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The effect of fluoromethyl groups on the diastereoselectivity in the electrophilic alkylation

Kenji Tamura [a], Takashi Yamazaki [b], Tomoya Kitazume [a,*], Toshio Kubota [c]

[a] *Graduate School of Bioscience and Bioengineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan*
[b] *Department of Applied Chemistry, Tokyo University of Agriculture and Technology, 2-24-16 Naka-machi, Koganei, Tokyo 184-8588, Japan*
[c] *Department of Materials Science, Ibaraki University, 4-12-1 Nakanarusawa, Hitachi, Ibariki 316-8511, Japan*

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Abstract

The effect of fluoromethyl groups on the diastereoselectivity in the electrophilic alkylation is described. In particular, the electrophilic alkylation of enolates with a trifluoromethyl group was proceeded with highly diastereofacial selectivity based on the steric and/or electrostatic effect of substituent with strong electron withdrawing.

Keywords: Diastereoselectivity; Electrophilic alkylation

1. Introduction

The reaction of ester enolate with asymmetric center is very effective as one of constructing methods for the stereocontrolled syntheses of the relative configuration of complicated natural product skeletons with many asymmetric center [1]. Diastereoselective alkylation of the chelation controlled enolates derived from β-hydroxyesters [2], β-aminoesters [3] and/or the tandem generated chiral enolates [4] have been extensively investigated. In this method for non-chelation controlled open-chain enolates, the utilities of 1,3-allylic strain effect [5], Houk model [6], McGarvey model [7] and Cieplak model [8] are mentioned. However, in the field of fluorinated materials [9], those synthetic strategies are not studied in detail except our works with highly diastereoselective syntheses [10]. Our research group have recently revealed highly diastereoselective Ireland-Claisen rearrangements [11]. When a THF solution of ketene silyl acetal was refluxed for 6 h in the presence of a Pd catalyst, the carboxylic acid was produced with 88% *syn* selectivity. Taking into account the fact that the steric size of a CF_3 group is regarded to be between *i*-Pr and *i*-Bu moieties [12], this relatively high *syn* preference should stem from the electrostatic environmental difference between two π-faces. Further, the Michael addition of various enolates toward γ-$CH_{3-n}F_n$-α,β-unsaturated ketones [13], was proven to smoothly furnish the 1,4-adducts with high *si* face selectivities which monotonously decreased by reduction in the number of fluorines. Although the Felkin–Anh model [14] correctly anticipates the present stereochemical outcome only with *E*-acceptors, the hyperconjugative stabilization states by electron donation from the allylic substituents (the Cieplak rule) explains the π-facial preference of both acceptors at least in a qualitative level. These intriguing examples encouraged us to investigate other systems, and we selected electrophilic alkylation reactions using carbonyl compounds with fluoromethyl groups and/or methyl group at their β-positions. In this paper, we would like to describe the experimental results of electrophilic alkylation of open-chain enolates prepared from β-$CH_{3-n}F_n$ substituted esters, which expected to explain a clear correlation between the

* Corresponding author. Tel.: +81 459245754; fax: +81 459245780.
E-mail address: tkitazum@bio.titech.ac.jp (T. Kitazume).

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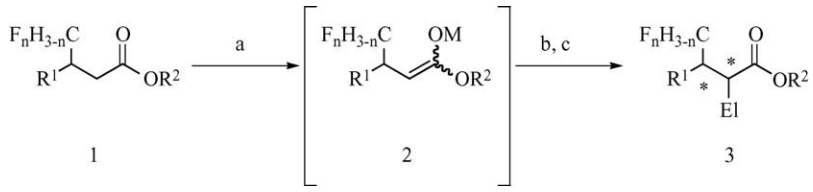


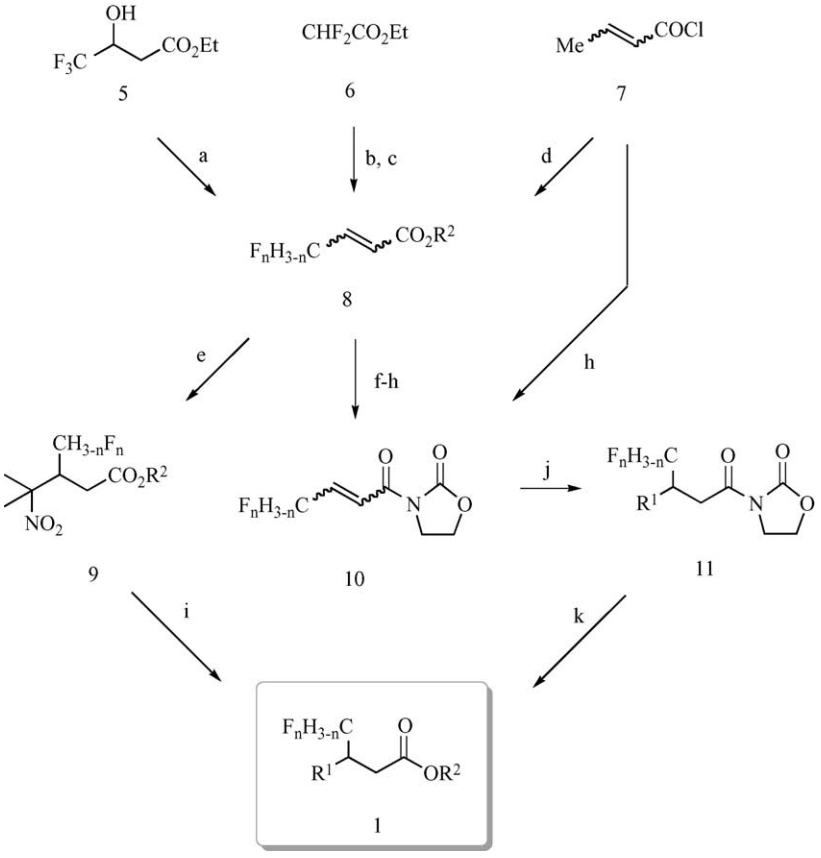
Scheme 1. (a) LHMDS/THF, (b) HMPA, (c) electrophiles.

number of fluorine atoms and diastereofacial selectivities (Scheme 1) [15].

2. Results and discussion

While the preparations of variously β-trifluoromethyl, difluoromethyl, and methyl esters (**1**) have been reported, several improvements in the procedure are noted below. Our synthetic approaches are outlined in Scheme 2. Synthetic strategies for the preparation of esters (**1**) have been based on two methods: (1) the radical denitration (R^1 = *i*-Pr) of compound **9a** prepared from the Michael addition of 2-nitropropane to compound **8a**, (2) the Michael addition of organometallic nucleophiles towards compound **10** (R^1 = alkyl, vinyl, and aryl) [15]. The latter Michael adducts (**11**) were transesterificated according to the method of Evans et al. [16]. Furthermore, difluorinated crotonates (**11b**) were derived from the reduction of compound **11** with LAH followed by way of the Hörner–Wadsworth–Emmons (HWE) reaction [17], and then β-difluorinated esters (**1**) ($n = 2$) were synthesized by the similar way of CF_3 derivatives. Further, non-fluorinated methyl esters (**1**) ($n = 0$) were synthesized from the commercially available material (**7**) in the same manner. The obtained materials are listed in Table 1.

Reactions of compounds **1b** (Entries 1, 2, 4–6, 8) with reactive electrophiles shown in Table 2 proceeded with highly diastereoselectivity (96:4). From the result of employing allyl halides as an electrophile, the corresponding bromide was most suitable (Entries 1–3) in these reaction types. Though the case of ethyl bromide, carbon disulfide,



Scheme 2. (a) TsCl, TEA/CH_2C1_2; (b) LAH/THF; (c) $(EtO)_3P(O)CH_2CO_2R^2$, TEA, LiBr/THF; (d) R^2OH, TEA/THF; (e) Me_2CHNO_2, DBU/MeCN; (f) NaOH/THF-H_2O; (g) $C_6H_4(COCl)_2$; (h) oxazolidin-2-one, *n*-BuLi/THF; (i) *n*-Bu_3SnH, cat. AIBN or BPO/PhH; (j) R^1MgX, $CuBrSMe_2$/THF-Me_2S; (k) R^2OH, *n*-BuLi/THF.

Table 1
The compounds category

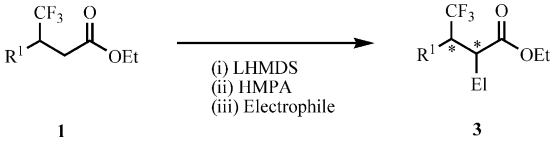
Compounds no.	$CH_{3-n}F_n$	R^1	R^2
8a	CF_3	–	Et
8b	CHF_2	–	Bn
9a	CF_3	*i*-Pr	Et
9b	CHF_2		Bn
10a	CF_3	–	–
10b	CHF_2	–	–
11a	CF_3	*n*-Bu	–
11b		*i*-Pr	–
11e		*t*-Bu	–
11d		Vinyl	–
11e		*p*-Anisyl	–
11f	CHF_2		–
1a	CF_3	*n*-Bu	Bn
1b		*i*-Pr	Et
1c			Bn
1d		*t*-Bu	
1e		Vinyl	
1f		*p*-Anisyl	Et
1g			*i*-Pr
1h			*t*-Bu
1i			Bn
1k	CHF_2	*i*-Pr	
1m		*p*-Anisyl	
1j	CH_3	*i*-Pr	
1l		*p*-Anisyl	

and azo compound also similarly conducted, the yields were moderate (Entries 5, 7, 8). It seems that the yields of adducts (**3**) are dependent on the steric hindrance around the reaction center of electrophiles (Scheme 3).

In the case of ester **1f** (Entries 9–14), it tended to be almost similar with electrophiles, however the ratios of *syn* and *anti* were reversed shown in Table 3. In the case of carbon disulfide as an electrophile, the order in which these type adducts **3be** and **3fe** appears has been reversed with other respectively (Entries 7 and 13). It has considered that the compound with CS_2Me group has occurred epimerization in the formation step from reactive intermediate to the quenched product with methyl iodide (Scheme 3).

In the case of allyl bromide as an electrophile, the result of examining substituent effect is shown in Table 3. The investigation for substituent effect of R^1 was carried out using benzyl esters as a substrate with the same benzyl group as R^2. It tends to improve the selectivity, when the electron-donating and the steric hindrance were increased with increments of substitution degree of alkyl groups as primary, secondary, and tertiary (Entries 1, 3, and 4). Vinyl and *p*-anisyl group with the electron donating according to the resonance effect as a R^1 resulted in also the similar diastereofacial selectivity (Entries 6, 11). On the other hand, the selectivity extremely lowered on decrease in the electron-donating of R^1 with nitro group (Entry 5). It has considered that the possibility of retro-Michael type of β-elimination reaction was present in the same time. Pair of sword relation of these major and minor peaks was tended to be similar priority in most cases of aliphatic substituents such as *n*-butyl, *iso*-propyl, *t*-butyl group, and so on (Entries 1–5). However, it was reversed in the case of R^1 with unsaturated and aromatic substituents such as vinyl and *p*-

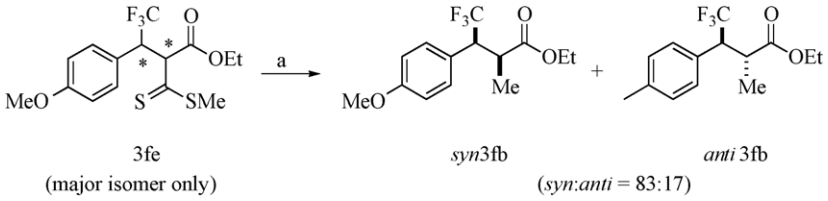
Table 2
Diastereomeric ratios of compounds **3**



1 **3**

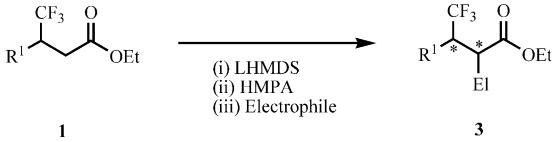
Entry[a]	Substrate	Electrophile	Adduct	Diastereomeric ratio[b]	Yield (%) by ^{19}F NMR[b]			
					syn **3**[c]	*anti* **3**[d]	**1**	Total
1	**1b**	Allyl-I	**3ba**	96:4	61	3	22	86
2		Allyl-Br		96:4	73	3	8	84
3		Allyl-Cl		84:16	19	4	54	77
4		MeI	**3bb**	97:3	72	2	5	79
5		EtBr	**3bc**	96:4	15	1	37	53
6		BnBr	**3bd**	92:8	65	6	13	84
7		(1) CS_2, (2) MeI	**3be**	25:75	20	58	8	86
8		BocN=NBoc	**3bf**	97:3	42	9	12	56
9	**1f**	Allyl-Br	**3fa**	14:86	14	82	4	100
10		MeI	**3fb**	16:84	15	75	5	95
11		EtBr	**3fc**	19:81	5	20	55	80
12		BnBr	**3fd**	10:90	9	82	8	99
13		(1) CS_2, (2) MeI	**3fe**	95:5	88	5	7	100
14		BocN=NBoc	**3ff**	19:81	4	16	4	26[e]

[a] LHMDS (1.5 equiv.), HMPA (7.2 equiv.), and electrophile (3.0 equiv.) were used in THF–hexane (15.5/1, v/v) as a solvent.
[b] The diastereomeric ratios and the yields were determined by ^{19}F NMR integral intensities using $PhCF_3$ as an internal standard.
[c] This isomer shows the peak in the lower magnetic field. The corresponding amides **4ba** and **4fb** derived from **3ba** and **3fb** respectively was *syn* isomer.
[d] This isomer shows the peak in the higher magnetic field. The corresponding amides **4ba** and **4fb** derived from **3ba** and **3fb** respectively was *anti* isomer.
[e] It was given the *syn* **3ff** and *anti* **3ff** together with 21% of other products.



Scheme 3. (a) Raney-Ni W-2/EtOH.

Table 3
Diastereoselectivities of compound **3**



Entry[a]	Substrate	R^1	R^2	Diastereomeric ratio[b]	Yield (%) by ^{19}F NMR[b]			
					syn **3**[c]	*anti* **3**[d]	**1**	Total
1	**1a**	*n*-Bu	Bn	73:27	45	16	21	82
2	**1b**	*i*-Pr	Et	96:4	73	3	8	84
3	**1c**		Bn	>99:<1	36	0	55	91
4	**1d**	*t*-Bu		>99:<1	39	0	61	100
5	**9a**	$Me_2C(NO_2)$	Et	48:52	11	12	29	52
6	**1e**	Vinyl	Bn	23:77	13	44	34	91
7	**1f**	4-$MeOC_6H_4$	Et	14:86	14	82	4	100
8[e]	**1g**		*i*-Pr	19:81	19	79	2	100
9				19:81	18	76	1	95
10	**1h**		*t*-Bu	34:66	1	3	92	96
11	**1i**		Bn	22:78	14	49	26	89

[a] LHMDS (1.5 equiv.), HMPA (7.2 equiv.), and allyl bromide (3.0 equiv.) were used in THF–hexane (15.5/1, v/v) as a solvent.
[b] The diastereomeric ratios and the yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard.
[c] This isomer shows the peak in the lower magnetic field. The corresponding amides **4ba** and **4fb** derived from **4ba** and **4fb** respectively was *syn* isomer.
[d] This isomer shows the peak in the higher magnetic field. The corresponding amides **4ba** and **4fb** derived from **3ba** and **3fb** respectively was *anti* isomer.
[e] 1.75 equiv. of base was used.

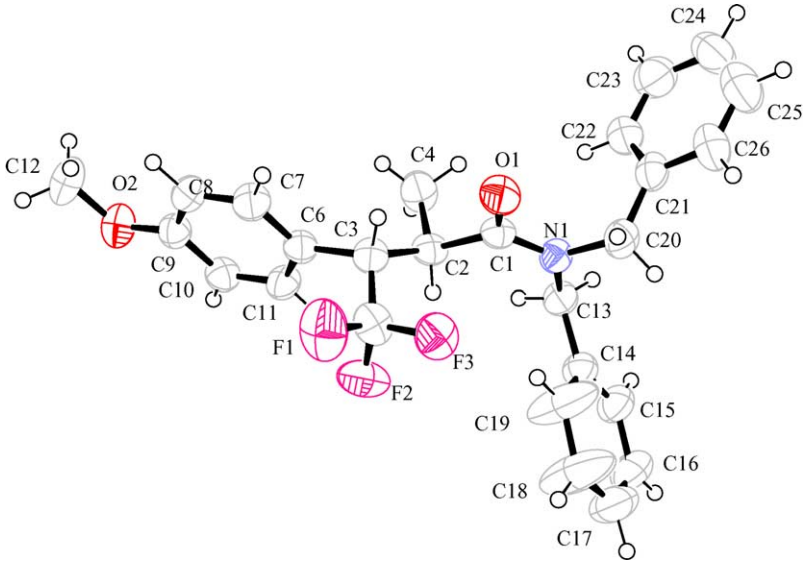
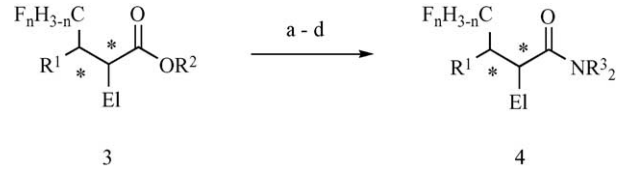


Fig. 1. X-ray structure.



3 4

Scheme 4. (a) NaOH/EtOH-H_2O, (b) $SOCl_2$/PhH, (c) R^3_2NH/THF, (d) recrystallization.

anisyl group (Entries 6–11). It has considered to reverse the order of the peaks of the diastereomers in the case of R^1 group bonded at the sp^2 carbon. The stereochemistry of the corresponding amides (**4**) derived from the major isomer of these adducts **3ba** and/or **3fb** were determined *syn* from **3ba** and *anti* from **3fb** forms by the measurements of X-ray diffraction of these crystal structures (**4ba** [12] and **4fb**; Fig. 1). It was made clear by the result of the structural analysis that the *syn* addition was taken priority in the case of aliphatic substituents such as *iso*-propyl group. On the other hand in the case of aromatic substituents such as *p*-anisyl group in which R^1 has bonded at the sp^2 carbon, the *anti* addition was taken (Scheme 4).

In comparison with an ester substituent R^2 and an adjacency substituent of the trifluoromethyl group R^1, it has found that the substituent effect on the π-face selection of electrophilic addition was small for R^2 (Entries 7–11).

In general, when the number of fluorine atoms on the β-$CH_{3-n}F_n$ group decrease from a CF_3 group to a CHF_2 group, it seems that the electron-withdrawing effect decreases. Based on the effect of fluoromethyl groups existed for β-position as shown in Table 4, we have found that the diastereoselectivity was controlled with the electron-withdrawing effect of β-fluoromethyl group (Entries 3–4 and 9–10). In contrast, the tendency of which diastereofacial selectivity was controlled for the relationship relative steric hindrance between R^1 and methyl group, was shown in the case of methyl group with the electron donating (Entries 1 and 7).

It is possible that the steric and/or electronic effect on the expression of the stereoselectivity in electrophilic reaction is considered to divide into next two models roughly, as shown in Fig. 2. The former is Houk model [6] and McGarvey model [7] and the latter is Cieplak model [8]. In Houk model, it was described as follows. In electrophilic reactions, the most electropositive substituent such as a CF_3 group should be *anti* to maximize electron donation from the high-lying σ_{C-R^1} orbital to the transition state LUMO, which consists of electrophile LUMO mixed with the enolate HOMO. The outside position is best, and the donor avoids the inside position, σ_{C-R^1} overlap with π^* will be negligible. Electronegative group such as a trifluoromethyl group prefers the inside or outside positions. The interaction of $\sigma^*_{C-CF_3}$ with the transition state LUMO is not itself destabilizing, since both orbitals are vacant, but the overlap of $\sigma^*_{C-CF_3}$ with the enolate HOMO will stabilize the latter and decrease its interaction with the electrophile LUMO. In other words, C–CF_3 favors the inside or outside positions to minimize electron withdrawal by $\sigma^*_{C-CF_3}$ from the already electron-deficient transition state. Whether inside or outside is the best location for a CF_3 group depends on the specific dihedral angles as well as the interactions between the attacking electrophile and groups at the inside or outside positions. In the case of a CF_3 group, **TS-1** at outside position is energetically more stable than **TS-2** at inside position. In McGarvey model, it was described as follows. In the event of electrophilic attack, however, the enolate HOMO governs the course of the reaction. In this instance, the π orbital mixes with the highest energy σ orbital, belonging to the substituent that most efficiently participates in hyperconjugative interactions to afford a more reactive MO. In other words, the

Table 4
Preparation and diastereomeric ratio of compound **3**

Entry[a]	Substrate	R^1	R^2	$CH_{3-n}F_n$	Diastereomeric ratio[b]	Yield (%) by ^{19}F NMR[b]			
						syn **3**[c]	*anti* **3**[d]	**1**	Total
1	**1j**	*i*-Pr	Bn	CH_3	90:10	60	7	32	99
2[e,f]					>99:<1	15	0	69	84
3	**1k**			CHF_2	53:47	22	20	28	70
4	**1c**			CF_3	>99:<1	36	0	55	91
5	**1b**		Et		96:4	73	3	8	84
6					85:15	7	1	60	68
7	**1l**	4-$MeOC_6H_4$	Bn	CH_3	48:52	44	48	4	96
8[e]					65:35	39	21	27	87
9	**1m**			CHF_2	52:48	30	27	0	57
10	**1i**			CF_3	22:78	14	49	26	89
11	**1f**		Et		14:86	14	82	4	100
12[e]					23:77	19	60	21	100

[a] LHMDS (1.5 equiv.), HMPA (7.2 equiv.), and allyl bromide (3.0 equiv.) were used in THF–hexane (15.5/1, v/v) as a solvent.
[b] The diastereomeric ratios were determined by ^1H or ^{19}F NMR using $MeNO_2$ or $PhCF_3$ as an internal standard.
[c] This isomer shows the peak in the lower magnetic field. The corresponding amides **4ba** and **4fb** derived from **4ba** and **4fb** respectively was *syn* isomer.
[d] This isomer shows the peak in the higher magnetic field. The corresponding amides **4ba** and **4fb** derived from **3ba** and **3fb** respectively was *anti* isomer.
[e] In the absent of HMPA.
[f] See Ref. [1].

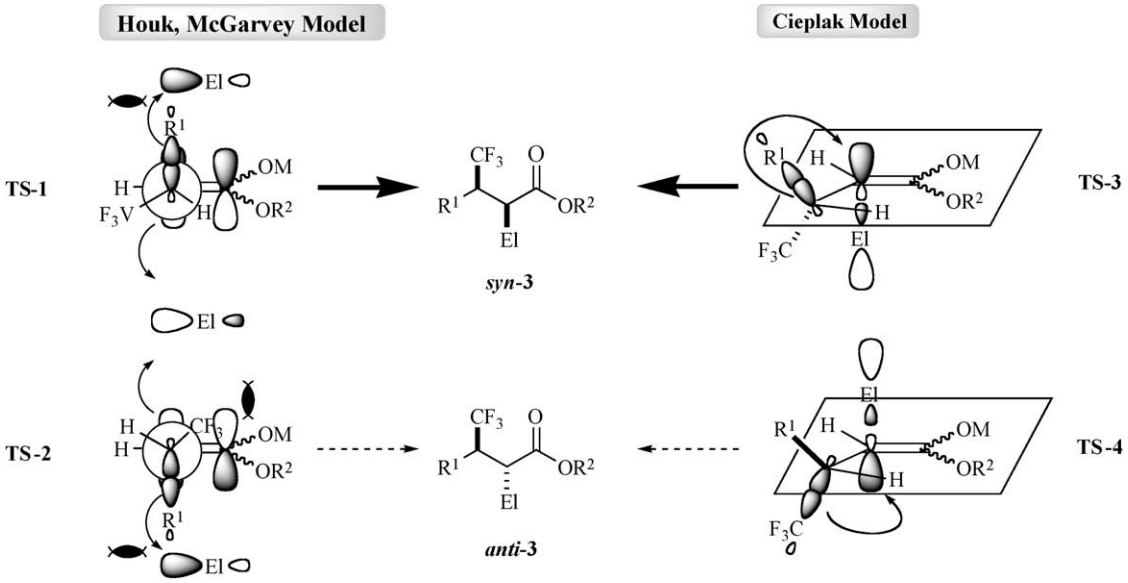


Fig. 2. The steric and/or electronic effect for the stereoselectivity.

energy level of the enolate HOMO was risen and activated by σ–π interaction. McGarvey model is same for appearance like Houk model. The enolate attacks an electrophile from the transition state of **TS-1** and **TS-2**, when this is applied to this reaction. According to the steric effect of trifluoromethyl group, priority is given to the route from **TS-1**. On the other hand, in Cieplak model [6], the interaction between antibonding orbital σ^* of newly forming σ-bond and bonding orbital σ of covalent bond, which linkage with the neighbor carbon stabilizes transition state. It is skillfully explained to react from opposite side of electron-donating group of allyl position to an electrophile. Though the transition states of **TS-3** and **TS-4** are considered, the enolate reacts with an electrophile by the route from **TS-3**, when the character of the electron donating is considered, ***syn*-3** was formed with precedence. The π electrons of the β-alkylated enolate **2b**, substituent R^1 with alkyl group such as *iso*-propyl, were attacked *syn* selective. As described above, this diastereoselectivity was explained in some advocated models shown in Fig. 3. As this type of enolate **2b** was very stable and low reactivity, enolate **2b** was possible to react with an electrophile via the route from the ideal transition states **TS-1** or **TS-3** by destabilization with addition of HMPA (Entries 1–2 and 5–6 respectively in Table 4). On the other, the attacking direction of π-face of β-arylated such as *p*-anisyl enolate **2f** was changed to *anti* selective in that π-

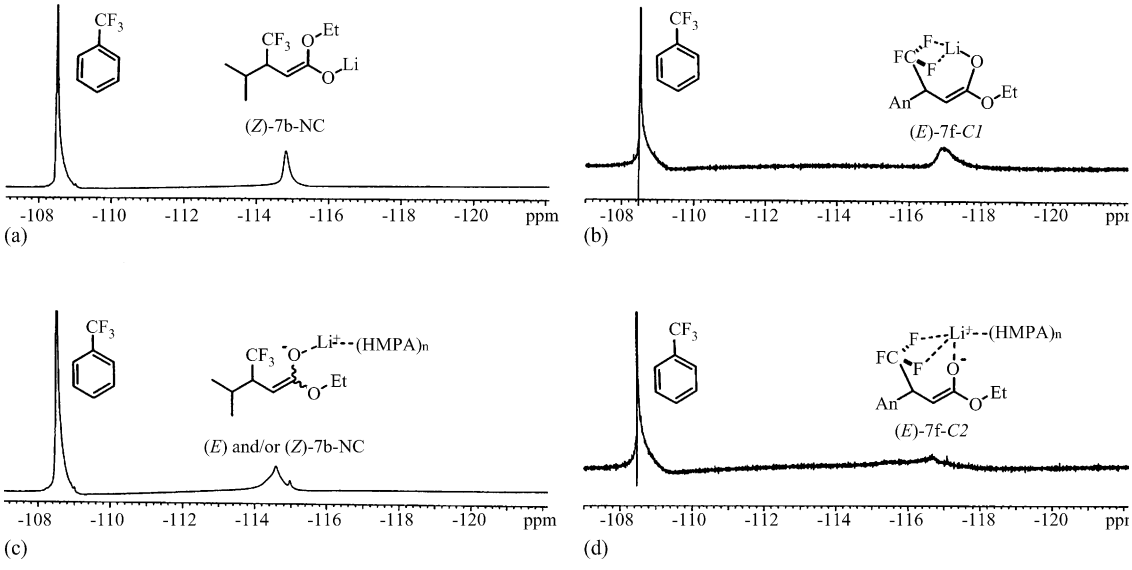
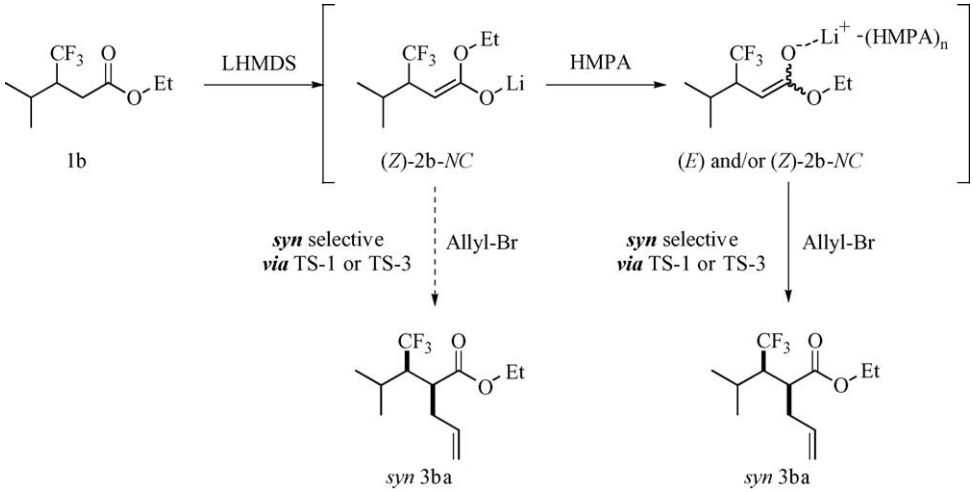
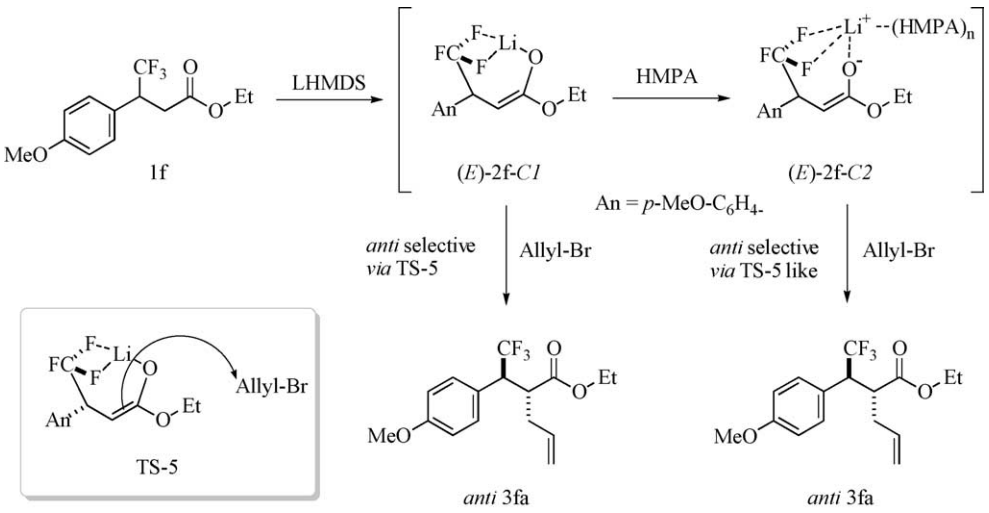


Fig. 3. ^{19}F NMR spectra of this electrophilic addition reaction at −78 °C in THF-d_8 using $PhCF_3$ as an internal standard: (a) **6b** + LHMDS; (b) (a) + HMPA; (c) **6f** + LHMDS; (d) (c) + HMPA.



Scheme 5. The structure of enolate **2b** and the π-facial selection.

face selection of β-alkylated enolate **2a** was dominant *syn* direction. As this type of enolate **2f** was unstable than **2b**, the enolate **2f** was possible to react with an electrophile smoothly without destabilization of addition of HMPA (Entries 7–8 and 11–12 respectively in Table 4) via the way of the ideal transition states **TS-1** or **TS-3**. This result was not explained in some advocated models shown in Fig. 3. The π-face selections of these electrophilic alkylation reactions were decided by both factors of steric hindrance and electronic property toward β-$CH_{3-n}F_n$ group and β-substituent R^1 group. The limitation range of some models in Fig. 2 has been exceeded in the case of β-CF_3-β-(*p*-anisyl)enolate **2f**. It seems to be able to not explain, if other factors are not considered either. From two results of ^{19}F NMR measurement at low temperature, we propose next two models towards the structure and π-facial selection of these enolates **2b** (Fig. 3(a) and (b) and Scheme 5) and **2f** (Fig. 3(c) and (d) and Scheme 6). The NMR study was 0.07 mmol scale experiment of this electrophilic addition reaction of **2b** or **2f** with allyl bromide in a NMR tube at −78 °C. In this experiment, THF-d_8 was used instead of THF. As shown in Fig. 3(a), a sharp brooding peak of (*Z*)-**2b**-NC and (b) two brooding peaks of (*E*) and/or (*Z*)-**2b**-NC, it is clear that the enolate **2b** was open-chain structure, therefore enolate **2b** was possible to react with allyl bromide via the route from the ideal transition states **TS-1** or **TS-3** (Scheme 5). This type π-facial selection was *syn* selective. On the other hand, as shown in Fig. 3(c), a brooding peak of (*E*)-**2f**-C1 and (d) a tailing peak of (*E*)-**2f**-C2, it is clear that the enolate **2f** was chelation structure. One possibility is that the lithium atom was chelated to fluorine atom of trifluoromethyl group as shown in Scheme 6. Therefore, the enolate **2f** was possible to react with allyl bromide via the route from **TS-5** (Scheme 6). Then, the π-electrons of the enolate **2f** attack on the less hindered side. This type π-facial selection was *anti* selective.



Scheme 6. The structure of enolate **2f** and the π-facial selection.

3. Conclusion

In conclusion, we have succeeded in the highly diastereoselective electrophilic alkylation reactions of β-fluoromethylated-β-substituted esters (**1**). We have clarified that the effects of β-fluoromethyl group and β-substituents R^1 group. In particular, we found that the π-face selections of enolates (**2**) derived from β-trifluoromethylesters (**1**) were reversed by β-substituents R^1 group.

4. Experimental section

4.1. General

^{1}H NMR spectra were recorded with Varian VXR-500 or VXR-300 (500 or 300 MHz respectively), and ^{13}C NMR spectra were recorded with a Varian VXR-300 (75 MHz). ^{19}F NMR spectra were recorded with Varian VXR-500 or VXR-300 (470 or 282 MHz respectively). In the ^{1}H, ^{13}C, and ^{19}F NMR spectra, chemical shifts are expressed in δ (ppm) downfield from TMS, and C_6F_6 respectively in $CDCl_3$. Infrared (IR) spectra were obtained on Perkin-Elmer FT-IR 1650 or JASCO FT/IR-230 spectrometer.

4.2. Ethyl 4,4,4-trifluoro-2-butenoate (*8a*)

This compound was prepared by a modification of the procedure of Roberts et al. [18]. To a mixture of ethyl 4,4,4-trifluoro-3-hydroxy-butanoate (**5**) (100 g, 537 mmol) and 4-toluenesulfonyl chloride (56 g, 591 mmol) in anhydrous dichloromethane (300 ml) was added dropwise triethylamine (150 ml, 537 mmol) under an atmosphere of argon at 0 °C. The reaction mixture was stirred and warmed to room temperature for 5 h. The deposition material which separated was removed by filtration. The filtrate washed with dichloromethane (3× 200 ml) and 3N HCl (300 ml) and dried over anhydrous magnesium sulfate. The dichloromethane was removed from the combined filtrate and washings by distillation throughout a rectifying column, and the corresponding crotonate **8a** was isolated as a colorless liquid by distillation (81 g, yield 90%): b.p. 110–112 °C. ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, t, J = 7.05 Hz), 4.28 (2H, q, J = 6.90 Hz), 6.49 (1H, qd, J = 1.80, 15.60 Hz), 6.78 (1H, qd, J = 6.60, 12.00 Hz). ^{13}C NMR ($CDCl_3$): δ 13.80, 61.46, 121.85 (q, J = 269.41 Hz), 128.68 (q, J = 6.26 Hz), 130.92 (q, J = 35.54 Hz), 163.52. ^{19}F NMR ($CDCl_3$): δ 66.77 (dd, J = 2.26, 6.49 Hz). IR (neat): γ 1670 (C=O) cm^{-1}. Anal. Calcd for $C_6H_7O_2F_3$: C, 42.87; H, 4.20. Found: C, 42.90; H, 4.18.

4.3. Benzyl 4,4-diifluoro-2-butenoate (*8b*)

This compound was prepared in the same procedure with the Hörner–Wadsworth–Emmons (HWE) reaction [17]. Yield 72%. ^{1}H NMR ($CDCl_3$): δ 5.21 (2H, s), 6.18 (1H, ddt, J = 1.20, 4.05, 54.92 Hz), 6.30 (1H, dtd, J = 0.90, 3.00, 15.90 Hz), 6.83 (1H, dtd, J = 4.20, 10.20, 15.90 Hz), 7.29–7.43 (Ar–H, m). ^{13}C NMR ($CDCl_3$): δ 66.88, 112.20 (t, J = 236.73 Hz), 126.77 (t, J = 10.57 Hz), 128.11, 128.26, 128.38, 134.99, 136.59 (t, J = 24.07 Hz), 164.08. ^{19}F NMR ($CDCl_3$): δ 117.1 (ddd, J = 2.54, 10.45, 54.92 Hz). IR (neat): γ 1661 (C=O) cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_2F_2$: C, 62.26; H, 4.75. Found: C, 61.80; H, 5.19.

4.4. Ethyl 3-(trifluoromethyl)-4-methyl-4-nitropentanoate (*9a*)

To a solution of corresponding β-fluoromethylcrotonate (**8a**) (5.00 g, 29.7 mmol) and 2-nitropropane (2.67 ml, 29.7 mmol) in anhydrous acetonitrile (50 ml) was added 1,8-diazabicyclo[5,4,0]-7-undecene (4.45 ml, 29.7 mmol) under an atmosphere of argon at room temperature. After 6 h stirring at room temperature, 3N HCl (30 ml) was added to the reaction mixture which was evaporated. The residue was extracted with diethyl ether (3× 30 ml), and dried over anhydrous magnesium sulfate and solvent was removed. The resulting crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 2:1) to give the desired Michael adduct **9a** as a yellow liquid (7.65 g, yield quant).

^{1}H NMR ($CDCl_3$): δ 1.29 (3H, t, J = 7.20 Hz), 1.61 (3H, s), 1.70 (3H, s), 2.38 (1H, dd, J = 5.25, 17.25 Hz), 2.68 (1H, dd, J = 6.60, 17.40 Hz), 4.04 (1H, ddq, J = 5.10, 6.60, 9.30 Hz), 4.21 (2H, q, J = 7.20 Hz). ^{13}C NMR ($CDCl_3$): δ 14.05, 23.26, 24.66, 30.86, 46.39 (q, J = 26.3 Hz), 61.66, 87.78, 125.68 (q, J = 280.9 Hz), 169.45. ^{19}F NMR ($CDCl_3$): δ 67.1 (d, J = 9.30 Hz). IR (neat): γ 1741 (C=O), 1553 (NO_2) cm^{-1}. Anal. Calcd for $C_9H_{14}NO_2F_3$: C, 42.03; H, 5.49; N, 5.45. Found: C, 41.68; H, 5.61; N, 5.34.

4.5. Benzyl 3-(difluoromethyl)-4-methyl-4-nitropentanoate (*9b*)

Yield 93%. ^{1}H NMR ($CDCl_3$): δ 1.58 (3H, s), 1.64 (3H, s), 2.39 (1H, dd, J = 5.70, 17.11 Hz), 2.69 (1H, dd, J = 7.50, 17.11 Hz), 3.42 (1H, dsextd, J = 3.00, 7.50, 4.50 Hz), 5.15 (2H, s), 5.96 (1H, dt, J = 3.00, 54.92 Hz), 7.32–7.40 (Ar–H, m). ^{13}C NMR ($CDCl_3$): δ 24.01, 24.49, 29.26 (t, J = 4.30 Hz), 46.06 (t, J = 19.47 Hz), 67.05, 88.14, 115.19 (t, J = 243.68 Hz), 128.10, 128.22, 128.36, 134.99, 170.23. ^{19}F NMR ($CDCl_3$): δ 123.4 (ddd, J = 18.92, 55.90, 290.81 Hz), 119.6 (ddd, J = 12.71, 54.35, 290.24 Hz). IR (neat): γ 1735 (C=O), 1546 (NO_2) cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4F_2$: C, 55.81; H, 5.69; N, 4.65. Found: C, 55.87; H, 6.09; N, 4.60.

4.6. 3-[(E)-4,4,4-Trifluorobut-2-enoyl]oxazolidin-2-one (*10a*)

These compounds were prepared from the corresponding crotonates **8a** or **8b** in the same procedure by hydrolysis

[19], chlorination [20] and condensation. These yields were isolated yield in the condensation step. Yield 70%. m.p. 82–85 °C. ^{1}H NMR ($CDCl_3$): δ 4.11 (2H, t, J = 8.10 Hz), 4.49 (2H, t, J = 7.95 Hz), 6.88 (1H, qd, J = 6.60, 15.60 Hz), 7.89 (1H, qd, J = 2.10, 15.60 Hz). ^{13}C NMR ($CDCl_3$): δ 42.45, 62.30, 121.84 (q, J = 269.84 Hz), 126.93 (q, J = 6.34 Hz), 131.57 (q, J = 35.56 Hz), 152.78, 162.24. ^{19}F NMR ($CDCl_3$): δ 66.5 (dd, J = 1.83, 6.91 Hz). IR (KBr): γ 1693 (C=O) cm^{-1}. Anal. Calcd for $C_7H_6NO_3F_3$: C, 40.20; H, 2.89; N, 6.70. Found: C, 40.23; H, 2.76; N, 6.40.

4.7. 3-[(E)-4,4-Difluorobut-2-enoyl]oxazolidin-2-one (**10b**)

Yield 50%. m.p. 69–72 °C. ^{1}H NMR ($CDCl_3$): δ 4.10 (2H, t, J = 8.40 Hz), 4.48 (2H, t, J = 7.80 Hz), 6.31 (1H, dt, J = 4.50, 54.92 Hz), 6.91 (1H, dtd, J = 4.50, 9.90, 15.60 Hz), 7.67 (1H, td, J = 2.40, 15.60 Hz). ^{13}C NMR ($CDCl_3$): δ 42.36, 62.21, 112.51 (t, J = 235.90 Hz), 125.63 (t, J = 10.94 Hz), 136.62 (t, J = 24.60 Hz), 152.94, 162.84. ^{19}F NMR ($CDCl_3$): δ 116.15 (ddd, J = 3.47, 9.88, 54.92 Hz). IR (KBr): γ 1662 (C=O) cm^{-1}. Anal. Calcd for $C_7H_7NO_3F_2$: C, 43.99; H, 3.69; N, 7.33. Found: C, 44.12; H, 3.62; N, 7.31.

4.8. 3-[3-(Trifluoromethyl)heptanoyl]oxazolidin-2-one (**11a**)

These compounds were prepared in the same procedure with the Michael addition of organocopper species [15]. Yield 36%. m.p. 39–40 °C. ^{1}H NMR ($CDCl_3$): δ 0.89 (3H, t, J = 6.90 Hz), 1.17–1.48 (6H, m), 2.91 (1H, dsept, J = 6.90, 11.25 Hz), 2.39 (1H, dd, J = 6.00, 16.50 Hz), 2.99 (1H, dd, J = 6.30, 18.30 Hz), 3.26 (1H, dsept, J = 5.40, 18.15 Hz), 4.03 (2H, t, J = 8.10 Hz), 4.44 (2H, t, J = 7.80 Hz). ^{13}C NMR ($CDCl_3$): δ 13.76, 22.52, 28.14, 28.69, 33.99, 38.26 (q, J = 26.11 Hz), 42.51, 62.09, 127.70 (q, J = 279.47 Hz), 153.16, 170.25. ^{19}F NMR ($CDCl_3$): δ 72.2 (d, J = 8.47 Hz). IR (neat): γ 1704 (C=O) cm^{-1}. Anal. Calcd for $C_{11}H_{16}NO_3F_3$: C, 49.44; H, 6.03; N, 5.24. Found: C, 49.87; H, 5.61; N, 4.78.

4.9. 3-[3-(Trifluoromethyl)-4-methylpentanoyl]-oxazolidin-2-one (**11b**)

Yield 24%. m.p. 48–49 °C. ^{1}H NMR ($CDCl_3$): δ 0.98 (6H, d, J = 6.90 Hz), 2.10 (1H, dsept, J = 3.50, 7.00 Hz), 2.91 (1H, dsept, J = 3.75, 5.00 Hz), 2.97 (1H, dd, J = 4.50, 17.85 Hz), 3.21 (1H, dd, J = 6.60, 18.45 Hz), 4.02 (2H, t, J = 7.50 Hz), 4.43 (2H, t, J = 7.80 Hz). ^{13}C NMR ($CDCl_3$): δ 18.70, 20.17, 26.93 (q, J = 1.66 Hz), 30.47 (q, J = 2.67 Hz), 43.06 (q, J = 24.60 Hz), 62.06, 127.71 (q, J = 280.60 Hz), 153.19, 170.58. ^{19}F NMR ($CDCl_3$): δ 68.8 (d, J = 9.60 Hz). IR (KBr): γ 1699 (C=O) cm^{-1}. Anal. Calcd for $C_{10}H_{14}NO_3F_3$: C, 47.43; H, 5.57; N, 5.53. Found: C, 47.77; H, 5.29; N, 5.36.

4.10. 3-[3-(Trifluoromethyl)-4,4-dimethylpentanoyl]-oxazolidin-2-one (**11c**)

Yield 86%. m.p. 96 °C. ^{1}H NMR ($CDCl_3$): δ 1.04 (9H, s), 2.96 (1H, dd, J = 3.60, 18.15 Hz), 2.95–3.16 (1H, m), 3.31 (1H, dd, J = 7.50, 19.35 Hz), 4.04 (2H, t, J = 9.00 Hz), 4.44 (2H, t, J = 8.40 Hz). ^{13}C NMR ($CDCl_3$): δ 14.17, 28.08, 31.68, 42.68, 46.51 (q, J = 23.47 Hz), 62.08, 127.95 (q, J = 282.03 Hz), 153.25, 170.97. ^{19}F NMR ($CDCl_3$): δ 65.0 (d, J = 9.60 Hz). IR (KBr): γ 1699 (C=O) cm^{-1}. Anal. Calcd for $C_{11}H_{16}NO_3F_3$: C, 49.44; H, 6.03; N, 5.24. Found: C, 49.57; H, 6.48; N, 5.11.

4.11. 3-[3-(Trifluoromethyl)pent-4-enoyl]oxazolidin-2-one (**11d**)

Yield 83%. m.p. 47–48 °C. ^{1}H NMR ($CDCl_3$): δ 3.24 (1H, dd, J = 4.65, 17.55 Hz), 3.36 (1H, dd, J = 8.85, 17.25 Hz), 3.55 (1H, dsext, J = 4.58, 8.85 Hz), 4.03 (2H, t, J = 8.10 Hz), 4.45 (2H, t, J = 7.95 Hz), 5.34 (1H, d, J = 9.90 Hz), 5.38 (1H, d, J = 15.6 Hz), 5.73 (1H, td, J = 9.90 17.85 Hz). ^{13}C NMR ($CDCl_3$): δ 33.82, 42.39, 43.27 (q, J = 27.56 Hz), 62.10, 121.49, 126.07 (q, J = 278.97 Hz), 130.05, 153.12, 169.19. ^{19}F NMR ($CDCl_3$): δ 72.3 (d, J = 8.74 Hz). IR (neat): γ 1706 (C=O) cm^{-1}. Anal. Calcd for $C_9H_{10}NO_3F_3$: C, 45.58; H, 4.25; N, 5.91. Found: C, 45.84; H, 4.47; N, 5.87.

4.12. 3-[4,4,4-Trifluoro-3-(4-methoxy-phenyl)butyryl]-oxazolidin-2-one (**11e**)

Yield quant. ^{1}H NMR ($CDCl_3$): δ 3.47 (1H, dd, J = 4.25, 18.25 Hz), 3.76 (1H, dd, J = 10.00, 18.00 Hz), 3.80 (3H, s), 3.91 (1H, td, J = 7.25, 9.25 Hz), 3.97 (1H, td, J = 7.25, 9.25 Hz), 4.04 (1H, dquint, J = 4.00, 9.50 Hz), 4.37 (1H, td, J = 7.00, 9.25 Hz), 4.41 (1H, td, J = 6.50, 9.50 Hz), 6.87–6.90 (2H, dm, J = 9.00 Hz), 7.30 (2H, d, J = 8.50 Hz). ^{13}C NMR ($CDCl_3$): δ 35.12 (q, J = 2.04 Hz), 42.34, 44.22 (q, J = 27.78 Hz), 55.11, 62.07, 113.83, 125.71 (q, J = 1.96 Hz), 126.32 (q, J = 279.27 Hz), 129.92, 153.13, 159.23, 169.24. ^{19}F NMR ($CDCl_3$): δ 71.4 (d, J = 8.93 Hz). IR (neat): γ 1705, 1614 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{14}NO_4F_3$: C, 53.00; H, 4.45; N, 4.41. Found: C, 52.88; H, 4.41; N, 4.31.

4.13. 3-[4,4-Difluoro-3-(4-methoxy-phenyl)butyryl]-oxazolidin-2-one (**11f**)

Yield 96%. ^{1}H NMR ($CDCl_3$): δ 3.43 (1H, dd, J = 4.80, 17.56 Hz), 3.55 (1H, dd, J = 8.10, 17.71 Hz), 3.63–3.78 (1H, m), 3.78 (3H, s), 3.93 (2H, td, J = 9.30, 16.20 Hz), 4.36 (2H, td, J = 7.20, 22.21 Hz), 5.92 (1H, dt, J = 2.70, 55.97 Hz), 6.90–6.84 (2H, dm, J = 6.90 Hz), 7.20–7.27 (2H, dm, J = 7.80 Hz). ^{13}C NMR ($CDCl_3$): δ 34.49 (t, J = 4.30 Hz), 42.40, 44.22 (t, J = 20.30 Hz), 55.13, 62.02, 113.91, 116.91 (t, J = 244.43 Hz), 127.67, 129.72, 153.19, 158.92, 170.30.

^{19}F NMR ($CDCl_3$): δ 123.7 (ddd, J = 17.22, 56.75, 284.7 Hz), 120.6 (ddd, J = 14.68, 56.75, 287.4 Hz). IR (neat): γ 1699 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_4F_2$: C, 56.19; H, 5.05; N, 4.68. Found: C, 55.87; H, 5.30; N, 4.66.

4.14. Ethyl 3-(trifluoromethyl)-4-methylpentanoate (*1b*)

To a solution of corresponding nitro compound **9a** (7.00 g, 27.2 mmol) and tributyltin hydride (7.32 ml, 27.2 mmol) in anhydrous benzene (20 ml) was added α,α′-azobis(isobutyronitrile) (0.89 g, 5.44 mmol) or benzoyl peroxide (1.32 g, 5.44 mmol) under an atmosphere of argon. After 6 h refluxed, the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 10:1) to give the desired denitro compound **1b** as a colorless liquid (3.75 g, yield 65%). ^{1}H NMR ($CDCl_3$): δ 0.97 (6H, dd, J = 7.20, 8.10 Hz), 1.25 (3H, t, J = 7.20 Hz), 2.09 (1H, dsept, J = 3.60, 6.75 Hz), 2.39 (1H, dd, J = 6.00, 16.50 Hz), 2.49 (1H, dd, J = 6.60, 16.50 Hz), 2.72 (1H, qq, J = 3.60, 6.60 Hz), 4.15 (2H, q, J = 7.20 Hz). ^{13}C NMR ($CDCl_3$): δ 14.02, 18.40 (q, J = 1.43 Hz), 20.26, 26.78 (q, J = 1.74 Hz), 29.82 (q, J = 2.87 Hz), 44.60 (q, J = 24.92 Hz), 60.89, 127.67 (q, J = 280.63 Hz), 171.30. ^{19}F NMR ($CDCl_3$): δ 69.3 (d, J = 10.15 Hz). IR (neat): γ 1741 (C=O) cm^{-1}. Anal. Calcd for $C_9H_{15}O_2F_3$: C, 50.94; H, 7.12. Found: C, 50.83; H, 6.77.

4.15. Benzyl 3-(difluoromethyl)-4-methylpentanoate (*1k*)

Yield 68%. ^{1}H NMR ($CDCl_3$): δ 0.94 (3H, d, J = 7.20 Hz), 0.97 (3H, d, J = 7.80 Hz), 1.92 (1H, dquint, J = 1.80. 5.10 Hz), 2.36 (1H, dsept, J = 2.40, 5.70 Hz), 2.40 (1H, dd, J = 5.70, 16.50 Hz), 2.56 (1H, dd, J = 6.30, 16.05 Hz), 5.13 (2H, s), 5.87 (1H, dt, J = 3.30, 56.10 Hz), 7.26–7.37 (Ar–H, m). ^{13}C NMR ($CDCl_3$): δ 19.29, 19.86, 27.10 (t, J = 3.17 Hz), 29.64 (t, J = 5.13 Hz), 44.48 (t, J = 18.04 Hz), 66.49, 117.35 (t, J = 241.64 Hz), 128.01, 128.04, 128.31, 135.48, 171.94. ^{19}F NMR ($CDCl_3$): δ 125.3 (ddd, J = 20.89, 56.89, 282.3 Hz), 120.9 (ddd, J = 11.86, 56.04, 282.62 Hz). IR (neat): γ 1734 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{19}O_2F_2$: C, 65.61; H, 7.08. Found: C, 65.62; H, 7.06.

4.16. Benzyl 3-(trifluoromethyl)heptanoate (*1a*)

The transesterification of oxazolidone derivatives (**11**) carried out the same procedure of Evans et al. [16] Yield 67%. ^{1}H NMR ($CDCl_3$): δ 0.80 (3H, t, J = 7.20 Hz), 1.18–1.36 (6H, m), 2.34 (1H, dd, J = 7.50, 16.35 Hz), 2.57 (1H, dd, J = 5.70, 16.20 Hz), 2.63 (1H, dsept, J = 16.20, 2.10 Hz), 5.07 (2H, s), 7.31–7.25 (Ar–H, m). ^{13}C NMR ($CDCl_3$): δ 13.77, 22.55, 27.97, 28.60, 33.33 (q, J = 2.87 Hz), 36.65 (q, J = 26.04 Hz), 66.73, 127.56 (q, J = 279.16 Hz), 128.15, 128.20, 128.38, 135.25, 170.71. ^{19}F NMR ($CDCl_3$): δ 72.6 (d, J = 9.60 Hz). IR (neat): γ 1742 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{19}O_2F_3$: C, 62.49; H, 6.64. Found: C, 62.26; H, 6.38.

4.17. Benzyl 3-(trifluoromethyl)-4-methylpentanoate (*1c*)

Yield 72%. ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, d, J = 6.60 Hz), 0.90 (3H, d, J = 7.20 Hz), 2.02 (1H, dsept, J = 3.60, 6.90 Hz), 2.38 (1H, dd, J = 6.00, 16.50 Hz), 2.49 (1H, dd, J = 6.60, 16.65 Hz), 2.68 (1H, qq, J = 3.30, 6.45 Hz), 5.07 (2H, s), 7.25–7.33 (Ar–H, m). ^{13}C NMR ($CDCl_3$): δ 18.47 (q, J = 1.43 Hz), 20.27, 26.80 (q, J = 1.66 Hz), 44.63 (q, J = 24.60 Hz), 66.80, 127.63 (q, J = 280.60 Hz), 128.11, 128.18, 128.38, 135.24, 171.18. ^{19}F NMR ($CDCl_3$): δ 69.3 (d, J = 9.60 Hz). IR (neat): γ 1742 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{17}O_2F_3$: C, 61.31; H, 6.25. Found: C, 61.56; H, 5.94.

4.18. Benzyl 3-(trifluoromethyl)-4,4-dimethylpentanoate (*1d*)

Yield 68%. ^{1}H NMR ($CDCl_3$): δ 1.05 (9H, s), 2.57 (1H, dd, J = 5.40, 9.15 Hz), 2.61 (1H, dd, J = 6.30, 16.50 Hz), 2.77 (1H, dquint, J = 5.10, 6.45 Hz), 5.18 (2H, s), 7.35–7.41 (Ar–H, m). ^{13}C NMR ($CDCl_3$): δ 14.06, 28.00 (q, J = 1.96 Hz), 31.15 (q, J = 3.40 Hz), 48.22 (q, J = 23.77 Hz), 66.80, 127.91 (q, J = 282.03 Hz), 128.06, 128.13, 128.36, 135.30, 171.57. ^{19}F NMR ($CDCl_3$): δ 65.2 (d, J = 10.16 Hz). IR (neat): γ 1743 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{19}O_2F_3$: C, 62.49; H, 6.64. Found: C, 62.37; H, 6.46.

4.19. Benzyl 3-(trifluoromethyl)-4-pentenoate (*1e*)

Yield 75%. ^{1}H NMR ($CDCl_3$): δ 2.57 (1H, dd, J = 9.90, 15.90 Hz), 2.79 (1H, dd, J = 4.20, 15.90 Hz), 3.37 (1H, dsext, J = 4.50, 9.00 Hz), 5.13 (2H, s), 5.29 (1H, s), 5.33 (1H, d, J = 4.80 Hz), 5.70 (1H, td, J = 8.40, 18.45 Hz), 7.30–7.41 (Ar–H, m). ^{13}C NMR ($CDCl_3$): δ 33.27 (q, J = 2.57 Hz), 44.44 (q, J = 28.07 Hz), 66.80, 121.58, 125.29 (q, J = 278.9 Hz), 128.38, 128.25, 128.19, 129.67 (q, J = 2.57 Hz), 135.13, 169.65. ^{19}F NMR ($CDCl_3$): δ 72.7 (d, J = 8.75 Hz). IR (neat): γ 1742 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{13}O_2F_3$: C, 60.46; H, 5.07. Found: C, 60.87; H, 4.87.

4.20. Ethyl 4,4,4-trifluoro-3-(4-methoxy-phenyl)-butanoate (*1f*)

Yield 75%. ^{1}H NMR ($CDCl_3$): δ 1.06 (3H, t, J = 7.20 Hz), 2.77 (1H, dd, J = 9.90, 16.20 Hz), 2.92 (1H, dd, J = 5.10, 16.20 Hz), 3.71 (3H, s), 3.79 (1H, dquint, J = 5.10, 9.30 Hz), 3.98 (2H, ddq, J = 8.10, 10.80, 11.70 Hz), 6.81 (2H, d, J = 8.70 Hz), 7.17 (2H, d, J = 8.10 Hz). ^{13}C NMR ($CDCl_3$): δ 13.96, 34.47, 45.27 (q, J = 27.70 Hz), 55.08, 60.86, 113.84, 125.40, 126.23 (q, J = 279.1 Hz), 129.76, 159.32,

169.76. ^{19}F NMR ($CDCl_3$): δ 71.9 (d, J = 9.60 Hz). IR (neat): γ 1740, 1615 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{15}O_3F_3$: C, 56.52; H, 5.06. Found: C, 56.49; H, 5.27.

4.21. Isopropyl 4,4,4-trifluoro-3-(4-methoxy-phenyl)-butanoate (**1g**)

Yield 87%. ^{1}H NMR ($CDCl_3$): δ 1.08 (3H, d, J = 6.30 Hz), 1.11 (3H, d, J = 6.30 Hz), 2.81 (1H, dd, J = 10.20, 15.60 Hz), 2.97 (1H, dd, J = 5.40, 15.75 Hz), 3.79 (3H, s), 3.84 (1H, dquint, J = 5.10, 9.60 Hz), 4.90 (1H, sept, J = 6.30 Hz), 6.88 (2H, d, J = 8.40 Hz), 7.24 (2H, d, J = 8.70 Hz). ^{13}C NMR ($CDCl_3$): δ 21.56, 34.75, 45.36 (q, J = 27.77 Hz), 55.12, 68.36, 113.80, 125.37, 126.23 (q, J = 279.2 Hz), 129.81, 159.30, 169.26. ^{19}F NMR ($CDCl_3$): δ 71.9 (d, J = 9.32 Hz). IR (neat): γ 1735, 1615 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{17}O_3F_3$: C, 57.93; H, 5.90. Found: C, 57.60; H, 5.75.

4.22. tert-Butyl 4,4,4-trifluoro-3-(4-methoxy-phenyl)-butanoate (**1h**)

Yield 60%. ^{1}H NMR ($CDCl_3$): δ 1.30 (9H, s), 2.77 (1H, dd, J = 10.20, 15.60 Hz), 2.94 (1H, dd, J = 5.40, 15.60 Hz), 3.80 (1H, dquint, J = 5.70, 9.30 Hz), 3.81 (3H, s), 6.89 (2H, td, J = 3.00, 9.00 Hz), 7.25 (2H, d, J = 8.70 Hz). ^{13}C NMR ($CDCl_3$): δ 27.75, 35.54, 45.49 (q, J = 27.77 Hz), 55.13, 81.18, 113.73, 125.52, 126.27 (q, J = 279.2 Hz), 129.85, 159.26, 168.90. ^{19}F NMR ($CDCl_3$): δ 71.9 (d, J = 8.75 Hz). IR (neat): γ 1734, 1614 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{19}O_3F_3$: C, 59.20; H, 6.29. Found: C, 59.14; H, 6.21.

4.23. Benzyl 4,4,4-trifluoro-3-(4-methoxy-phenyl)-butanoate (**1i**)

Yield 94%. ^{1}H NMR ($CDCl_3$): δ 2.86 (1H, dd, J = 10.20, 15.90 Hz), 2.99 (1H, dd, J = 4.80, 16.20 Hz), 3.73 (3H, s), 3.81 (1H, dquint, J = 4.80, 9.30 Hz), 4.96 (2H, s), 6.80 (2H, d, J = 8.40 Hz), 7.16 (2H, d, J = 8.40 Hz), 7.10–7.30 (Ar–H, m). ^{13}C NMR ($CDCl_3$): δ 13.97, 34.47, 45.29 (q, J = 27.77 Hz), 55.08, 113.88, 125.13, 126.15 (q, J = 279.2 Hz), 127.93, 128.07, 128.27, 129.76, 135.07, 159.33, 169.63. ^{19}F NMR ($CDCl_3$): δ 71.9 (d, J = 9.32 Hz). IR (neat): γ 1741, 1614 (C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{17}O_3F_3$: C, 63.90; H, 5.06. Found: C, 63.83; H, 5.18.

4.24. Benzyl 4,4-difluoro-3-(4-methoxy-phenyl)-butanoate (**1m**)

Yield quant. ^{1}H NMR ($CDCl_3$): δ 2.81 (1H, dd, J = 9.50, 16.00 Hz), 2.98 (1H, dd, J = 6.00, 16.25 Hz), 3.59 (1H, dqd, J = 5.10, 13.65, 3.45 Hz), 3.80 (3H, s), 5.04 (2H, s), 5.88 (1H, td, J = 56.49, 3.00 Hz), 6.85–6.86 (2H, dm, J = 8.50 Hz), 7.17–7.19 (2H, dm, J = 9.00 Hz), 7.19–7.33 (Ar–H, m). ^{13}C NMR ($CDCl_3$): δ 33.60 (t, J = 3.70 Hz), 45.04 (t, J = 20.38 Hz), 55.08, 66.44, 113.93, 116.76 (t, J = 244.5 Hz), 127.20, 127.89, 127.98, 128.25, 129.54, 135.30, 158.98, 170.60. ^{19}F NMR ($CDCl_3$): δ 125.1 (ddd, J = 18.3, 56.4, 278.0 Hz), 120.6 (ddd, J = 13.64, 56.44, 278.0 Hz). IR (neat): γ 1734, 1613 (C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{18}O_3F_2$: C, 67.49; H, 5.66. Found: C, 67.48; H, 5.99.

4.25. Benzyl 3,4-dimethylpentanoate (**1j**)

Total yield 46% (three steps; esterification, Michael addition, and radical denitration). ^{1}H NMR ($CDCl_3$): δ 0.84 (3H, d, J = 6.50 Hz), 0.87 (6H, d, J = 7.00 Hz), 1.25–1.39 (1H, m), 1.94–1.86 (1H, m), 2.13 (1H, dd, J = 9.50, 15.00 Hz), 2.40 (1H, dd, J = 5.50, 14.75 Hz), 5.12 (2H, s), 7.10–7.46 (Ar–H, m). ^{13}C NMR ($CDCl_3$): δ 15.75, 18.18, 19.72, 31.98, 35.80, 39.08, 65.87, 127.85, 127.90, 128.24, 135.87, 173.14. IR (neat): γ 1734 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.55; H, 8.90.

4.26. Benzyl 3-(4-methoxy-phenyl)butanoate (**1l**)

Total yield 18% (three steps; condensation, Michael addition, and transesterification). ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, d, J = 7.20 Hz), 2.57 (1H, dd, J = 5.70, 13.80 Hz), 2.64 (1H, dd, J = 7.50, 13.8 Hz), 3.25 (1H, sext, J = 7.20 Hz), 3.79 (3H, s), 5.05 (2H, s), 6.80–6.83 (2H, dm, J = 8.40 Hz), 7.11–7.16 (2H, dm, J = 8.70 Hz), 7.24–7.27 (2H, m), 7.29–7.38 (3H, m). ^{13}C NMR ($CDCl_3$): δ 21.88, 35.57, 42.91, 54.84, 65.74, 113.49, 127.27, 127.68, 127.71, 128.05, 135.59, 137.18, 157.66, 171.65. IR (neat): γ 1734 (C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.00; H, 7.13.

4.27. General procedure for electrophilic alkylation reactions of the β-fluoromethylated ester enolates

A dry two-necked flask equipped with a rubber septum was placed under an argon atmosphere and charged with anhydrous tetrahydrofuran (3 ml) and distilled 1,1,1,3,3,3-hexamethyldisilazane (0.15 ml, 0.707 mmol). This solution was reacted with 1.6 M solution of *n*-butyllithium in hexane (0.44 ml, 0.707 mmol) at 0 °C for 30 min. In a dry separate flask, 0.471 mmol of substrate ester (**1**) was dissolved in anhydrous tetrahydrofuran (3 ml) and cooled to −78 °C under an atmosphere of argon. The solution of lithium hexamethyldisilazane described above was then added dropwise, and stirred at −78 °C for 30 min. The solution of lithium enolate was treated with distilled hexamethylphosphoramide (0.59 ml, 3.39 mmol), which was further stirred at −78 °C for 30 min. Then, 1.41 mmol of an electrophile was added dropwise to the reaction mixture. After stirring at −78 °C for 2 h, and the reaction mixture warmed to room temperature, which was further stirred at room temperature for 2 h. The reaction mixture was quenched with 3N hydrochloric acid, and extracted with diethyl ether (3× 10 ml). The etheral layers dried over anhydrous magnesium

sulfate and evaporated. The isomer ratio was determined by ^{19}F NMR or ^{1}H NMR spectroscopy of the resultant crude product. Because a mixture of diastereomeric pairs and substrate (**1**) [21] obtained usually were inseparable or difficult to be separated, typically purification furnished their diastereomeric pairs and thus only major products were shown here. In the representative example, after conversion of crude products (**3**) to the corresponding amide derivative (**4**), their isomers were separated and determined their relative configuration between β-trifluoromethyl group and α-substitute derived from the electrophile.

*4.28. Ethyl 4-methyl-2-(methylthiothioxomethyl)-3-(trifluoromethyl)pentanoate (**3be**)*

Major isomer; Yield 58%. ^{1}H NMR ($CDCl_3$): δ 1.11 (6H, d, J = 6.30 Hz), 1.32 (3H, t, J = 7.20 Hz), 2.15 (1H, dsept, J = 6.60, 13.20 Hz), 2.33 (3H, s), 3.84 (1H, qd, J = 9.60, 9.60 Hz), 4.16 (1H, dquint, J = 7.20, 13.20 Hz), 4.27 (2H, q, J = 7.20 Hz). ^{13}C NMR ($CDCl_3$): δ 13.88, 16.57, 21.50, 27.41, 54.08 (q, J = 26.05 Hz), 62.21, 125.62 (q, J = 281.84 Hz), 135.20, 142.81, 165.95. ^{19}F NMR ($CDCl_3$): δ 63.75 (d, J = 9.31 Hz). Minor isomer; Yield 20%. ^{1}H NMR ($CDCl_3$): δ 1.00 (6H, d, J = 6.60 Hz), 1.26 (3H, t, J = 7.20 Hz), 1.96–2.09 (1H, m), 2.31 (3H, s), 3.44 (1H, qd, J = 9.00, 9.15 Hz), 4.16 (1H, dquint, J = 7.20, 13.20 Hz), 4.27 (2H, q, J = 7.20 Hz). ^{13}C NMR ($CDCl_3$): δ 13.74, 17.48, 20.92, 26.42, 50.92 (q, J = 23.48 Hz), 62.14, 125.62 (q, J = 281.84 Hz), 135.20, 142.81, 165.95. ^{19}F NMR ($CDCl_3$): δ 62.1 (d, J = 8.46 Hz). IR (neat): γ 1725 (C=O) cm^{-1}. Anal. Calcd for $C_{11}H_{17}O_2S_2F_3$: C, 43.69; H, 5.67. Found: C, 43.62; H, 5.65.

*4.29. N,N′-Dimethyl-3-(trifluoromethyl)-4-methyl-2-(prop-2′-enyl)pentanoylamide (**4ba**)*

To a solution of crude product (**3ba**) (0.312 g, 1.24 mmol) in ethanol (20 ml) was added 10% aqueous sodium hydroxide (30 g). After stirring at room temperature for 5 h, the reaction mixture was evaporated. The resultant residue was washed with hexane (1× 10 ml), followed by the water layer was added diethyl ether (50 ml) and 6N hydrochloric acid (200 ml). The mixture was extracted with diethyl ether (3× 30 ml). The ethereal layers dried over anhydrous magnesium sulfate and evaporated to give the corresponding crude acid (0.245 g, crude yield 88%). To a stirred solution of the crude acid (0.245 g, 1.09 mmol) in anhydrous benzene (10 ml) was added distilled thionyl chloride (0.8 ml, 11.0 mmol) at 0 °C under an argon atmosphere. After 5 h reflux and the removal of the volatiles in vacuo, the residue diluted with distilled tetrahydrofuran (10 ml) and the solution was added 50% aqueous dimethylamine (1.63 g, 11.0 mmol) at 0 °C. After stirring at 0 °C for 2 h, the reaction was quenched with 3N hydrochloric acid (10 ml) and extracted with diethyl ether (3× 20 ml). The ethereal layers dried over anhydrous magnesium sulfate and evaporated. The purification by silica gel column chromatography (hexane/ethyl acetate, 5:1) afforded major isomer and minor isomer of **4ba**. Major isomer; Yield 64%. m.p. 41–43 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (3H, d, J = 7.20 Hz), 1.04 (3H, d, J = 7.20 Hz), 1.71 (1H, sept, J = 7.20 Hz), 2.36 (2H, tm, J = 7.20 Hz), 2.61 (1H, dsept, J = 2.40, 8.70 Hz), 2.92 (3H, s), 3.01 (3H, s), 3.10 (1H, dt, J = 2.40, 8.70 Hz), 4.97 (1H, d, J = 9.90 Hz), 5.05 (1H, d, J = 17.10 Hz), 5.63 (1H, ddt, J = 17.25, 9.75, 7.50 Hz). ^{13}C NMR ($CDCl_3$): δ 16.98, 22.61, 28.13, 35.52, 35.61, 37.61, 40.21, 50.06 (q, J = 22.94 Hz), 117.45, 128.16 (q, J = 283.2 Hz), 134.24, 172.79. ^{19}F NMR ($CDCl_3$): δ 60.4 (d, J = 10.45 Hz). Minor isomer; Yield 7%. ^{1}H NMR ($CDCl_3$): δ 1.01 (3H, dd, J = 1.20, 7.35 Hz), 1.11 (3H, dd, J = 1.50, 7.05 Hz), 2.15–2.37 (2H, m), 2.63 (1H, dsept, J = 2.40, 9.45 Hz), 2.93 (3H, s), 2.99 (3H, s), 3.05 (1H, dt, J = 5.10, 9.45 Hz), 5.00 (1H, dm, J = 10.20 Hz), 5.08 (1H, dm, J = 17.10 Hz), 5.66 (1H, ddt, J = 17.25, 10.20, 7.20 Hz). ^{13}C NMR ($CDCl_3$): δ 17.51, 22.03, 25.11, 34.47, 35.79, 37.36, 38.55, 48.89 (q, J = 22.04 Hz), 117.46, 128.18 (q, J = 283.45 Hz), 134.25, 173.41. ^{19}F NMR ($CDCl_3$): δ 63.7 (d, J = 10.16 Hz). IR (neat): γ 1733, 1652 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{20}NOF_3$: C, 57.36; H, 8.02; N, 5.57. Found: C, 57.74; H, 8.14; N, 5.58.

*4.30. N,N′-Dimethyl-4,4,4-trifluoro-3-(4-methoxyphenyl)-2-(prop-2′-enyl)pentanoylamide (**4fa**)*

Major isomer; Yield 63%. m.p. 71–72 °C. ^{1}H NMR ($CDCl_3$): δ 2.64 (3H, s), 2.71 (3H, s), 3.40 (1H, dt, J = 6.00, 9.15 Hz), 3.63–3.85 (1H, m), 3.79 (3H, S), 5.03 (1H, d, J = 10.20 Hz), 5.15 (1H, d, J = 16.80 Hz), 5.68 (1H, ddt J = 16.95, 10.20, 3.00 Hz), 6.83 (2H, d, J = 8.70 Hz), 7.19 (2H, d, J = 8.10 Hz). ^{13}C NMR ($CDCl_3$): δ 35.40, 37.38, 43.74, 51.33 (q, J = 26.56 Hz), 55.10, 113.56, 117.64, 126.44, 126.92 (q, J = 280.28 Hz), 128.57, 129.52, 130.67, 134.18, 158.91, 171.63. ^{19}F NMR ($CDCl_3$): δ 63.95 (d, J = 10.45 Hz). Minor isomer; Yield 17%. ^{1}H NMR ($CDCl_3$): δ 3.02 (3H, s), 3.12 (3H, s), 3.36 (1H, dt, J = 3.60, 10.95 Hz), 3.81 (1H, dquint, J = 1.80, 9.00 Hz), 3.82 (3H, S), 4.90 (1H, dm, J = 5.40 Hz), 4.95 (1H, s), 5.68 (1H, ddt J = 17.70, 9.30, 7.20 Hz), 6.91 (2H, d, J = 8.70 Hz), 7.23 (2H, d, J = 8.70 Hz). ^{13}C NMR ($CDCl_3$): δ 36.01, 37.46, 40.26, 51.26 (q, J = 25.51 Hz), 55.08, 113.95, 117.50, 124.89, 126.42 (q, J = 280.50 Hz), 130.33, 133.77, 159.18, 172.84. ^{19}F NMR ($CDCl_3$): δ 68.9 (d, J = 8.75 Hz). IR (KBr): γ 1634 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{20}NO_2F_3$: C, 60.94; H, 6.39; N, 4.44. Found: C, 60.98; H, 6.42; N, 4.42.

*4.31. N,N′-Dibenzyl-4,4,4-trifluoro-3-(4-methoxyphenyl)-2-methylbutyramide (**4fb**)*

Major isomer; Yield 69%. Crystals suitable for X-ray diffraction were obtained by recrystallization from acetonitrile/methanol/2-propanol/dichloromethane, 5.0/5.0/0.5/0.1. m.p. 130–132 °C. ^{1}H NMR ($CDCl_3$): δ 0.85 (2H, d,

J = 7.00 Hz), 3.33 (1H, dq, J = 10.50, 7.00 Hz), 3.80 (3H, s), 4.00 (1H, quint, J = 9.00 Hz), 4.50 (1H, d, J = 17.50 Hz), 4.56 (1H, d J = 14.50 Hz), 4.60 (1H, d, J = 17.00 Hz), 4.84 (1H, d, J = 14.50 Hz), 6.86–6.88 (2H, dm, J = 8.50 Hz), 7.16 (2H, d, J = 8.50 Hz), 7.22 (2H, d, J = 7.50 Hz), 7.25–7.44 (10H, m). ^{13}C NMR ($CDCl_3$): δ 17.55, 35.17, 48.87, 49.78, 51.47 (q, J = 25.51 Hz), 55.13, 113.92, 124.96, 126.32, 126.65 (q, J = 280.58 Hz), 127.30, 127.54, 128.34, 128.40, 128.78, 130.59, 136.20, 136.92, 159.18, 175.02. ^{19}F NMR ($CDCl_3$): δ 68.6 (d, J = 9.41 Hz). IR (KBr): γ 1639, 1616 (C=O) cm^{-1}. Anal. Calcd for $C_{26}H_{26}NO_2F_3$: C, 70.73; H, 5.94; N, 3.17. Found: C, 70.77; H, 6.02; N, 3.11.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2005.04.001.

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[21] It was found that through the ^{19}F NMR measurement at −78 °C of small scale experiments of the electrophilic alkylation reactions in a NMR tube that after the substrate esters (**6**) converted to the enolates (**7**) perfectly with lithium hexamethyldisilazane, the starting material (**6**) was also generated with the alkylated compounds (**8**) by addition of an electrophile in the same time.