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Convenient stereoselective synthesis of β-perfluoroalkyl α,β-unsaturated esters via Hörner–Wadsworth–Emmons reactions

Takashi Yamazaki *, Noriko Mano, Reo Hikage, Tsutomu Kaneko, Tomoko Kawasaki-Takasuka, Shigeyuki Yamada

Division of Applied Chemistry, Institute of Engineering, Tokyo University of Agriculture and Technology, 2-24-16 Nakamachi, Koganei, 184-8588, Japan

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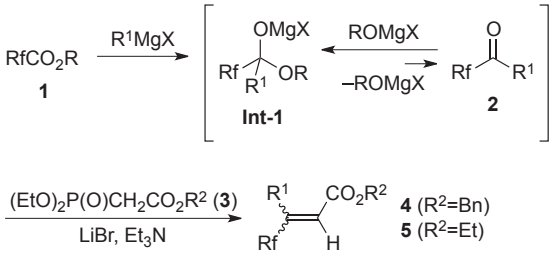
ABSTRACT

Condensation of Hörner–Wadsworth–Emmons reagents **3** and ketones **2** with a perfluoroalkyl (Rf) moiety prepared in situ was proved to be significantly efficient and powerful methods for the construction of a wide variety of α,β-unsaturated esters with Rf and R^1 groups both at the β-position due to convenient avoidance of usually tedious as well as troublesome isolation steps of these ketones **2**.

1. Introduction

Versatility of α,β-unsaturated carbonyl compounds with a perfluoroalkyl (Rf) group at the β position has been demonstrated thus far as, for example, acceptors for Michael addition reactions,[1] Diels–Alder cycloaddition,[2] and 1,3-dipolar addition,[3] and substrates for asymmetric dihydroxylation.[4] The high potency appeared in these instances is mainly attributable to their lower-lying LUMO energy levels,[1a] which are apparently affected by the strongly electron-withdrawing Rf moieties directly connected to the π-systems. Since most of these synthetic applications are known to proceed in a stereospecific manner, stereoselective construction of such molecules at the olefinic site is regarded as one of the most important subjects.

Among this type of compounds, preparation of β-Rf-α,β-unsaturated esters with a variety of an additional substituent at the β position was required for our purpose, and literature search suggested that Wittig type processes were one of the most plausible routes for their syntheses.[5,6] However, it should be pointed out that only a few fluorinated ketones were commercially available and their preparations are not always easy especially for 'small molecules' among this category due to their possibly low boiling points. For solving these problems, we have envisioned convenient synthetic route as shown in Scheme 1.[7] Thus, reaction of readily available perfluorinated esters **1** and appropriate Grignard reagents R^1MgX should furnish intermediary magnesium acetals **Int-1**. In spite of greater stability of **Int-1**, the corresponding ketones **2** present in their equilibrating relationship[8] are considered to be trapped in situ by the Hörner–Wadsworth–Emmons (HWE) reagents **3** activated by LiBr and Et_3N to produce the desired **4** and **5** with avoiding tedious isolation steps of ketones **2**.[9,10] Moreover, a similar type of intermediates to **Int-1** could be constructed by such opposite combination as RfLi and appropriate non-fluorinated esters, which would open an alternative route to get access to the identical target molecules.



Scheme 1. Basic concept of the present method.

* Corresponding author. Tel./fax: +81 42 388 7038; e-mail address: tyamazak@cc.tuat.ac.jp (T. Yamazaki).

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0040-4020/

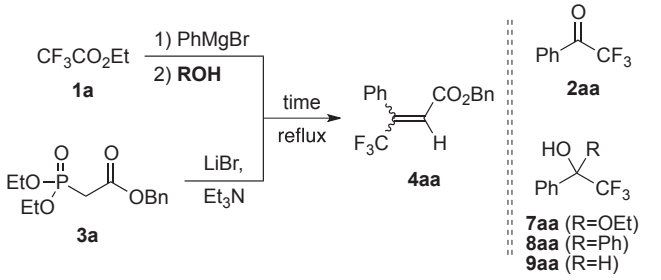
In this article are described our recent results based on this concept which actually enabled the particularly convenient as well as efficient preparation of the requisite α,β-unsaturated esters **4** and **5** in moderate to excellent chemical yields even when Rf and R^1 are, for example, CF_3 and Et, respectively in smaller lab scale reactions.[11]

2. Results and discussion

Determination of suitable reaction conditions was set as the starting point of our investigation using ethyl trifluoroacetate **1a** (Rf: CF_3, R: Et), phenylmagnesium bromide (R^1: Ph, X: Br), and benzyl diethyl phosphonoacetate **3a**[12] (R^2: Bn) as the representative combination whose results were collected in Table 1. To a solution of **Int-1aa** (Rf: CF_3, R^1: Ph, R: Et) formed by treatment of **1a** with PhMgBr in THF at −80 °C for 1 h, followed by 0 °C for an additional 1 h was introduced a mixture containing the HWE reagent **3a**, LiBr, and Et_3N in THF, and the whole solution was refluxed for the indicated period. In addition to approximately 30% detection of the desired **4aa** by ^{19}F NMR, formation of the major byproduct, trifluoroacetophenone ethyl hemiacetal **7aa**, was noticed to some extent in entries 2 to 5. This phenomena would be interpreted as a consequence of significant energetic preference of **Int-1aa** to **2aa** even at the THF reflux temperature, leaving a larger amount of the former seemingly intact. Then, for alteration of their equilibrium composition, 5 equiv of a proton source was added before introduction of the enolate derived from **3a**. H_2O actually affected the reaction (entries 6 vs 7), and a catalytic amount of quaternary ammonium salt was also effective (entries 8–10). EtOH (entry 9) was proved to record slightly better yield of **4aa** but, at the same moment, 2,2,2-trifluoro-1-phenylethanol **9aa** was detected in 34% yield possibly due to existence of the competing Meerwein–Ponndorf–Verley type pathway which has been already demonstrated[13] to be smoothly promoted by the in situ-formed EtOMgBr under THF reflux conditions. For suppression of this undesired conversion, *t*-BuOH without no hydrogen at the oxygen-attached carbon atom was selected as the adequate proton source to nicely improve the yield of the target **4aa** to 75% (69% isolated yield) with the excellent 95% *E* isomer preference.

By employment of the optimized conditions thus determined, we have further investigated the scope and limitation of the present procedure whose results were compared with the ones obtained by the condensation with isolated fluorinated ketones **2** ('conventional method'). Our procedure allowed to isolate the desired **4aa** and **4ak** in 69% and 72% total yields for two steps (entries 1 and 12, Table 2, respectively), which were well compared with the yields obtained by the 'conventional method' only in a single condensation step (82% and 87%, entries 2 and 13). In the case of 4-$MeOC_6H_4$ as R^1, 25% lower yield with respect to the 'conventional method' was, at least in part, due to formation of the byproduct, 2,2,2-trifluoro-1,1-diphenyl-ethanol **8aa** in 27% yield. Possible destabilization of **Int-1** by the electron-donating MeO group would shift the equilibrium to **2** at the Grignard reaction step, which was considered as the major reason of this undesired result. Such situation was compensated by employment of the corresponding lithium species instead of the Grignard reagent, attaining 79% chemical yield with 95% *E* selectivity (entries 5–7). One important issue to be mentioned at this point is the unfortunate contamination of the corresponding ethyl (entries 3 and 7) and methyl (entry 16) esters as byproducts when organolithium was used as nucleophiles, and these byproducts should stem from transesterification by the alcohols originally included in the substrate esters **1**. This drawback was readily overcome by use of the substrate ester **1a** and

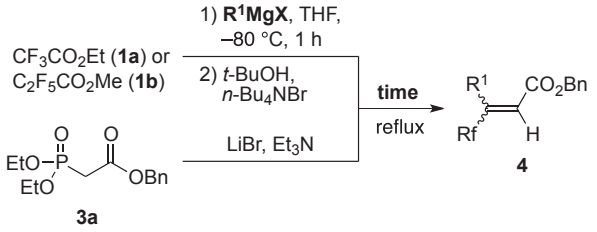
Table 1
Investigation of reaction conditions



Entry	Solv.[a]	Time (h)	**ROH**	^{19}F NMR yield[b] (%)	
				4aa	Byproducts
1	Et_2O	2	—	1	33 (**8aa**)
2	THF	2	—	36 [89]	27 (**7aa**), 5 (**8aa**)
3	THF	6	—	27 [78]	27 (**7aa**), 6 (**8aa**)
4[c]	THF	6	—	31 [87]	42 (**7aa**), 3 (**8aa**)
5[c]	THF	6	—	33 [85]	44 (**7aa**), 4 (**8aa**)
6	THF[d]	5	—	2	95 (**7aa**)
7	THF[d]	2	H_2O	35 [97]	7 (**2aa**), 36 (**8aa**)
8[e]	THF[d]	2	H_2O	47 [>99]	3 (**2aa**), 40 (**8aa**)
9[e]	THF[d]	2	EtOH	50 [94]	9 (**2aa**), 34 (**9aa**)
10[e]	THF[d]	2	*t*-BuOH	75 [95]	3 (**2aa**), 7 (**8aa**)

[a] Solvent both for the reaction with **3a** and the preparation of PhMgBr.
[b] In the bracket was shown the percentage of the *E* isomer determined by ^{19}F NMR.
[c] 2 (entry 4) and 3 (entry 5) equiv of **3a** were used (1.3 equiv for other cases).
[d] PhMgBr in Et_2O was employed.
[e] 4 mol % of *n*-Bu_4NBr was added right after addition of ROH.

Table 2
Reactions with a variety of combination of esters and Grignard reagents



Entry	Rf	R^1	Time[a] (h)	Product	Isolated yield (%)
1	CF_3	Ph	2	**4aa**	69 (95:5)
2[b]	CF_3	Ph	2	**4aa**	82 (90:10)
3[c]	CF_3	Ph	2	**4aa**	70[d] (92:8)
4[c,e]	CF_3	Ph	2	**4aa**	86 (91:9)
5	CF_3	4-$MeOC_6H_4$	2	**4ab**	46[f] (99:1)
6[b]	CF_3	4-$MeOC_6H_4$	6	**4ab**	71 (92:8)
7[c]	CF_3	4-$MeOC_6H_4$	2	**4ab**	79[d] (95:5)
8	CF_3	C_2H_5	2	**4af**	54 (89:11)
9[c]	CF_3	*n*-C_4H_9	2	**4ah**	67 (90:10)
10	CF_3	*c*-C_6H_{11}	2	**4ai**	27[g] (89:11)
11[b]	CF_3	*c*-C_6H_{11}	6	**4ai**	77 (71:29)
12	CF_3	*n*-C_8H_{17}	1	**4ak**	72 (98:2)
13[b]	CF_3	*n*-C_8H_{17}	6	**4ak**	87 (90:10)
14	C_2F_5	Ph	2	**4ba**	26[g] (>99:1)
15[b]	C_2F_5	Ph	6	**4ba**	83 (>99:1)
16[c]	C_2F_5	Ph	2	**4ba**	81[d] (>99:1)
17[c]	C_2F_5	4-$MeOC_6H_4$	2	**4bb**	52[h] (>99:1)
18	C_2F_5	CH_3	2	**4be**	32 (>99:1)
19[c]	C_2F_5	CH_3	2	**4be**	30 (>99:1)

[a] Reaction time under reflux after mixing the enolate from **3a** and ketone precursors **Int-1**.
[b] Results obtained under the 'conventional method'.
[c] RLi was used instead of RMgX without addition of a proton source.
[d] The corresponding ethyl esters (12% (**5aa**) in entry 3, 13% (**5ab**) in entry 7) or methyl ester (7% (**6ba**) in entry 16) were contained in the isolated products.
[e] **3b** was used instead of **3a**, giving **5aa** as the product.
[f] 27% of 2,2,2-trifluoro-1,1-diphenylethanol **8aa** was obtained.
[g] Determined by ^{19}F NMR.
[h] This lower isolated yield (88% by ^{19}F NMR) was due to the presence of some unidentified byproducts with the close Rf values to **4bb**.

the HWE reagent **3b** both with the same alcohol part, affording pure **5aa** (the ethyl ester of **4aa**) in 86% yield basically in an identical *E*/*Z* ratio (entry 4). A major gap in the yield between our route and the 'conventional method' was noticed in the case of *c*-$C_6H_{11}MgBr$ (entries 10 and 11), which was clearly explained by a separate experiment to be as a consequence of the sluggish reaction of ethyl trifluoroacetate **1a** with *c*-$C_6H_{11}MgBr$ only attaining 15% isolated yield (33% by ^{19}F NMR) of the desired cyclohexyl trifluoromethyl ketone **2ai**.[14] Linear alkyl substituents as shown in entries 8 and 9 were found to work in a similar manner, producing the desired enoates **4af** and **4ah** in good yields. Methyl pentafluoropropionate **1b** was also applicable to the present process as the substrate ester, leading to successful construction of the corresponding α,β-unsaturated esters **4**. The low yield in entry 14 would be the direct reflection of the higher stability of the magnesium hemiacetal obtained from pentafluorinated propiophenone **Int-1ba** than the corresponding intermediates with a CF_3 group, affording the desired product **4ba** only in 26% yield along with 29% (both determined by ^{19}F NMR) of the unreacted ketone **2ba** as the byproduct. The corresponding lithium reagents improved the reaction with realizing a similar level of the chemical yield to the one of the 'conventional method' (entries 15 and 16), in spite of a small amount of the possible contamination as described above. *E* stereoselectivity for all the products was confirmed by comparison of the reported data (**4aa** and **4ab**[15]) as well as by our independent NOE experiment for **4ai**, showing the distinct NOE cross peak between vinylic H at the α position and the allylic H at the γ position only for the minor isomer. Major isomers of other new products were estimated as *E* on the basis of these instances.

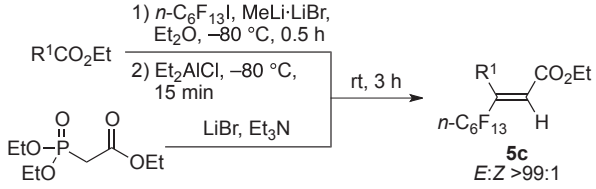
Different from the strategy starting from perfluorinated esters **1**, an alternative incorporation pathway of a *n*-C_6F_{13} moiety to the α,β-unsaturated ester framework was envisioned by using *n*-$C_6F_{13}Li$ generated from the readily available iodide. Thus, smooth lithium–halogen exchange of *n*-$C_6F_{13}I$ was performed by subjection of MeLi complexed with LiBr to a mixture of this iodide and $PhCO_2Et$ in Et_2O.[16] Spontaneous nucleophilic attack of thus prepared *n*-$C_6F_{13}Li$ was occurred to the benzoate, and the following introduction of the **3b**-based enolate stereospecifically furnished the product enoate **(*E*)-5ca** in 77% isolated yield (entry 1 in Table 3). At this point, we have encountered reproducibility problems of this reaction. With reference to the previous report by Pastor et al.[9b] on the synthesis of β-Rf-acrylates from the **3b**-derived enolate and $RfCO_2Et$ by way of the in situ DIBAL reduction of the latter, the lithium hemiacetal in our hands was transmetallated to the corresponding aluminium acetal by the addition of Et_2AlCl, which nicely solved this serious problem. Because of the possible fluorous characteristics of **5ca** by its higher fluorine content of 50.0% than the other α,β-unsaturated esters **4** and **5** with shorter Rf chains, Vertrel® (1,1,1,2,2,3,4,5,5,5-decafluoropentane) was employed as the extraction solvent instead of diethyl ether to effectively improve its isolated yield to 94% (entry 2). Avoidance of extractive workup procedures was found to be similarly valid, and chromatographic purification of crude materials after addition of NaF to a reaction mixture and filtration through a pad of silica gel led to semiquantitative isolation of **(*E*)-5ca** in 98% yield (entry 3). Instability of *n*-$C_6F_{13}Li$ even at low temperature and its weak nucleophilicity rendered the expediency of the present process lower especially for the benzoate with the electron-donating MeO group as R^1 (entry 4). On the other hands, the opposite trend was also noticed and the quantitative yield was attained by the one with the electron-withdrawing CF_3 substituent (entry 5). Applicability of acetate, propanoate, and octanoate was clarified to this modified route without any significant problem, while the corresponding isobutyrate was proved not to be a good substrate possibly because of steric hindrance around the carbonyl moiety. The already reported data for the compound **5ce** (entry 6)[17] in connection to the cases of Rf=CF_3 or C_2F_5 allowed us to speculate the same *E* stereochemistry constructed at the olefinic part for other products.

As shown above, Tables 2 and 3 unambiguously demonstrated the utility of the present protocol for stereoselective construction of α,β-unsaturated esters **4** and **5** with Rf and R groups both at the β-position. Especially important feature was exemplified by the instances of entries 8–10, 18, and 19 in Table 2 and entries 6–8 in Table 3: in spite of presence of such 'small' R^1 substituents as Me, Et, *n*-Bu, and *c*-Hex, syntheses of the product enoates **4** and **5** were attained in moderate to high yields even in a small scale process. As pointed out in the introductory part, the 'conventional method' requires the preparation of the requisite ketones **2** at first, while it is quite apparent that their syntheses are not always easy task by considering their low boiling points and high volatility.[18] Successful elimination of this possibly troublesome steps unveiled the considerable advantage of the present protocol over the previously reported methods.

The reaction mechanism was elucidated as shown in Scheme 2. In the first ketone formation step, appropriate Grignard reagents R^1MgBr were reacted with perfluoroalkylated esters $RfCO_2R$ **1** to furnish magnesium acetals **Int-1** (X: MgBr), which were substantially stabilized by the strongly electron-withdrawing Rf moieties. The higher nucleophilicity of magnesium alkoxides was considered to play an important role in increase of the preference of **Int-1** to **2**, leading to final production of hemiacetals **7** and/or ketones **2** after THF refluxing even in the presence of the activated HWE reagents **3**. Thus, in this circumstance, it was assumed that only an extraordinarily small amount of **2** was present, which reacted quickly with ROMgBr rather than the **3**-based reagents. However, addition of a proton source converted **Int-1** to the corresponding hemiacetals **7** whose transformation to **2** would be more feasible on the basis of lower nucleophilicity of the resultant ROH than the one of ROMgBr. An electron-donating R^1 group should destabilize **Int-1** at the ketone formation stage to increase the amount of **2** which would follow the further reaction with other R^1MgBr molecules to afford **8**.

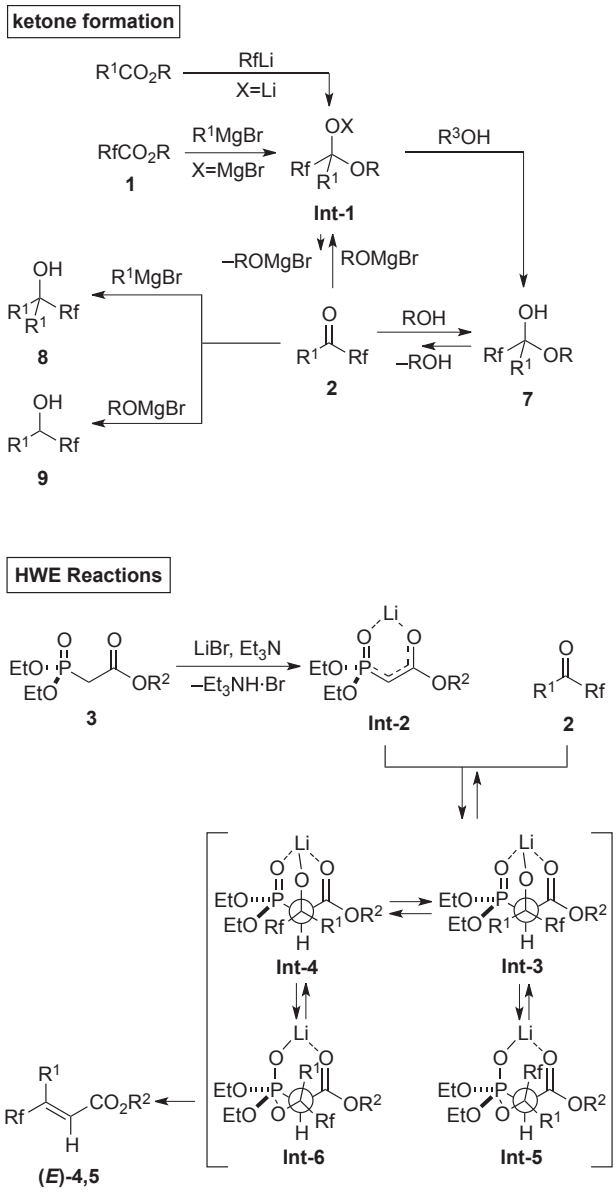
An equilibrium mixture containing ketones **2** and hemiacetals **7** was subjected to a solution of the reactive enolates **Int-2** conveniently derived from HWE reagents **3**, LiBr, and Et_3N in a separate flask. This operation led to facile carbon–carbon bond formation to construct diastereomeric **Int-3** and **Int-4**, which were further

Table 3
Synthesis of α,β-Unsaturated esters with a *n*-C_6F_{13} group by way of *n*-$C_6F_{13}Li$



Entry	R^1	Product	Isolated yield (%)
1	Ph	**5ca**	77[a,b]
2	Ph	**5ca**	94[a,c]
3	Ph	**5ca**	98
4	4-$MeOC_6H_4$	**5cb**	49
5	4-$F_3CC_6H_4$	**5cc**	>99
6	CH_3	**5ce**	71
7	C_2H_5	**5cf**	42
8	*i*-C_3H_7	**5cg**	22
9	*n*-C_7H_{15}	**5cj**	56

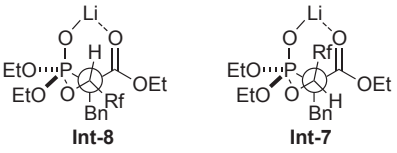
[a] Et_2AlCl was not used.
[b] Et_2O was used for extraction.
[c] Vertrel® (1,1,1,2,2,3,4,5,5,5-decafluoropentane) was used as the extraction solvent.

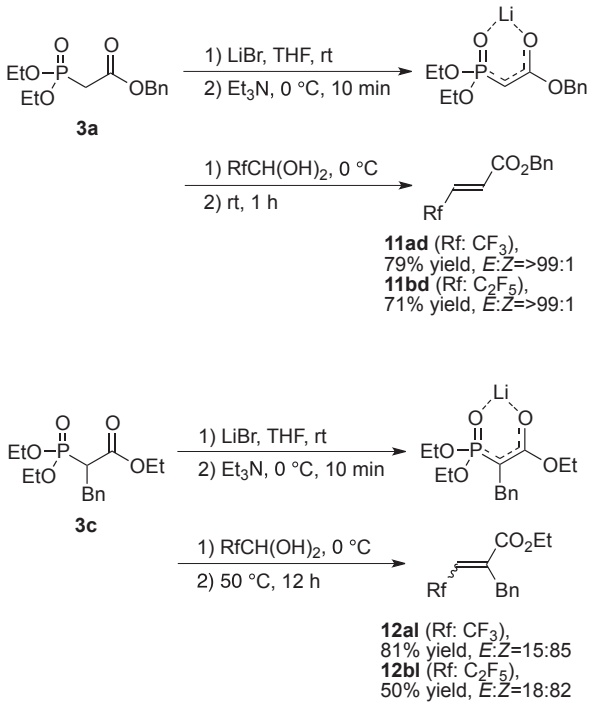


Scheme 2. Possible reaction mechanism.

converted to the corresponding oxaphosphetanes **Int-5** and **Int-6**, respectively. Judging from the experimental results, determinant of stereoselectivity would be the electronically repulsive interaction between Rf and CO_2R^2 moieties, and thus, the reaction might proceed via the more preferable **Int-6** to furnish the desired α,β-unsaturated esters **4** and **5** with high (*E*)-stereochemistry.[19] This mechanistic consideration consistently explained the (*E*)-stereospecificity for the cases of C_2F_5 or *n*-C_6F_{13} as Rf which apparently caused severer electronic as well as steric repulsion than the case of intermediates with a CF_3 group, the latter of which were, different from the former, suffered from a small amount of the corresponding (*Z*)-isomers (1–15%).

Extension of the present method was also carried out for the synthesis of β-Rf-α,β-unsaturated esters **11** and **12**, the latter of which possessed an additional substituent α to the ester moiety (Scheme 3). As our expectation, the enolate from **3a** smoothly condensed with perfluorinated aldehyde hydrates to furnish the desired compounds **11** in a stereospecific fashion. On the other hand, construction of **12** with a benzyl group was realized by treatment of the same trifluorinated hydrates with **3c**,[20] and longer period and higher temperature were found to be required for attainment of a good level of conversion. In the latter case, as shown below, the steric repulsion between Bn and Rf groups in **Int-8** seemed to surpass the electronic interaction between Rf and CO_2Et in **Int-7**, giving rise to formation of the corresponding (*Z*)-isomers in a preferential manner. These two types of destabilizing factors in the intermediary oxaphosphetanes should be the definitive reason for requirement of more forcing conditions to prepare the desired α-substituted α,β-unsaturated esters **12** rather than the instances of **11**.





Scheme 3. Preparation of other types of α,β-unsaturated esters.

3. Conclusion

As depicted above, we have successfully demonstrated the convenient syntheses of α,β-unsaturated esters **4**–**6** with Rf and R^1 groups both at the β position in good to excellent isolated yields with a high level of (*E*)-stereoselectivity by way of the condensation reactions of the in situ-produced Rf-possessing ketones **2** and HWE reagents **3**. Moreover, construction of other types of β-Rf-containing acrylates **11** and **12** has also been succeeded by simple extension of this method. The most important feature of this procedure is that no isolation was required for ketones **2** with an Rf group, which realized the incorporation of 'smaller' Rf and R^1 moieties in good to high chemical yields even in a small scale process. We believe this method opens an avenue to synthesize a wide variety of α,β-unsaturated esters with an Rf moiety at the β-position.

4. Experimental section

4.1. General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. All manipulations involving air-sensitive materials were performed under argon. Anhydrous Et_2O, THF and CH_2Cl_2 were purchased and were used without further purification.

^1H, ^{13}C, and ^{19}F NMR spectra were recorded with a JEOL JNM-LA300 (^1H: 300.40 MHz, ^{13}C: 75.45 MHz, and ^{19}F: 282.65 MHz), in $CDCl_3$. Chemical shifts were recorded in parts per million (ppm), downfield from internal tetramethylsilane (for ^1H and ^{13}C NMR, Me_4Si: δ 0.00 ppm, and for ^{19}F NMR, C_6F_6: δ −163 ppm). ^{13}C NMR spectra of minor isomers may not be fully reported because of difficult visualization of peaks with small intensities even after a long data acquisition time. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 spectrometer, and all spectra were reported in wave numbers (cm^{-1}). Analytical thin-layer chromatography (TLC) on silica gel 60 F_{254} (Merck) was routinely used for monitoring reactions. Column chromatography was conducted with silica gel 60 N (spherical, neutral, 63–210 nm, Kanto). Elemental analyses were performed by Perkin–Elmer SeriesII CHNS/O analyzer. High resolution mass spectra in a FAB mode were acquired on a JEOL JMS-700.

4.2. General procedure for preparation of β-Rf-β-substituted α,β-unsaturated esters (4 and 5)

To a solution of ethyl trifluoroacetate **1a** 0.10 mL (1.00 mmol) in THF (2.0 mL) was slowly added at −80 °C 0.92 mL of PhMgBr (1.3 *M* in Et_2O, 1.20 mmol) and the mixture was stirred for 1 h at that temperature, followed by 1 h at 0 °C where *t*-BuOH 0.48 mL (5.00 mmol) and Bu_4NBr 0.012 g (0.04 mmol) were further added. The enolate solution from a crude HWE reagent **3a**[12] (0.37 g, 1.30 mmol), LiBr (0.14 g, 1.60 mmol), Et_3N 0.19 mL (1.40 mmol) in THF (1.0 mL) prepared above was, after cooling to 0 °C again, slowly introduced to the Grignard mixture with the aid of cannula (0.5 mL of THF was added for rinsing inside after transfer the solution), and the resultant materials were stirred at 50 °C for 2 h. The mixture was quenched by the addition of 1 *M* HCl aq so as to control the pH of the solution from 6 to 7, and the usual workup and purification by column chromatography (*n*-hexane:AcOEt=4:1) afforded 0.211 g of benzyl 4,4,4-trifluoro-3-phenylbut-2-enoate **4aa** (0.689 mmol, 69% yield, *E*:*Z*=95:5) as a colourless oil.

*4.2.1. Preparation of benzyl 4,4,4-trifluoro-3-phenylbut-2-enoate (**4aa**).*[14] R_f=0.81 (*n*-hexane:AcOEt=1:1). ^1H NMR δ 5.02 (2H, s; *E* isomer) and 5.27 (2H, s; *Z* isomer), 6.64 (1H, s; *E* isomer) and 6.36 (1H, s; *Z* isomer), 7.25–7.41 (10H, m). ^{13}C NMR δ 66.8 (*E* isomer) and 67.4 (*Z* isomer), 122.4 (q, *J*=273.9 Hz), 124.2 (q, *J*=5.6 Hz), 128.22, 128.26, 128.3, 128.4, 128.5, 130.8, 134.7 (*E* isomer) and 134.9 (*Z* isomer), 142.5 (q, *J*=31.0 Hz), 163.8 (*E* isomer) and 164.2 (*Z* isomer). ^{19}F NMR δ −68.81 (s; *E* isomer) and −61.30 (s; *Z* isomer).

*4.2.2. Benzyl 4,4,4-trifluoro-3-(4-methoxyphenyl)but-2-enoate (**4ab**).*[14] Yield: 46%, *E*:*Z*=99:1 (Yield: 79%, *E*:*Z*=95:5 with 13% of the corresponding ethyl ester **5ab** by way of 4-$MeOC_6H_4Li$ instead of the corresponding Grignard reagent). Rf=0.40 (*n*-hexane:AcOEt=4:1). ^1H NMR δ 3.82 (3H, s; *E* isomer) and 3.84 (3H, s; *Z* isomer), 5.05 (2H, s; *E* isomer) and 5.26 (2H, s; *Z* isomer), 6.56 (1H, q, *J*=1.2 Hz; *Z* isomer) and 6.60 (1H, q, *J*=1.2 Hz; *E* isomer), 6.85–6.93 (2H, m), 7.12–7.21 (4H, m), 7.29–7.39 (3H, m). ^{13}C NMR δ 54.9 (*E* isomer) and 55.0 (*Z* isomer), 66.7 (*E* isomer) and 67.2 (*Z* isomer), 113.6, 120.7, 122.5 (q, *J*=274.6 Hz), 123.6 (q, *J*=5.0 Hz), 128.18, 128.20, 128.3, 130.0, 134.8, 142.1 (q, *J*=30.4 Hz), 160.4, 164.7. ^{19}F NMR δ −68.73 (s; *E* isomer) and −61.32 (s; *Z* isomer).

*4.2.3. Benzyl 3-(trifluoromethyl)pent-2-enoate (**4af**).* 54% yield, *E*:*Z*=89:11. Rf=0.41 (*n*-hexane: AcOEt=20:1). ^1H NMR δ 1.14 (3H, t, *J*=7.2 Hz; *Z* isomer) and 1.17 (3H, t, *J*=7.5 Hz; *E* isomer), 2.33 (2H, dq, *J*=1.5, 7.2 Hz; *Z* isomer) and 2.70 (2H, q, *J*=7.5 Hz; *E* isomer), 5.20 (2H, s; *Z* isomer) and 5.21 (2H, s; *E* isomer), 6.06 (1H, s; *Z* isomer) and 6.34 (1H, s; *E* isomer), 7.38–7.39 (5H, m). ^{13}C NMR δ 11.5 (*Z* isomer) and 13.2 (*E* isomer), 20.2 (q, *J*=1.2 Hz), 66.7 (*E* isomer) and 67.2 (*Z* isomer), 121.3 (q, *J*=6.2 Hz), 123.5 (q, *J*=274.6 Hz), 128.4, 128.5, 128.6, 135.3, 148.2 (q, *J*=28.5 Hz), 164.3. ^{19}F NMR δ −70.32 (s; *E* isomer) and −64.48 (s; *Z* isomer). IR (neat) ν 2982, 2944, 1730, 1456, 1311, 1255, 1190, 1132, 1040, 971, 746, 698. Anal. Calcd for $C_{13}H_{13}F_3O_2$: C, 60.46; H, 5.07. Found: C, 60.59; H, 5.22.

*4.2.4. Benzyl 3-(trifluoromethyl)hept-2-enoate (**4ah**).* 67% yield, *E*:*Z*=90:10. Rf=0.48 (*n*-hexane: AcOEt=4:1). ^1H NMR δ 0.93 (3H, t, *J*=7.2 Hz; *Z* isomer) and 1.17 (3H, t, *J*=7.5 Hz; *E* isomer), 1.35 (2H, sex, *J*=7.5 Hz), 1.46–1.56 (2H, m), 2.62–2.67 (2H, m), 5.20 (2H, s), 6.35 (1H, s), 7.38–7.39 (5H, m). ^{13}C NMR δ 13.57 (*E* isomer) and 13.61 (*Z* isomer), 22.0 (*Z* isomer) and 22.8 (*E* isomer), 26.6, 29.5 (*Z* isomer) and 31.0 (*E* isomer), 66.6 (*E* isomer) and 67.1 (*Z* isomer), 121.5 (q, *J*=6.2 Hz), 123.4 (q, *J*=274.6 Hz), 128.4, 128.5, 128.6, 135.3, 148.3 (q, *J*=28.5 Hz), 164.3. ^{19}F NMR δ −70.32 (s; *E* isomer) and −64.48 (s; *Z* isomer). IR (neat) ν 2962, 2875, 1731, 1457, 1364, 1314, 1188, 1127, 973, 894, 747, 697. Anal. Calcd for $C_{15}H_{17}F_3O_2$: C, 62.93; H, 5.99. Found: C, 63.07; H, 6.08.

*4.2.5. Benzyl 3-cyclohexyl-4,4,4-trifluorobut-2-enoate (**4ai**).* ^{19}F NMR yield: 27%, *E*:*Z*=89:11 (77% isolated yield, *E*:*Z*=79:21 by the conventional method. The following physical properties were recorded by the material obtained from the conventional method).

(*E*)-isomer R_f=0.61 (*n*-hexane:AcOEt=10:1). ^1H NMR δ 1.46–1.79 (10H, m), 3.30–3.41 (1H, m), 5.21 (2H, s), 6.32 (1H, m), 7.34–7.40 (5H, m). ^{13}C NMR δ 14.1, 25.6, 26.5, 30.5, 38.1, 66.7, 121.6 (q, *J*=6.8 Hz), 123.5 (q, *J*=276.9 Hz), 128.4, 128.5, 128.6, 135.2, 149.8 (q, *J*=26.6 Hz), 164.6. ^{19}F NMR δ −63.51 (s). IR (neat) ν 2932, 1730, 1656, 1498, 1452, 1328, 1276, 1189, 1134, 1093, 1003, 897, 747, 696. HRMS *m*/*z* calcd for $C_{17}H_{19}F_3O_2$ $[M]^+$: 312.1337; found: 312.1357.

(*Z*)-isomer R_f=0.46 (*n*-hexane:AcOEt=10:1). ^1H NMR δ 1.55–1.90 (10H, m), 2.22–2.30 (1H, m), 5.19 (2H, s), 6.04 (1H, m), 7.35–7.39 (5H, m). ^{13}C NMR δ 13.9, 25.7, 26.3, 32.3, 39.2, 67.2, 122.8 (q, *J*=276.9 Hz), 123.1 (q, *J*=3.8 Hz), 128.5, 128.6, 135.1, 144.3 (q, *J*=28.6 Hz), 165.2. ^{19}F NMR δ −65.34 (s). IR (neat) ν 2934, 1739, 1660, 1497, 1453, 1351, 1271, 1166, 1132, 981, 839, 751, 698. HRMS *m*/*z* calcd for $C_{17}H_{19}F_3O_2$ $[M]^+$: 312.1337; found: 312.1344.

*4.2.6. Benzyl 3-(trifluoromethyl)undec-2-enoate (**4ak**).* Yield: 72%, *E*:*Z*=98:2. R_f=0.58 (*n*-hexane: AcOEt=10:1). ^1H NMR δ 0.89 (3H, br t, *J*=6.9 Hz), 1.26–1.34 (10H, m), 1.52–1.55 (2H, m), 2.61–2.66 (2H, m), 5.20 (2H, s), 6.34 (1H, s; *E* isomer) and 6.06 (1H, s; *Z* isomer), 7.36–7.39 (5H, m). ^{13}C NMR δ 14.00 (*Z* isomer) and 14.04 (*E* isomer), 22.60 (*Z* isomer) and 22.64 (*E* isomer), 26.9, 27.4, 28.9, 29.2, 29.7, 31.77 (*Z* isomer) and 31.82 (*E* isomer), 66.7 (*E* isomer) and 67.1 (*Z* isomer), 121.5 (q, *J*=6.2 Hz), 123.5 (q, *J*=274.6 Hz), 128.4, 128.5, 128.5, 128.6, 135.3, 147.1 (q, *J*=29.2 Hz), 164.3. ^{19}F NMR δ −70.27 (s; *E* isomer) and −64.46 (s; *Z* isomer). IR (neat) ν 2926, 2855, 1732, 1669, 1457, 1313, 1193, 1131, 894, 747, 696. Anal. Calcd for $C_{19}H_{25}F_3O_2$: C, 66.65; H, 7.36. Found: C, 66.24; H, 7.52.

*4.2.7. Benzyl 4,4,5,5,5-pentafluoro-3-phenylpent-2-enoate (**4ba**).* ^{19}F NMR yield: 22%, *E*:*Z*=>99:1 (Yield: 81%, *E*:*Z*=>99:1 with 7% of the corresponding ethyl ester **8a** by using PhLi instead of PhMgBr). Rf=0.54 (*n*-hexane:AcOEt=4:1). ^1H NMR δ 5.00 (2H, s), 6.67 (1H, s), 7.07–7.11 (2H, m), 7.21–7.26 (2H, m), 7.29–7.40 (6H, m). ^{13}C NMR

δ 66.9, 127.2 (t, *J*=8.1 Hz), 112.1 (qt, *J*=37.8, 252.0 Hz), 118.7 (tq, *J*=39.1, 282.9 Hz), 128.1–129.2, 131.0, 134.7, 142.1 (t, *J*=21.7 Hz), 163.7. ^{19}F NMR δ −83.24 (3F, s), −116.36 (2F, s). IR (neat) ν 3066, 3036, 1738, 1457, 1446, 1332, 1210, 1161, 1056, 751, 697, 653. Calcd for $C_{18}H_{13}F_5O_2$: C, 60.68; H, 3.68. Found: C, 60.83; H, 3.70.

*4.2.8. Benzyl 4,4,5,5,5-pentafluoro-3-(4-methoxyphenyl)pent-2-enoate (**4bb**).* 52% yield, *E*:*Z*=>99:1. R_f=0.38 (*n*-hexane:AcOEt=4:1). ^{1}H NMR δ 3.75 (3H, s), 5.02 (2H, s), 6.62 (1H, t, *J*=1.2 Hz), 6.83–6.86 (2H, m), 7.13–7.16 (4H, m), 7.31–7.32 (3H, m). ^{13}C NMR δ 55.1, 66.9, 112.2 (qt, *J*=39.1, 255.8 Hz), 113.6, 118.7 (tq, *J*=37.8, 286.7 Hz), 123.0, 126.9 (t, *J*=8.1 Hz), 128.36, 128.39, 128.41, 130.3, 134.8, 141.8 (q, *J*=21.1 Hz), 160.3, 164.0. ^{19}F NMR δ −83.33 (s), −116.55 (s). IR (neat) ν 3067, 3036, 2960, 2841, 1737, 1610, 1514, 1458, 1252, 1211, 1162, 1055, 834, 745, 698. HRMS (FAB) *m/z* calcd for $C_{19}H_{15}F_5O_3$ $[M]^+$: 386.0941; found: 386.0971.

*4.2.9. Benzyl 4,4,5,5,5-pentafluoro-3-methylpent-2-enoate (**4be**).* 32% yield, *E*:*Z*=>99:1. R_f=0.68 (*n*-hexane:AcOEt=4:1). ^{1}H NMR δ 2.28 (3H, s), 5.21 (2H, s), 6.36 (1H, q, *J*=1.3 Hz), 7.38–7.40 (5H, m). ^{13}C NMR δ 13.0 (m), 66.8, 116.6 (qt, *J*=38.5, 290.9 Hz), 118.7 (tq, *J*=37.8, 286.6 Hz), 124.1 (t, *J*=8.7 Hz), 128.4, 128.5, 128.5, 128.7, 135.2, 142.6 (t, *J*=21.1 Hz), 164.3. ^{19}F NMR δ −84.52 (3F, s), −119.69 (2F, s). IR (neat) ν 3037, 2960, 1732, 1666, 1498, 1456, 1330, 1263, 1209, 1109, 1014, 886, 751, 697. HRMS *m/z* calcd for $C_{13}H_{11}F_5O_3$ $[M]^+$: 294.0679; found: 294.0688.

4.3. General procedure for preparation of β-*n*-C_6F_{13}-β-substituted α,β-unsaturated esters (5)

To a solution of 1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexyl iodide (0.22 mL, 1.0 mmol), ethyl benzoate (0.16 mL, 1.1 mmol) in Et_2O (3 mL) was added at −80 °C methyllithium (1.5 *M* in Et_2O with lithium bromide; 0.73 mL, 1.1 mmol) and stirring was continued for 30 min at the same temperature where diethyl-aluminium chloride (1 *M* in *n*-hexane; 1.1 mL, 1.1 mmol) was gradually added and further stirring for 15 min at −80 °C.

In a separate flask, lithium bromide (0.12 g, 1.4 mmol), triethyl phosphonoacetate (0.26 mL, 1.3 mmol), and THF (1 mL) was mixed at 0 °C where triethylamine (0.19 mL, 1.4 mmol) was added and the solution was stirred for 10 min at room temperature. This mixture was slowly introduced to an aluminium acetal solution prepared above with the aid of cannula and the whole mixture was further stirred for 1 h at room temperature. To this solution were successively added Et_2O (3 mL), NaF (0.185 g, 4.4 mmol) and H_2O (59 mg, 3.3 mmol), which was stirred for 0.5 h at room temperature. Filtration with a pad of silica gel and concentration furnished a crude mixture which was purified by silica gel column chromatography (*n*-hexane:CH_2Cl_2=6:1) to afford 0.484 g (0.979 mmol, 98% yield, *E*:*Z*=>99:1) of the title compound **5ca** as a colourless oil.

*4.3.1. Ethyl 4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-3-phenylnon-2-enoate (**5ca**).* R_f=0.30 (*n*-hexane:CH_2Cl_2=4:1). ^{1}H NMR δ 1.03 (3H, t, *J*=7.1 Hz), 4.02 (2H, q, *J*=7.1 Hz), 6.62 (1H, t, *J*=1.4 Hz), 7.24–7.26 (2H, m), 7.35–7.43 (3H, m). ^{13}C NMR δ 13.6, 61.1, 106.3–122.9 (m), 128.0, 128.3 (t, *J*=8.7 Hz), 129.1, 129.2, 142.1 (t, *J*=21.7 Hz), 164.0. ^{19}F NMR δ −127.39 (2F, m), −124.08 (2F, m), −122.86 (2F, m), −120.90 (2F, m), −112.36 (2F, t, *J*=14.9 Hz), −82.05 (3F, m). IR (neat): ν 2988, 1739, 1446, 1365, 1242, 1200, 1146, 1122, 1071, 1028, 714, 698, 664, 621. Anal. Calcd for $C_{17}H_{11}F_{13}O_2$: C, 41.31; H, 2.24. Found: C, 41.47; H, 2.22.

*4.3.2. Ethyl 4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-3-(p-methoxy-phenyl)non-2-enoate (**5cb**).* 49% yield, *E*:*Z*=>99:1. Rf=0.15 (*n*-hexane:CH_2Cl_2=4:1). ^{1}H NMR δ 1.09 (3H, t, *J*=7.1 Hz), 3.83 (3H, s), 4.05 (2H, q, *J*=7.2 Hz), 6.57 (1H, t, *J*=1.4 Hz), 6.85 (2H, td, *J*=2.4, 8.7 Hz), 7.19 (3H, d, *J*=8.7 Hz). ^{13}C NMR δ 13.7, 55.1, 61.1, 105.0–119.5 (m), 113.5, 123.4, 127.8 (t, *J*=8.7 Hz), 130.6, 141.8 (t, *J*=21.7 Hz), 160.4, 164.2. ^{19}F NMR δ −127.42 (2F, m), −124.08 (2F, m), −122.88 (2F, m), −120.98 (2F, m), −112.51 (2F, t, *J*=14.8 Hz), −82.05 (m). IR (neat) ν 2986, 2941, 2910, 2843, 1737, 1610, 1515, 1364, 1294, 1243, 1203, 1146, 1121, 1070, 1035, 834, 736, 713. Anal. Calcd for $C_{18}H_{13}F_{13}O_3$: C, 41.24; H, 2.50. Found: C, 41.54; H, 2.44.

*4.3.3. Ethyl 4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-3-[p-(tri-fluoromethyl)phenyl]non-2-enoate (**5cc**).* Quantitative yield, *E*:*Z*=>99:1. Rf=0.15 (*n*-hexane:CH_2Cl_2=4:1). ^{1}H NMR δ 1.05 (3H, t, *J*=7.1 Hz), 4.04 (2H, q, *J*=7.1 Hz), 6.68 (1H, t, *J*=1.4 Hz), 7.39 (2H, d, *J*=8.1 Hz), 7.7 (2H, d, *J*=8.1 Hz). ^{13}C NMR δ 13.5, 61.4, 104.6–119.5 (m), 123.8 (q, *J*=271.7 Hz), 125.0 (q, *J*=3.7 Hz), 129.2 (t, *J*=8.7 Hz), 129.7, 131.5 (q, *J*=32.9 Hz), 135.1, 141.1 (t, *J*=22.3 Hz), 163.4. ^{19}F NMR δ −127.42 (2F, m), −124.05 (2F, m), −122.87 (2F, m), −120.83 (2F, m), −112.27 (2F, t, *J*=16.0 Hz), −82.06 (3F, m), −64.19 (3F, s). IR (neat) ν 2990, 1738, 1620, 1410, 1328, 1244, 1203, 1137, 1069, 1022, 994, 910, 842, 806, 766, 745, 714, 666, 633. Anal. Calcd for $C_{18}H_{13}F_{13}O_3$: C, 41.24; H, 2.50. Found: C, 41.54; H, 2.44.

*4.3.4. Ethyl 4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-3-methylnon-2-enoate (**5ce**).*[16] Yield: 71%, *E*:*Z*=>99:1. R_f=0.46 (*n*-hexane:CH_2Cl_2=4:1). ^{1}H NMR δ 1.32 (3H, t, *J*=7.2 Hz), 2.28 (3H, q, *J*=1.3 Hz), 4.24 (2H, q, *J*=7.1 Hz), 6.30 (1H, q, *J*=1.3 Hz). ^{13}C NMR δ 13.2 (m), 14.0, 61.0, 106.7–123.4 (m), 124.9 (t, *J*=9.3 Hz), 142.4 (t, *J*=21.1 Hz), 164.6. ^{19}F NMR δ −127.39 (2F, m), −124.04 (2F, m), −123.06 (2F, m), −122.73 (2F, m), −115.50 (2F, t, *J*=14.8 Hz), −82.03 (3F, m). IR (neat) ν 2989, 2965, 2914, 1733, 1666, 1449, 1354, 1243, 1120, 1147, 1122, 1106, 1041, 905, 886, 837, 808, 779, 745, 722, 702, 648. Anal. Calcd for $C_{12}H_9F_{13}O_2$: C, 33.35; H, 2.10. Found: C, 33.38; H, 2.02.

*4.3.5. Ethyl 3-ethyl-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononon-2-enoate (**5cf**).* 42% yield, *E*:*Z*=>99:1 by Method 4. R_f=0.41 (*n*-hexane:CH_2Cl_2=4:1). ^{1}H NMR δ 1.81 (3H, t, *J*=7.5 Hz), 1.33 (3H, t, *J*=7.2 Hz), 2.69 (2H, q, *J*=7.4 Hz), 4.24 (2H, q, *J*=7.1 Hz), 6.26 (1H, t, *J*=1.5 Hz). ^{13}C NMR δ 13.8, 14.0, 21.0, 61.0, 104.7–119.7 (m), 125.1 (t, *J*=9.3 Hz), 148.5 (t, *J*=20.5 Hz), 164.2. ^{19}F NMR δ −127.39 (2F, m), −124.05 (2F, m), −122.91 (2F, m), −122.58 (2F, m), −114.49 (2F, t, *J*=13.7 Hz), −82.05 (3F, m). IR (neat) ν 2987, 2948, 2888, 1733, 1658, 1468, 1383, 1364, 1295, 1245, 1202, 1147, 1121, 1070, 1041, 1019, 899, 806, 769, 744, 710, 660. Anal. Calcd for $C_{13}H_{11}F_{13}O_2$: C, 34.99; H, 2.48. Found: C, 34.92; H, 2.35.

*4.3.6. Ethyl 4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-3-isopropyl-non-2-enoate (**5cg**).* 22% yield, *E*:*Z*=>99:1. R_f=0.51 (*n*-hexane:CH_2Cl_2=4:1). ^{1}H NMR δ 1.27 (6H, d, *J*=6.9 Hz), 1.33 (3H, t, *J*=7.1 Hz), 3.23 (1H, sept, *J*=7.1 Hz), 4.25 (2H, q, *J*=7.1 Hz), 6.25 (1H, m). ^{13}C NMR δ 14.0, 20.4, 28.5, 61.2, 104.7–123.0 (m), 126.0 (t, *J*=9.9 Hz), 149.5 (t, *J*=19.8 Hz), 164.7. ^{19}F NMR δ −127.41 (2F, m), −124.05 (2F, m), −122.90 (2F, m), −121.71 (2F, m), −111.40 (2F, t, *J*=16.0 Hz), −82.05 (3F, m). IR (neat) ν 2987, 2948, 2888, 1733, 1658, 1468, 1383, 1364, 1295, 1245, 1202, 1147, 1121, 1070, 1041, 1019, 900, 806, 769, 744, 711, 660. Anal. Calcd for $C_{14}H_{13}F_{13}O_2$: C, 36.54; H, 2.85. Found: C, 36.67; H, 2.74.

*4.3.7. Ethyl 3-(1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexyl)dec-2-enoate (**5cj**).* 56% yield, *E*:*Z*=>99:1. R_f=0.53 (*n*-hexane:CH_2Cl_2=4:1). ^{1}H NMR δ 0.88 (3H, t, *J*=6.8 Hz), 1.24–1.42 (11H, m), 1.48–1.58 (2H, m), 2.62 (2H, m), 4.24 (2H, q, *J*=7.2 Hz), 6.25 (1H, m). ^{13}C NMR δ 13.97, 13.99, 22.6, 27.8, 28.9, 29.8, 30.0, 31.8, 60.9, 104.2–123.4 (m), 125.0 (t, *J*=9.3 Hz), 147.4 (t, *J*=20.8 Hz), 164.3. ^{19}F NMR δ −127.47 (2F, m), −124.11 (2F, m), −122.96 (2F, m), −122.63 (2F, m), −111.47 (2F, t, *J*=15.8 Hz), −82.07 (3F, m). IR (neat) ν 2960, 2933, 2860, 1732, 1657, 1468, 1377, 1363, 1242, 1198, 1147,

1122, 1077, 1039, 889, 839, 809, 778, 738, 722, 710, 659. Anal. Calcd for $C_{18}H_9F_{13}O_2$: C, 41.87; H, 4.10. Found: C, 42.00; H, 3.93.

4.4. General procedure for preparation of β-CF_3-α,β-unsaturated esters (11)

To an enolate solution from the HWE reagent **3a** (2.86 g, 10.0 mmol), LiBr (1.08 g, 12.3 mmol), Et_3N 1.53 mL (11.3 mmol) in THF (10 mL) prepared above, was slowly introduced at 0 °C 1.27 g (10.9 mmol) of trifluoroacetaldehyde hydrate, $CF_3CH(OH)_2$, and the resultant materials were stirred at rt for 1 h. The mixture was quenched by the addition of 1 *M* HCl aq so as to control the pH of the solution from 6 to 7, and the usual workup and purification by column chromatography (*n*-hexane: AcOEt=5:1) afforded 1.82 g of benzyl 4,4,4-trifluoro-3-phenyl-but-2-enoate **11ad** (7.9 mmol, 79% yield, *E*:*Z*=>99:1) as a colourless oil.

*4.4.1. Preparation of benzyl 4,4,4-trifluorobut-2-enoate (**11ad**).*[1a] Rf=0.59 (*n*-hexane:AcOEt=5:1). ^{1}H NMR δ 5.24 (2H, s), 6.53 (1H, qd, *J*=1.9, 15.7 Hz), 6.81 (1H, qd, *J*=6.5, 15.8 Hz), 7.25–7.29 (5H, m). ^{13}C NMR δ 67.2, 121.9 (q, *J*=269.9 Hz), 128.3, 128.5, 128.6 (q, *J*=6.2 Hz), 131.5, 131.9, 167.2. ^{19}F NMR δ −66.93 (d, *J*=7.1 Hz). IR (neat) ν 3000, 1730, 1665, 1375, 1310, 1260, 1190, 1130, 965, 740, 700.

*4.4.2. Benzyl 4,4,5,5,5-pentafluoropent-2-enoate (**11bd**).* R_f=0.55 (*n*-hexane/AcOEt=10:1). ^{1}H NMR δ 5.24 (2H, s), 6.59 (1H, td, *J*=2.0, 15.8 Hz), 6.84 (1H, td, *J*=11.4, 15.8 Hz), 7.31–7.46 (5H, m). ^{13}C NMR δ 67.5, 111.5 (qt, *J*=39.1, 251.4 Hz), 118.5 (tq, *J*=36.7, 284.8 Hz), 128.5, 128.7, 130.7 (t, *J*=8.7 Hz), 130.8 (t, *J*=24.0 Hz), 163.4. ^{19}F NMR δ −118.50 (2F, d, *J*=11.6 Hz), −85.86 (3F, s). IR (neat) ν 3250, 2950, 2550, 2400, 2150, 1950, 1930, 1900, 1880, 1850, 1835, 1810, 1780, 1755, 1740, 1725, 1580, 1565, 1440, 1340, 1280, 1200, 1120, 1040, 970, 730, 700, 540, 480. HRMS (FAB) *m/z* calcd for $C_{12}H_9F_5O_2$ $[M+H]^+$: 281.0601; found: 281.0586.

4.5. General procedure for preparation of β-CF_3-α-substituted α,β-unsaturated esters (12)

To an enolate solution from the α-benzylated HWE reagent **3c**[19] (0.94 g, 3.0 mmol), LiBr (0.313 g, 3.60 mmol), Et_3N 0.46 mL (3.3 mmol) in THF (5.0 mL) prepared above was slowly introduced at 0 °C 0.38 g (3.3 mmol) of $CF_3CH(OH)_2$, and the resultant materials were stirred at 50 °C for overnight. The mixture was quenched by the addition of 1 *M* HCl aq so as to control the pH of the solution from 6 to 7, and the usual workup and purification by column chromatography (*n*-hexane:AcOEt=10:1) afforded 0.625 g of ethyl 2-benzyl-4,4,4-trifluorobut-2-enoate **12al** (2.42 mmol, 81% yield, *E*:*Z*=15:85) as a colourless oil.

*4.5.1. Ethyl 2-benzyl-4,4,4-trifluorobut-2-enoate (**12al**).* **(*E*)-isomer:** R_f=0.63 (*n*-hexane:AcOEt=10:1). ^{1}H NMR δ 1.21 (3H, t, *J*=7.1 Hz), 3.89 (2H, br s), 4.17 (2H, q, *J*=7.0 Hz), 6.76 (1H, q, *J*=8.4 Hz), 7.17–7.41 (5H, m). ^{13}C NMR δ 13.7, 33.6, 61.8, 122.8 (q, *J*=271.3 Hz), 126.0 (q, *J*=34.8 Hz), 126.6, 128.5, 128.6, 136.8, 142.3 (q, *J*=5.0 Hz), 165.4. ^{19}F NMR δ −58.94 (d, *J*=6.78 Hz). IR (neat) ν 2930, 1725, 1705, 1665, 1605, 1440, 1360, 1260, 1205, 1140, 1075, 1020, 940, 750, 700. Anal. Calcd for $C_{13}H_{13}F_3O_2$: C, 60.46; H, 5.07. Found: C, 60.57; H, 5.05.

(*Z*)-isomer: R_f=0.51 (*n*-hexane:AcOEt=10:1). ^{1}H NMR δ 1.24 (3H, t, *J*=7.1 Hz), 3.67 (2H, dq, *J*=4.2, 2.1 Hz), 4.20 (2H, q, *J*=7.0 Hz), 5.47 (1H, qt, *J*=7.8, 1.8 Hz), 7.17–7.41 (5H, m). ^{13}C NMR δ 13.7, 40.1, 61.7, 119.4 (q, *J*=35.7 Hz), 122.1 (q, *J*=270.3 Hz), 127.3, 128.8, 129.3, 135.0, 144.7 (q, *J*=5.2 Hz), 166.5. ^{19}F NMR δ −60.82 (d, *J*=6.8 Hz). IR (neat) ν 2930, 1730, 1705, 1680, 1380, 1285, 1250, 1190, 1140, 1020, 860, 740, 700. Anal. Calcd for $C_{13}H_{13}F_3O_2$: C, 60.46; H, 5.07. Found: C, 60.41; H, 5.05.

*4.5.2. Ethyl 2-benzyl-4,4,5,5,5-pentafluoropent-2-enoate (**12bl**).* **(*E*)-isomer:** R_f=0.55 (*n*-hexane:AcOEt=10:1). ^{1}H NMR δ 1.20 (3H, t, *J*=7.2 Hz), 3.92 (2H, br s), 4.17 (2H, q, *J*=7.0 Hz), 6.70 (1H, t, *J*=14.7 Hz), 7.18–7.37 (5H, m). ^{13}C NMR δ 13.8, 33.5 (t, *J*=2.5 Hz), 62.0, 108.5–120.7 (m), 123.7 (t, *J*=22.9 Hz), 126.7, 128.49, 128.54, 129.3, 136.8 (t, *J*=1.2 Hz), 144.3 (t, *J*=3.7 Hz), 165.3 (t, *J*=1.3 Hz). ^{19}F NMR δ −86.37 (s), −112.09 (d, *J*=13.6 Hz). IR (neat) ν 3200, 2950, 2550, 2400, 2150, 1950, 1920, 1890, 1870, 1850, 1830, 1800, 1780, 1750, 1735, 1720, 1340, 1320, 1250, 1190, 1110, 1030, 810, 730, 700, 600, 530, 480. HRMS (FAB) *m/z* calcd for $C_{14}H_{14}F_5O_2$ $[M+H]^+$: 309.0914; found: 309.0941.

(*Z*)-isomer: R_f=0.48 (*n*-hexane:AcOEt=10:1). ^{1}H NMR δ 1.20 (3H, t, *J*=7.2 Hz), 3.69 (2H, m), 4.19 (2H, q, *J*=7.2 Hz), 5.35 (1H, t, *J*=14.1 Hz), 7.17–7.41 (5H, m). ^{13}C NMR δ 13.6, 41.0 (t, *J*=1.2 Hz), 61.7, 107.5–121.0 (m), 115.4 (t, *J*=20.4 Hz) 127.4, 128.8, 129.3, 134.8, 147.1 (t, *J*=5.6 Hz), 166.9 (t, *J*=1.9 Hz). ^{19}F NMR δ −86.33 (s), −113.88 (d, *J*=13.9 Hz). IR (neat) ν 3250, 2950, 2600, 2400, 2200, 1950, 1930, 1900, 1880, 1850, 1840, 1810, 1780, 1755, 1740, 1725, 1380, 1320, 1280, 1200, 1130, 1040, 820, 730, 700, 600, 540, 480. HRMS (FAB) *m/z* calcd for $C_{14}H_{14}F_5O_2$ $[M+H]^+$: 309.0914; found: 309.0931.

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References and notes

1. (a) Shinohara, N.; Haga, J.; Yamazaki, T.; Kitazume, T.; Nakamura, S. *J. Org. Chem.* **1995**, *60*, 4363–4374; (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Van Meervelt, L. *Tetrahedron* **1999**, *55*, 12045–12058; (c) Molteni, M.; Volonterio, A.; Zanda, M. *Org. Lett.* **2003**, *5*, 3887–3890; (d) Christophe, C.; Billard, T.; Langlois, B. R. *Eur. J. Org. Chem.* **2005**, 3745–3748; (e) Powell, A.; Al Nakeeb, M.; Wilkinson, B.; Micklefield, J. *J. Chem. Soc., Chem. Commun.* **2007**, 2683–2685; (f) Zhang, F.; Liu, Z.-J.; Liu, J.-T. *Tetrahedron* **2010**, *66*, 6864–6868; (g) Dong, X.-Q.; Fang, X.; Wang, C.-J. *Org. Lett.* **2011**, *13*, 4426–4429.
2. (a) Okano, T.; Nagai, T.; Eguchi, S.; Kimoto, H. *Heterocycles* **1999**, *50*, 53–56; (b) uger, J.; Blond, G.; Fröhlich, R.; Billard, T.; Haufe, G.; Langlois, B. R. *J. Org. Chem.* **2006**, *71*, 2735–2739; (c) Shibatomi, K.; Kobayashi, F.; Narayama, A.; Fujisawa, I.; Iwasa, S. *Chem. Commun.* **2012**, 413–415.
3. (a) Li, Q.-H.; Tong, M.-C.; Li, J.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2011**, 11110–11112; (b) Li, Q.-H.; Xue, Z.-Y.; Tao, H.-Y.; Wang, C.-J. *Tetrahedron Lett.* **2012**, *53*, 3650–3653; (c) Schmidt, M. A.; Katipally, K.; Ramirez, A.; Soltani, O.; Hou, X.-P.; Zhang, H.-P.; Chen, B.-C.; Qian, X.-H.; Deshpande, R. P. *Tetrahedron Lett.* **2012**, *53*, 3994–3997.
4. Wang, H.; Zhao, X.-M.; Li, Y.-H.; Lu, L. *J. Org. Chem.* **2006**, *71*, 3278–3281.
5. (a) Dong, K.-W.; Li, Y.; Wang, Z.; Ding, K.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 14191–14195; (b) Xiao, Y.-L.; Chang, W.-C.; Liu, H.-W.; Liu, P.-H. *Org. Lett.* **2011**, *13*, 5912–5915; (c) Wang, P.; Tang, Y.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 6900–6906; (d) Konno, T.; Takehana, T.; Mishima, M.; Ishihara, T. *J. Org. Chem.* **2006**, *71*, 3545–3550; (e) Pinna, G. A.; Cignarella, G.; Ruiu, S.; Loriga, G.; Murineddu, G.; Villa, S.; Grella, G. E.; Cossu, G.; Fratta, W. *Bioorg. Med. Chem.* **2003**, *11*, 4015–4026.
6. Preparation methods other than Wittig protocols. Michael addition to β-CF_3-propynoate, see (a) Zine, K.; Petrignet, J.; Thibonnet, J.; Abarbri, M. *Synlett* **2012**, 755–759; (b) Wang, P.-A.; Deng, M.-Z.; Pan, R.-Q.; Zhang, S.-Y. *J. Fluorine Chem.* **2003**, *124*, 93–97 Coupling with β-CF_3-β-I-acrylates, see; (c) Hafner, A.; Brase, S. *Adv. Synth. Catal.* **2011**, *353*, 3044–3048; (d) Thibonnet, J.; Duchene, A.; Parrain, J.-L.; Abarbri, M. *J. Org. Chem.* **2004**, *69*, 4262–4264 Perkin reaction, see; (e) Cserenyi, S.; Felfoeldi, K.; Forgo, P.; Palinko, I. *J. Fluorine Chem.* **2006**, *127*, 850–853 Diazoacetate; (f) Chen, Y.; Huang, L.-Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 5925–5929 Coupling with β-CF_3-acrylates, see; (g) Gong, Y.; Kato, K.; Kimoto, H. *J. Fluorine Chem.* **2000**, *105*, 169–173.
7. The following article includes an important method which enables the construction of β-substituted β-Rf-α,β-unsaturated esters in excellent yields. See Shen, Y.-C.; Gao, S. *J. Org. Chem.* **1993**, *58*, 4564–4566.
8. (a) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3–11; (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004; (c) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, UK, 2006; (d) Yamazaki, T.; Taguchi, T.; Ojima, I. In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley: West Sussex, UK, 2009; pp 3–46.
9. In situ formation of aldehydes by DIBAL reduction of esters, followed by successive HWE type condensation, see (a) Thenappan, A.; Burton, D. J. *J. Org. Chem.* **1990**, *55*, 4639–4642; (b) Lanier, M.; Haddach, M.; Pastor, R.; Riess, J. G. *Tetrahedron Lett.* **1993**, *34*, 2469–2472.

10. For the two-step procedures of 1) transformation of $RfCO_2R$ to $RfCH(OH)OR$, followed by 2) condensation with HWE reagents, see (a) Tsukamoto, T.; Kitazume, T. *Synlett* **1992**, 977–979; (b) Nakamura, Y.; Okada, M.; Koura, M.; Tojo, M.; Saito, A.; Sato, A.; Taguchi, T. *J. Fluorine Chem.* **2006**, *127*, 627–636.
11. We have found out one example, which, on the synthesis of ethyl 3-(trifluoromethyl)pent-2-enoate, used a crude mixture of 1,1,1-tifluorobutan-2-one obtained from CF_3CO_2Et and EtMgBr. After quenching of this Grignard reaction and extraction, the resultant ethereal layer was added to the HWE reagent 3b after treatment with NaH. The obtained product was further hydrogenated and reduced to the saturated alcohol, which was eventually tosylated to isolate the corresponding tosylate in a total yield of 42%. See Miyazaki, H. WO 2008143332.
12. Brendan, M.; O'Leary, B. M.; Szabo, T.; Sventrup, N.; Schalley, C. A.; Lutzen, A.; Schafer, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 11519–11533.
13. Yamazaki, T.; Terajima, T.; Kawasaki-Takasuka, T. *Tetrahedron* **2008**, *64*, 2419–2424.
14. In this case, *c*-$C_6H_{11}MgBr$ was prepared in a 30 mmol scale, and only one report was found for the construction of the same ketone **2ai** in 66% yield by *c*-$C_6H_{11}MgCl$. See Creary, X. *J. Org. Chem.* **1987**, *52*, 5026–5030.
15. (a) Yamada, S.; Takahashi, T.; Konno, T.; Ishihara, T. *Chem. Commun.* **2007**, 3679–3681; (b) Yamada, S.; Takahashi, T.; Konno, T.; Ishihara, T. *J. Fluorine Chem.* **2013**, *149*, 95–103.
16. (a) Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Fluorine Chem.* **1984**, *26*, 341–358; (b) Uno, H.; Shiraishi, Y.; Shimokawa, K.; Suzuki, H. *Chem. Lett.* **1987**, 1153–1156; (c) Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem.* **1987**, *52*, 2481–2490.
17. Yajima, T.; Jahan, I.; Tonoi, T.; Shinmen, M.; Nishikawa, A.; Yamaguchi, K.; Sekine, I.; Nagano, H. *Tetrahedron* **2012**, *68*, 6856–6861.
18. For example, boiling points of representative fluorinated ketones are as follows. Trifluoroacetone **2ae** ($CF_3C(O)CH_3$): 22 °C, 1,1,1-trifluorobutan-2-one **2af** ($CF_3C(O)C_2H_5$): 44–45 °C, 1,1,1,2,2-pentafluorobutan-3-one **2be** ($C_2F_5C(O)CH_3$): 41.9 °C (data from the catalog of SynQuest Laboratory); 1,1,1-trifluorohexan-2-one **2ah** ($CF_3C(O)C_4H_9$): 89 °C Trabelsi, H.; Bertaina, B.; Cambon, A. *Can. J. Chem.* **1985**, *63*, 426–431.
19. For the mechanistic study of HWE reactions, see Ando, K. *J. Org. Chem.* **1999**, *64*, 6815–6821.
20. Hackelöer, K.; Schnakenburg, G.; Waldvogel, S. R. *Eur. J. Org. Chem.* **2011**, 6314–6319.