type of reactivity.

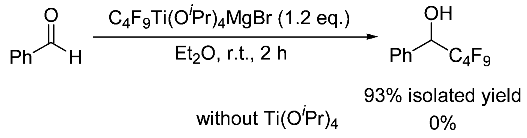


(1)

We have already reported that the metal enolates of α-trifluoromethyl (CF_3) ketones can be generated quantitatively without defluorination using $TiCl_4$ and Et_3N in spite of the strong affinity of Ti and F.[5] The structures of Li-, Ti-, and Ti-ate enolates of α-CF_3-acetone were thus clarified by DFT calculation[6,7] (Figure 1).

In the Li-case, strong interaction between Li and fluorine is observed in the *s*-cis configuration, and defluorination can be recognized to readily take place. In the Ti-enolate, the Ti−O−C angle is 170.2°, and Ti−F interaction cannot be observed.[8] In the Ti-ate enolate, in contrast, the Ti−O−C bond has no more linearity but *s*-trans configuration with respect to the fluorine group. Therefore, Ti−F interaction cannot be observed. The *s*-trans configuration of the Ti-ate enolate probably stems from the electronic and steric repulsion between Ti-ate complex and CF_3.

With this stable form of Ti-ate enolates, we thought that perfluoroalkyl titanate-type reagents might also be stable to prevent α- or β-F-elimination. Therefore, the corresponding perfluoroalkyl titanate-type reagents were prepared; First perfluoroalkyl Grignard reagent was prepared at −78 °C,[9] and titanium tetra(iso-propoxide)[10] was added. The perfluoroalkyl titanate-type reagent was then reacted with benzaldehyde at room temperature to give perfluoroalkyl alcohol in 93% isolated yield (eq 2). Without titanium tetra(isopropoxide), the Grignard reagent did not give the alcohol at that temperature. We have thus developed *stable* perfluoroalkyl metal reagents.



(2)

Esters were then examined. Surprisingly, the perfluoroalkyl titanate-type reagent reacted with benzoate ester to give a "reductive" perfluoroalkylation product, *sec*-alcohol in quantitative yield (Scheme 1), because ordinary alkyl titanate-type reagents were unreactive therewith.[11] By contrast, the perfluoroalkyl lithium reagents have been reported to give ketones or the *tert*-alcohols thereof.[12]

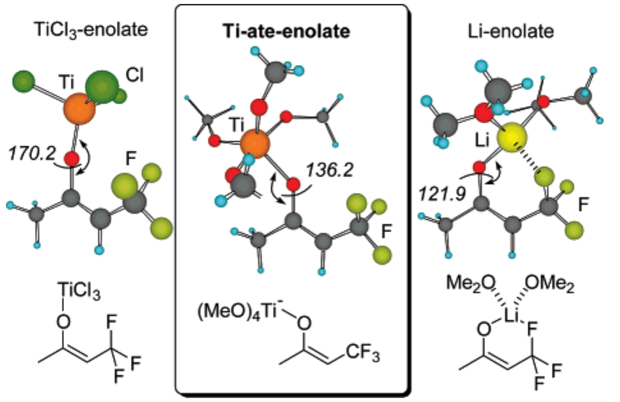
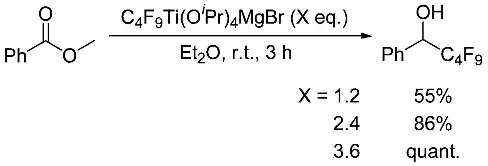


Figure 1. The 3D structures of Ti-, Ti-ate- and Li-enolates: the bond lengths are in Å, the bond angles (italics) are in degrees.

Scheme 1



The time course of this reductive perfluoroalkylation of the ester was traced (Figure 2). In the reaction of the ester substrate (green squares), the corresponding ketone intermediate (orange triangle) was first observed. With decrease of the ketone intermediate (orange triangle), the perfluoroalkylated *sec*-alcohol product (blue circle) was finally obtained. The tandem[4] sequence of this reductive perfluoroalkylation of esters via the ketone intermediate was thus proven.

Formation of the *sec*-alcohol can be rationalized by the Meerwein−Pondrov−Valley reduction of the ketone intermediate with isopropoxide. Indeed, treatment of the ketone with the perfluoroalkyl titanate-type reagent gave the *sec*-alcohol (Scheme 2).[13,14]

Several esters were then investigated (Table 1). Other perfluoroalkyl groups such as C_3F_7 and C_6F_{13} could also be introduced into the reductive perfluoroalkylation products in high yields (76 and 87%, respectively) (entries 2 and 3). Even when R^2 is a sterically demanding phenyl group, the tandem product was also obtained in good yield (88%) (entry 4). With electron withdrawing or donating groups (4-CF_3 and 4-OMe), the reductive perfluoroalkylation products were formed in high yields (84% and 72%) (entries 5 and 6). In the case of sterically demanding 1- and 2-naphthyl groups, the reductive perfluoroalkylation products were also obtained in excellent yields (94% and 99%) (entries 7 and 8). α,β-Unsaturated ester substrate (R^1 = PhCH═CH) also provided the 1,2-reductive perfluoroalkylation product in 73% yield, without formation of the 1,4-product (entry 9). Even in the case of enolizable esters bearing α-protons (Bn, n-C_7H_{15}), the reductive perfluoro-

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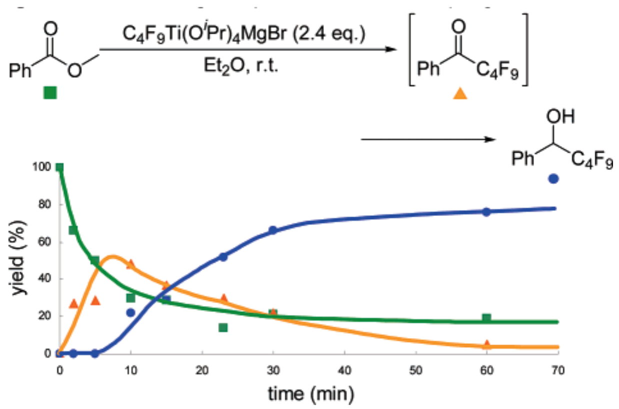


Figure 2. The change of products with time progress.

Scheme 2

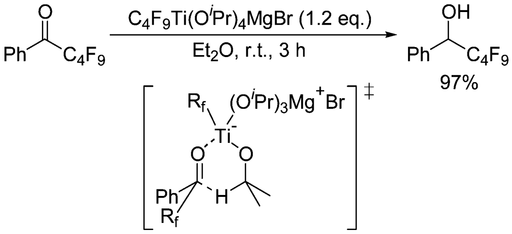
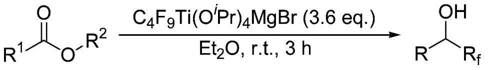


Table 1. Tandem Reductive Perfluoroalkylation of Esters.



entry	R^1	R^2	R_f	yield [%][a]
1	Ph-	Me	C_4F_9	quant[b]
2	Ph-	Me	C_3F_7	76
3	Ph-	Me	C_6F_{13}	87
4	Ph-	Ph	C_4F_9	88[b]
5	4-CF_3-C_4H_4-	Me	C_4F_9	84
6	4-MeO-C_4H_4-	Me	C_4F_9	72
7[c]	1-Naph-	Me	C_4F_9	94
8	2-Naph-	Me	C_4F_9	99
9	(*E*) -PhCH=CH-	Me	C_4F_9	73
10[c]	Bn	Me	C_4F_9	41
11[c]	$^nC_7H_{15}$	Me	C_4F_9	51

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Reaction run using 6.0 equiv of $C_4F_9Ti(O^iPr)_4MgBr$ for 20 h.

alkylation products were obtained though in moderate yields (41% and 51%, respectively) (entries 10 and 11).

We have reported the generation of *stable* perfluoroalkyl titanate-type reagents and the new type of reaction, tandem reductive perfluoroalkylation of esters to give fluoroalkyl *sec*-alcohols. Further application to the "enantioselective" synthesis could provide highly enantio-enriched organofluorine compounds with high physiological activity and remarkable physical properties.

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Supporting Information Available: Complete ref 6; detailed experimental procedure; Cartesian coordinates of the calculation model. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) When aluminium tri(iso-propoxide) was used for the reaction of perfluoroalkyl metal-ate reagent with aldehyde, no perfluoroalkylation took place.

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