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Highly Diastereoselective Michael Addition Reactions of Lithium Enolates to Ethyl 3-Trifluoromethylacrylate

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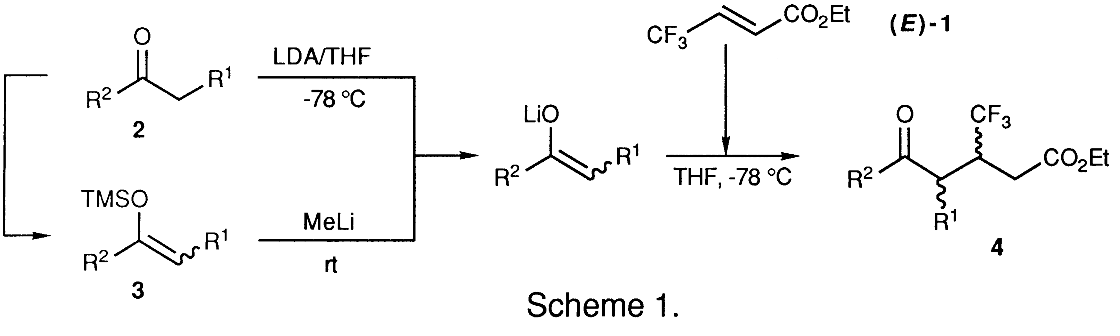
Michael addition reactions of lithium enolates derived from ketones, esters, and amides to ethyl 3-trifluoromethylacrylate were found to proceed smoothly in moderate to excellent chemical yields as well as with a high degree of diastereoselectivity at the newly formed carbon-carbon bond.

Recently, Heathcock[1)] and Yamaguchi[2)] have independently reported the general applicability of enolate-Michael addition reactions[3)] as a tool for the diastereoselective construction of a new carbon-carbon bond to reveal the important relationship between the enolate geometry and the mode of stereoselectivity in products. The nature of this process, on the other hand, was computationally analyzed by Houk[4)] (on its reaction course) and Bernardi[5)] (on its transition state model), and they succeeded in quantitatively explaining the above data. In our continuing effort to develop new pathways for the regio- and stereoselective introduction of a trifluoromethyl (CF_3) group into organic molecules,[6)] we would like to describe the use of ethyl 3-trifluoromethylacrylate **(*E*)-1** as a Michael acceptor, demonstrating the formation of a new carbon-carbon framework in a highly diastereoselective fashion.

Lithium enolates were selected as the nucleophilic species as shown in Table 1 (compare Entries 1 to 3). Among the reaction conditions examined, the Lewis acid-mediated procedure with the corresponding enol silyl ether did not proceed at all (Entry 4) even on the addition of up to 5 equiv. of Lewis acid at ambient temperature.[7)] From the Table 1, the unique characteristics shown by each enolates are noteworthy: thus, the substituent (CH_3 or H for R^1 in Scheme 1) of the enolate affected the reactivity significantly. For ester enolates, a methyl substituent afforded a complex reaction mixture[8)] while the corresponding hydrogen protocol led to the clean formation of the adduct (Entries 9 and 10). On the other hand, the enolate from propiophenone (R^1 : CH_3) demonstrated much higher reactivity as a Michael donor than the one from acetophenone[8)] (R^1 : H, Entries 1 and 5). It is interesting to note that the amide enolates furnished the adducts in good yields irrespective of their



Scheme 1.

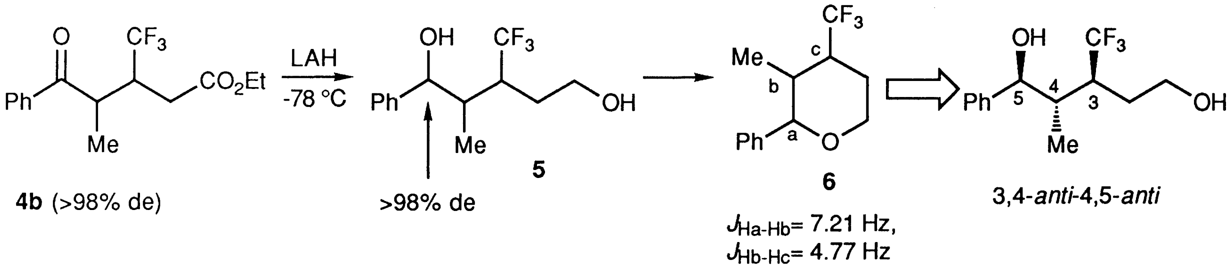
Table 1. Reaction of Ethyl 3-Trifluoromethylacrylate with Various Enolates

Entry	Product	R^1	R^2	Method[a]	Time/h	Yield[b]/%	Diastereoselectivity[e]/% de
1	**4a**	H	Ph	A	1	33 (58)	
2[c]	**4a**	H	Ph	A	1	(14)	
3[c]	**4a**	H	Ph	A	1	(12)	
4[c]	**4a**	H	Ph	B	1	(0)	
5	**4b**	Me	Ph	C	0.5	98	>98 (*anti*)
6	**4c**	Me	Et	C	0.5	97	84 (*anti*)
7[d]	**4c**	Me	Et	C	0.5	97	>98 (*anti*)
8[d]	**4c**	Me	Et	C	0.5	97	96 (*anti*)
9	**4d**	H	OEt	A	1	82	
10	**4e**	Me	OEt	C	1	54	78 (*anti*)
11	**4f**	H	NMe_2	C	1.5	86	
12	**4g**	Me	NMe_2	C	1.5	89	70 (*syn*)

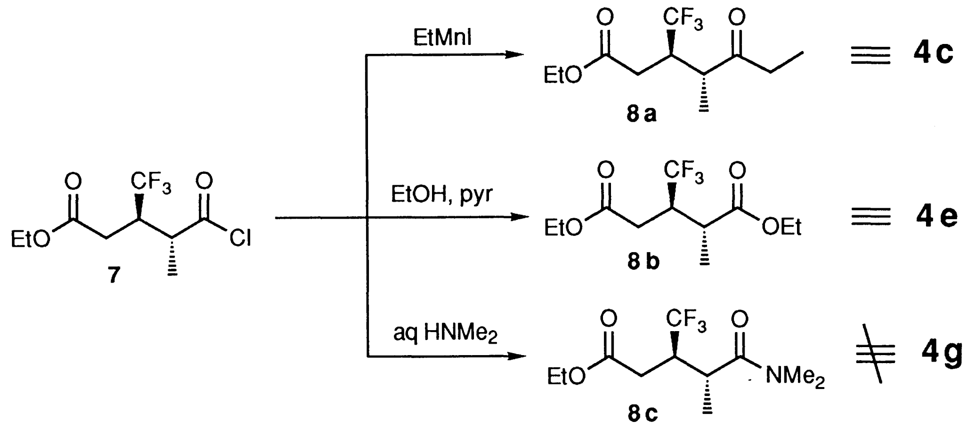
a) A: in THF at -78 °C to rt, B: in CH_2Cl_2 at -78 °C with $BF_3{\bullet}OEt_2$, C: in THF at -78 °C. b) In the parentheses were shown yields determined by ^{19}F NMR. c) Magnesium (MgBr; Entry 2), aluminum ($AlEt_2$; Entry 3), and trimethylsilyl ($SiMe_3$; Entry 4) enolates were employed. d) Lithium enolate prepared from the corresponding enol silyl ether **3** ((*E*):(*Z*) = 10:90; Entry 7) or ((*E*):(*Z*) = 76:24; Entry 8) was employed. e) In the parentheses were shown the relative stereochemistry of the major product.

substitution patterns (Entries 11 and 12). Another important result was obtained from the reaction with diethyl ketone enolate. Thus, the independent treatment of (*E*)-**1** with the enolate from the corresponding enol silyl ether containing (*E*)- or (*Z*)-isomer predominantly led to the almost quantitative formation of the products *with the same sense of diastereoselection. This information strongly suggests that the reaction proceeds via an acyclic transition state at least for the Michael addition with ketone enolates.*

For the clarification of the relative stereochemistry, the Michael adduct from propiophenone **4b** was transformed into the pyran derivative **6**[9] as described in Scheme 2 following the reported procedure.[2a] Close examination of ^1H NMR data of this six-membered cyclic product **6** led us to assign its structure as axial for H^a and H^b, and equatorial for H^c. Compound **4b** was thus proved to have the *anti* relationship between the methyl and CF_3 moieties. On the other hand, chiral acid chloride **7** derived from the optically active Michael adduct with *anti* configuration[10] was independently allowed to react with EtMnI, EtOH, and aqueous dimethylamine



Scheme 2.



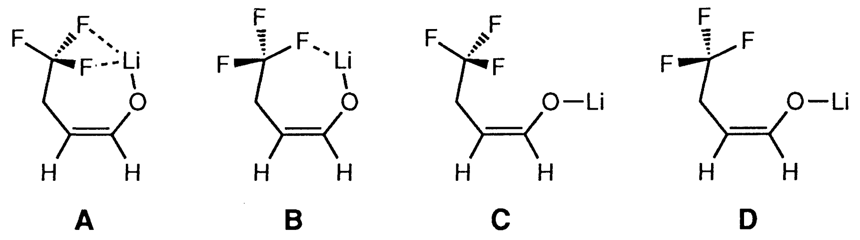
Scheme 3.

giving **8a**, **8b**, and **8c**, respectively, without any evidence of epimerization by ^{19}F NMR in each case. Comparison of their ^{1}H and ^{13}C NMR with those of racemic Michael adducts **4c**, **4e**, and **4g** has led us to correlate their structures (major isomer) as *anti*, *anti*, and *syn*, respectively (Scheme 3).

The results described above showed sharp contrast with the ones when non-fluorinated substrates were employed: thus, i) substituent of enolates did not give any significant effect on its reactivity when esters or amides were employed as a Michael donor,[2b)] ii) ketone enolates usually follow retro-Michael process. While the origin of the first difference was not clear yet, the fact that 3-trifluoromethylacrylate was a good Michael acceptor even towards ketone enolates suggests the existence of some special driving force such as interaction between fluorine and lithium, which was previously postulated[11)] or expected from the computational calculations.[12)] Then, for the verification of this hypothesis, *ab initio* calculations[13)] were carried out on the conformationally isomeric model molecules, **A** to **D**,[15)] to assess the stabilization of **A** by concurrent coordination of two fluorine atoms to lithium with the distance of 2.015 Å (Table 2). The energy differences determined might be overestimated since monomers are assumed, however they unambiguously reveal an interesting property of fluorine atom, which might play an important role in the present Michael addition reactions.

In this article, the efficient diastereoselective construction of new carbon-carbon framework with a CF_3 group by enolate-Michael addition reactions was realized, where fluorine-lithium interaction was revealed to be

Table 2. *Ab initio* calculation of four model conformers



	Relative energy / kcal·mol^{-1}			
	A	B	C	D
6-31G*//3-21G	0.00	10.35	16.47	25.57
3-21G	0.00	11.68	27.01	38.70

a strong driving force for the present reactions by the *ab initio* calculations of the model compounds.

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7) This reaction did not proceed when $\mathrm{TiCl_4}$ or $\mathrm{ZnBr_2}$ were employed as a Lewis acid instead of $\mathrm{BF_3{\cdot}OEt_2}$
8) These products with lower isolated yields (Entries 1 and 10 in Table 1) showed many peaks by ^{19}F NMR, which would be a result of formation of polymerized materials as well as the desired 1,4-addition product.
9) R_f 0.59 (hexane:AcOEt = 5:1). ^{1}H NMR δ 0.99 (3 H, dq, J = 7.32, 1.83 Hz, $\mathrm{C}H_3$), 1.86 (1 H, ddtq, J = 13.31, 8.45, 5.13, 0.85 Hz, $\mathrm{C}H_2\mathrm{CH_2O}$), 2.06 (1 H, dddd, J = 13.95, 6.17, 5.07, 3.94 Hz, $\mathrm{C}H_2\mathrm{CH_2O}$), 2.37 (1 H, ddqq, J = 7.32, 7.21, 4.90, 1.03 Hz, $\mathrm{CH_3C}H$), 2.56 (1 H, dddq, J = 11.05, 6.11, 4.94, 4.88 Hz, $\mathrm{CF_3C}H$), 3.80 (1 H, dddq, J = 11.84, 6.47, 5.13, 1.10 Hz, $\mathrm{C}H_2\mathrm{O}$), 3.82 (1 H, dddq, J = 11.84, 8.55, 3.66, 1.47 Hz, $\mathrm{C}H_2\mathrm{O}$), 4.54 (1 H, dq, J = 7.21, 1.17 Hz, $\mathrm{PhC}H$), 7.36 (5 H, s, Ph). ^{13}C NMR δ 14.65 (q, J = 1.8 Hz, $C\mathrm{H_3}$), 24.05 (q, J = 2.8 Hz, $\mathrm{CH_3}C\mathrm{H}$), 34.04 (s, $C\mathrm{H_2CH_2O}$), 39.88 (q, J = 25.1 Hz, $\mathrm{CF_3}C\mathrm{H}$), 62.59 (s, $C\mathrm{H_2O}$), 80.81 (s, $\mathrm{Ph}C\mathrm{H}$), 127.27 and 128.22 (s each, Ph), 128.53 (q, J = 282.7 Hz, $C\mathrm{F_3}$), 129.01 and 140.56 (s each, Ph). ^{19}F NMR δ 14.7 (d, J = 10.3 Hz). IR (neat) ν 2975, 2950, 2875 $\mathrm{cm^{-1}}$. HRMS calculated for $\mathrm{C_{13}H_{15}F_3O}$ *m/e* 244.1075, found 244.1090.
10) In detail, see the following issue of this paper.
11) Y. Morizawa, A. Yasuda, and K. Uchida, *Tetrahedron Lett.*, **27**, 1833 (1986); C.-P. Qian, T. Nakai, D. A. Dixon, and B. E. Smart, *J. Am. Chem. Soc.*, **112**, 4602 (1991); T. Hanamoto and T. Fuchikami, *J. Org. Chem.*, **55**, 4969 (1990) (for Al-F chelation).
12) Quite recently, lithium-fluorine interaction was suggested by the *ab initio* calculation of the model reaction of 2-fluoropropionaldehyde with lithium hydride. S. S. Wong and M. N. Paddon-Row, *J. Chem. Soc., Chem. Commun.*, **1991**, 327.
13) The calculation was done by Gaussian 88 program$^{14)}$ and geometries were fully optimized with C_s symmetry for the closed shell ground state configuration by the RHF level energy gradient method of the 3-21G basis set. To obtain more accurate relative stability, the RHF energy by the 6-31G* basis set is calculated on the above optimized geometries.
14) M. J. Frisch, M. Head-Gordon, H. B. Schlegel, K. Raghavachari, J. S. Binkley, C. Gonzalez, D. J. Defrees, D. J. Fox, R. A. Whiteside, R. Seeger, C. F. Melius, J. Baker, R. L. Martin, L. R. Kahn, J. J. P. Stewart, E. M. Fluder, S. Topiol, and J. A. Pople, Gaussian, Inc., Pittsburgh, PA.
15) The fact that Michael addition was proved experimentally$^{1)}$ and computationally$^{4)}$ to proceed via *s-cis* conformation for the acceptor to afford (**Z**)-enolate prompted us to calculate only (**Z**)-enolate.

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