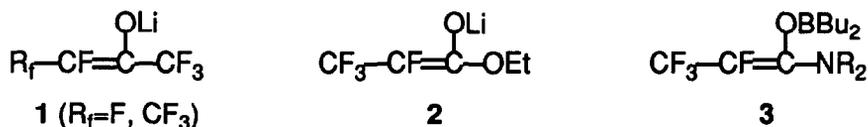


**PERFLUORO-ENOLATE CHEMISTRY:
AN "ELECTROPHILE-COEXISTING" PROCEDURE FOR CARBON-CARBON BOND
FORMING REACTIONS WITH AN ESTER LITHIUM F-ENOLATE**

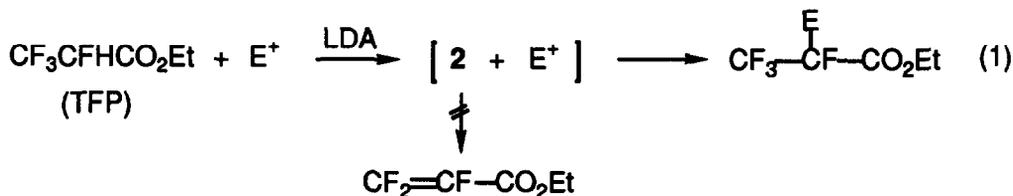
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Summary: A novel "electrophile-coexisting" procedure is developed for effecting aldol reactions and Michael additions with the lithium *F*-enolate of ethyl tetrafluoropropionate without appreciable occurrence of defluorination from the *F*-enolate.

The chemistry of perfluorinated enolates (*F*-enolates) has currently attracted increasing interest from the standpoint of both enolate chemistry and organofluorine synthesis.¹ Recently we have reported the facile, selective generation of ketone *F*-enolates of type 1 and their unique reactivities.^{2,3} In a continuation of these studies, we were intrigued by the synthetic utility of the ester lithium *F*-enolate (2) which undoubtedly raises a serious problem associated with its great instability due to the easy loss of the β -fluorine.⁴ Ishihara and co-workers have recently reported a good solution to this problem by the successful generation and utilization of the boron *F*-enolates of type 3.⁵



Herein we wish to report that the lithium *F*-enolate 2, when generated from the tetrafluoropropionate (TFP)⁶ with lithium diisopropylamide (LDA) *in the coexistence of carbon-electrophiles* (E^+), gave rise to the coupling product in respectable yield without appreciable occurrence of the defluorination (eq 1). Thus, the "electrophile-coexisting" procedure provides a simple, efficient solution to the inherent problem described above.



First, we tested the applicability of the conventional stepwise procedure in the aldol reaction concerned. Thus, TFP was treated with LDA in THF at $-90\text{ }^{\circ}\text{C}$ and then benzaldehyde was added to the enolate solution to afford only 36% yield of the aldol adduct (**4a**), together with a considerable amount of complex byproducts (eq 2). In contrast, similar treatment of a mixture of TFP and benzaldehyde (1.5 equiv) in THF with LDA at $-90\text{ }^{\circ}\text{C} \sim -70\text{ }^{\circ}\text{C}$ was found to afford a much higher yield of **4a** without appreciable contamination by byproducts (eq 3). The present procedure is applicable to a wide variety of carbonyl partners (Table I).⁷ Particularly notable is that the homo-aldol product was not formed in detectable amounts when the carbonyl partners bearing an α -hydrogen were employed. The success of the present procedure is obviously due to the essentially exclusive deprotonation on TFP that is more acidic than any carbonyl partners added. Unfortunately, the diastereoselectivities thus observed were quite low, suggesting that the *E/Z* selectivity in the enolization step is not high.

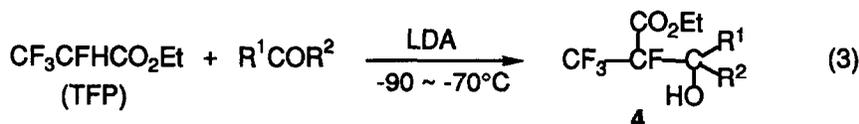
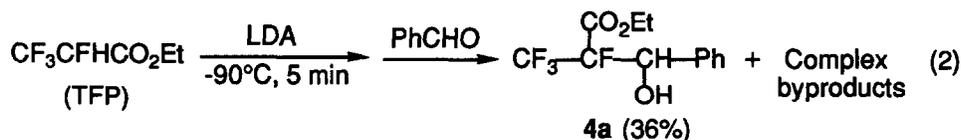


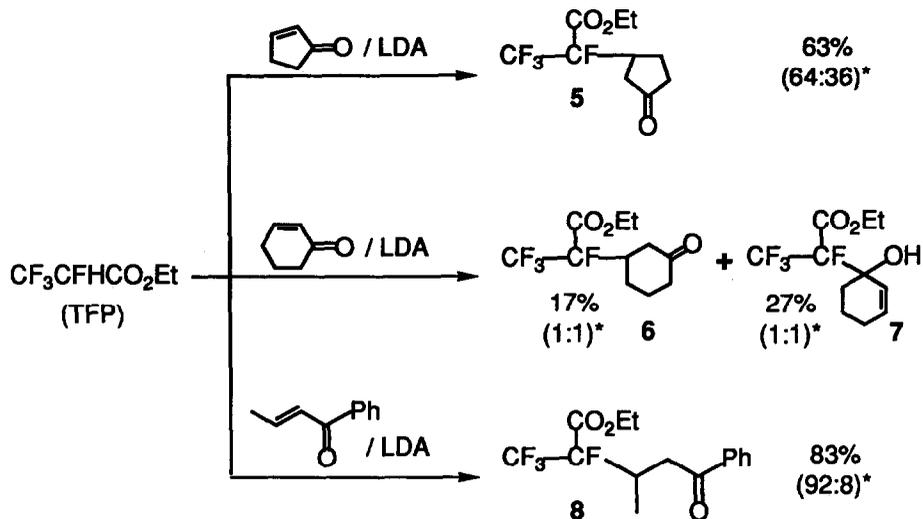
Table I. The "electrophile-coexisting" aldol reactions with TFP

Run	Carbonyl partner	Time	Product	%Yield
1	$\text{R}^1 = \text{Ph}, \text{R}^2 = \text{H}$	2 h	4a	80 (53:47)*
2	$\text{R}^1 = \text{C}_2\text{H}_5, \text{R}^2 = \text{H}$	2 h	4b	73 (52:48)*
3	$\text{R}^1 = \text{CH}=\text{CHCH}_3, \text{R}^2 = \text{H}$	2 h	4c	76 (54:46)*
4	$\text{R}^1 = \text{R}^2 = \text{CH}_3$	6 h	4d	66
5	$\text{R}^1, \text{R}^2 = -(\text{CH}_2)_5-$	6 h	4e	69

* Refers to the diastereomeric ratio determined by ^{19}F NMR (ref 7); the stereochemistry of the diastereomers has not been assigned yet.

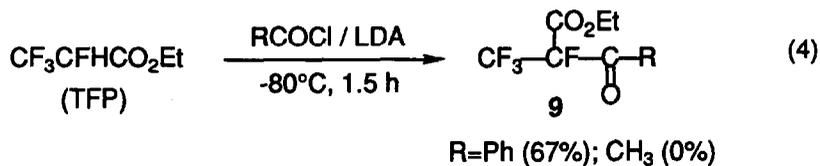
The present procedure is also applicable to the reactions of TFP with α,β -unsaturated ketones which provide exclusively the 1,4-addition product except for the cyclohexenone case where a mixture of the 1,2- and 1,4-addition product was obtained (Scheme I).⁸

Scheme I



^{*} Refers to the diastereomeric ratio determined by ¹⁹F NMR (ref 8); the stereochemistry of the diastereomers has not been assigned yet.

Finally, we also found that the present procedure worked well also for benzoylation of TFP with benzoyl chloride to give the β -keto ester **9** in 67% yield (eq 4), although a similar reaction with acetyl chloride totally failed.



In summary, we have developed a novel "electrophile-coexisting" procedure which allows for the C-C bond forming reactions with the TFP-derived lithium *F*-enolate to afford a variety of α -fluoro- α -trifluoromethyl ester derivatives, classes of compounds which are otherwise difficult to prepare. We are now investigating the applicability of the present procedure to generations and utilizations of different fluorinated enolates.

Acknowledgment

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References and Notes

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7. For the isomers of **4a**: ^{19}F NMR (AcOEt, ex. TFA), δ -4.0 (d, $J=4.7$ Hz, CF_3) and -3.4 (d, $J=6.0$ Hz, CF_3); IR (film), 3496 (OH) and 1758 cm^{-1} (C=O). For the isomers of **4b**: ^{19}F NMR, δ -4.0 (d, $J=5.3$ Hz, CF_3) and -3.0 (d, $J=5.6$ Hz, CF_3); IR, 3432 (OH) and 1756 cm^{-1} (C=O). For the isomers of **4c**: ^{19}F NMR, δ -4.3 (d, $J=5.3$ Hz, CF_3) and -3.7 (d, $J=5.6$ Hz, CF_3); IR, 3450 (OH) and 1758 cm^{-1} (C=O). For **4d**: ^{19}F NMR, δ -5.5 (d, $J=5.5$ Hz, CF_3); IR, 3382 (OH) and 1756 cm^{-1} (C=O). For **4e**: ^{19}F NMR, δ -6.8 (d, $J=5.6$ Hz, CF_3); IR, 3450 (OH) and 1756 cm^{-1} (C=O).
8. For the isomers of **5**: ^{19}F NMR (AcOEt, ex. TFA), δ -2.7 (d, $J=5.3$ Hz, CF_3) and -1.9 (d, $J=5.3$ Hz, CF_3); IR (film), 1750 cm^{-1} (C=O). For the isomers of **6**: ^{19}F NMR, δ -3.9 (d, $J=5.6$ Hz, CF_3) and -4.1 (d, $J=5.6$ Hz, CF_3); IR, 1750 cm^{-1} (C=O). For the isomers of **7**: ^{19}F NMR, δ -6.2 (d, $J=5.8$ Hz, CF_3) and -6.4 (d, $J=5.8$ Hz, CF_3); IR, 3446 (OH) and 1750 cm^{-1} (C=O). For the isomers of **8**: ^{19}F NMR, δ -4.5 (d, $J=4.7$ Hz, CF_3) and -4.1 (d, $J=5.3$ Hz, CF_3); IR, 1754 (CO_2Et) and 1690 cm^{-1} (COPh).
9. ^{19}F NMR (AcOEt, ex. TFA), δ -3.3 (d, $J=5.6$ Hz, CF_3); IR (film), 1706 (CO_2Et) and 1707 cm^{-1} (COPh)

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