Article

# F-Free Deoxyhydrotrifluoromethylation of #-Keto Esters with Ph3P+CF2CO2-: Synthesis of #-CF3-Substituted Esters

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# $F^-$-Free Deoxyhydrotrifluoromethylation of α-Keto Esters with $Ph_3P^+CF_2CO_2^-$: Synthesis of α-$CF_3$-Substituted Esters

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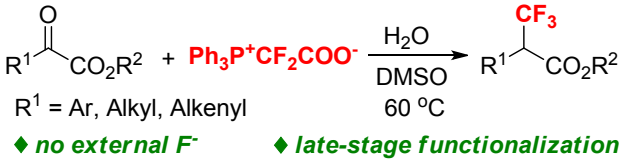



## ABSTRACT

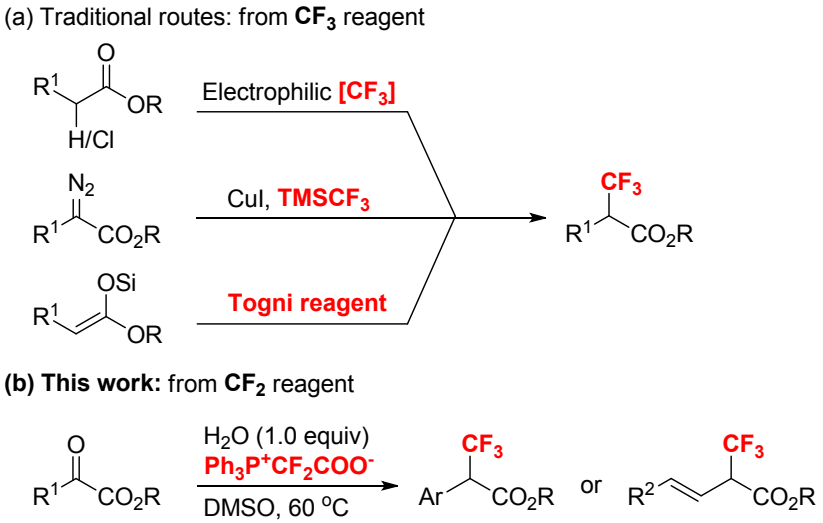
Trifluoromethylated compounds are usually obtained via trifluoromethylation reaction by use of $CF_3SiMe_3$, $NaSO_2CF_3$, Umemoto's and Togni's reagent. Here, an external fluorine anion-free direct deoxyhydrotrifluoromethylation of α-keto esters with a difluoromethylating reagent has been achieved in which the employment of water can promote the dissociation of $CF_2$ group to form $CF_3$ moiety, which provides the successful transformation. The current protocol demonstrates one of the most practical approaches to generate α-trifluoromethyl esters with a broad substrate scope and high functional group compatibility, in which it is applicable to late-stage modification of biologically active compounds and can be readily scaled up. Mechanistic investigation reveals that an in situ generated *gem*-difluoroalkene intermediate is decomposed by water, giving rise to acid fluoride and HF.

## INTRODUCTION

Trifluoromethyl ($CF_3$) containing organic compounds do not exist in natural products.[1] The development of efficient synthetic methodologies for the incorporation of $CF_3$ group into organic molecules has received more attention in recent years.[2] Owing to its unique physical, chemical and biological properties, $CF_3$ group can substantially alter an organic molecule's lipophilicity, metabolic stability and ability to cross the blood-brain barrier, trifluoromethylated compounds have found wide application in the medicinal, pharmaceutical, agricultural, and material sciences.[3]

Although significant advancements in this field have been made in the direct introduction of $CF_3$ group into organic moieties, such as nucleophilic, electrophilic, and free radical reactions,[2] the methods for the synthesis of functionalized α-trifluoromethylated carboxylic acid esters is still relatively limited.[6-11] In addition, α-trifluoromethylated carboxylic acids, which have been identified as bioactive compounds[4] and versatile intermediates[5] in synthetic chemistry. To this end, a few elegant work showed that the synthesis of α-$CF_3$ esters could be achieved by the reaction of ester derivatives,[6] α-diazo esters[7] and sensitive ketene silyl acetals[8] with Togni's reagent,[9] Umemoto's reagent,[6a,10] $CF_3I$ and $TMSCF_3$ (Scheme 1a). Most of these methods required highly activated substrates such as β-keto esters, α-nitro esters or silyl enol ethers, catalyst and/or excess base. Consequently, the substrate scope and practicality of such methodologies are limited.

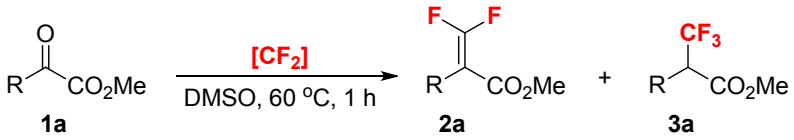
**Scheme 1. Direct Trifluoromethylation for the Synthesis of α-$CF_3$ Esters**




More recently, Kobayashi and co-workers[11] have developed an alternative approach to access α-trifluoromethyl esters or acids through fluorocarboxylation of *gem*-difluoroalkenes. However, this version requires stoichiometric quantities of CsF for constructing $CF_3$ group from difluoroalkene and the use of high pressure $CO_2$ as starting materials, which impedes its wide applications. Therefore, it is still of great demand to develop a practical, more convenient and suitable method for large-scale preparation procedure for the synthesis of α-$CF_3$ esters with wide functional group compatibility. Given the widespread availability of difluoromethylating reagents, we wondered whether the formation of α-$CF_3$ esters from a difluoromethylating reagent should proceed in a practical and sustainable fashion under neutral conditions without the presence of a catalyst. There are many methods that have reported *gem*-difluoroalkene which can be served as an alternative $CF_3$ precursor. However, an additional fluoride anion reagent, such as $Et_3N{\cdot}HF$, KF, CsF, AgF, or $Bu_4NF$ is necessary in order to construct a trifluoromethyl moiety.[11-12] Currently, various types of difluoromethylating reagents, especially that serve as the difluorocarbene precursors, have been developed and their reactivity towards different

nucleophiles and electrophiles studied.[13] It is step- and atom-economy if a $CF_3$ group is formed directly from a difluoromethylating reagent without an extra fluoride anion reagent. Herein, we describe a novel and catalyst-free process for the synthesis of functionalized α-trifluoromethyl esters through deoxyhydrotrifluoromethylation of α-keto esters, in which a difluoromethylating reagent $Ph_3P^+CF_2CO_2^-$ [14] is the sole $CF_3$ source (Scheme 1b).

**Scheme 2. Initial Trials with Different Difluoromethy-lating Reagent**




R = styryl

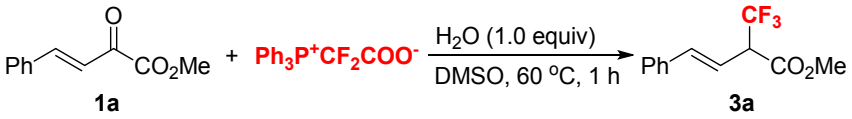
| [$CF_2$] | **2a** (%) | **3a** (%) |
|---|---|---|
| $HCF_2Cl/PPh_3$ | 0 | 0 |
| $ClCF_2CO_2Na/PPh_3$ | 0 | trace |
| $Ph_3P^+CF_2CO_2^-$ | 0 | 17 |

With our continued interests on the development of fluoroalkylation based on difunctionalization strategy,[15] we began our investigation of this transformation by attempting the deoxyhydrotrifluoromethylation of *trans*-methyl 2-oxo-4-phenylbut-3-enoate **1a**. According to previous reports, the treatment of aldehydes and ketones with typical difluorocarbene precursors, such as $ClCF_2H$, $ClCF_2COONa$, $Ph_3P^+CF_2CO_2^-$, etc, *gem*-difluoroalkenes could be readily formed in the absence of an additional fluoride anion reagent.[14a,14b,16] Obviously, a key challenge for such process is to avoid the reaction progress terminated at *gem*-difluoroalkene. Initially, when $ClCF_2H$ /$PPh_3$, $ClCF_2COONa/PPh_3$ or $Ph_3P^+CF_2CO_2^-$ were employed as difluoromethylating reagent and react with **1a** in dimethyl sulfoxide (DMSO) at 60 °C under an argon atmosphere for 1 h (Scheme 2). Surprisingly, no *gem*-difluoroalkene could be detected by $^{19}F$ NMR spectroscopy. The desired trifluoromethylated product **3a** was observed in 17% yield from $Ph_3P^+CF_2CO_2^-$. Encouraged by these preliminary results, several other commonly difluoromethylating reagents such as $BrCF_2PO(OEt)_2$/*t*BuOK, $BrCF_2COOK$, $BrCF_2COOEt$ and $TMSCF_2Br$ were also investigated, however, no fluorinated products were observed except for the complex reaction system.

Interestingly, when 1.0 equiv of water was added, the yield of the expected product **3a** was increased significantly to 98% (85% yield was isolated, Table 1, entry 1). Decreasing or increasing the amount of water reduced the yields of product to 78% and 86%, respectively (Table 1, entries 2-3). When the other protonic additives such as MeOH, EtOH, and *i*PrOH were employed instead of water, the expected reaction could also take place, albeit in lower yields (Table 1, entries 4-6). The product **3a** almost could not be obtained when relatively strong acidic additive AcOH was used (Table 1, entry 7). The results indicate that the efficiency of trifluoromethylation depends on the additive, with an

appropriate acidity. Then, several other solvents such as toluene, MeCN, THF, $CH_2Cl_2$, EtOAc, and DMF were screened (Table 1, entries 8-13), but the yield of **3a** was less than 63%. Finally, when the reaction was carried out at room temperature, **3a** was observed in less than 5% yield (Table 1, entry 14). It is noteworthy that the *gem*-difluoroalkene **2a** was not observed in all these conditions.

**Table 1. Investigation of the Reaction Conditions**[a]



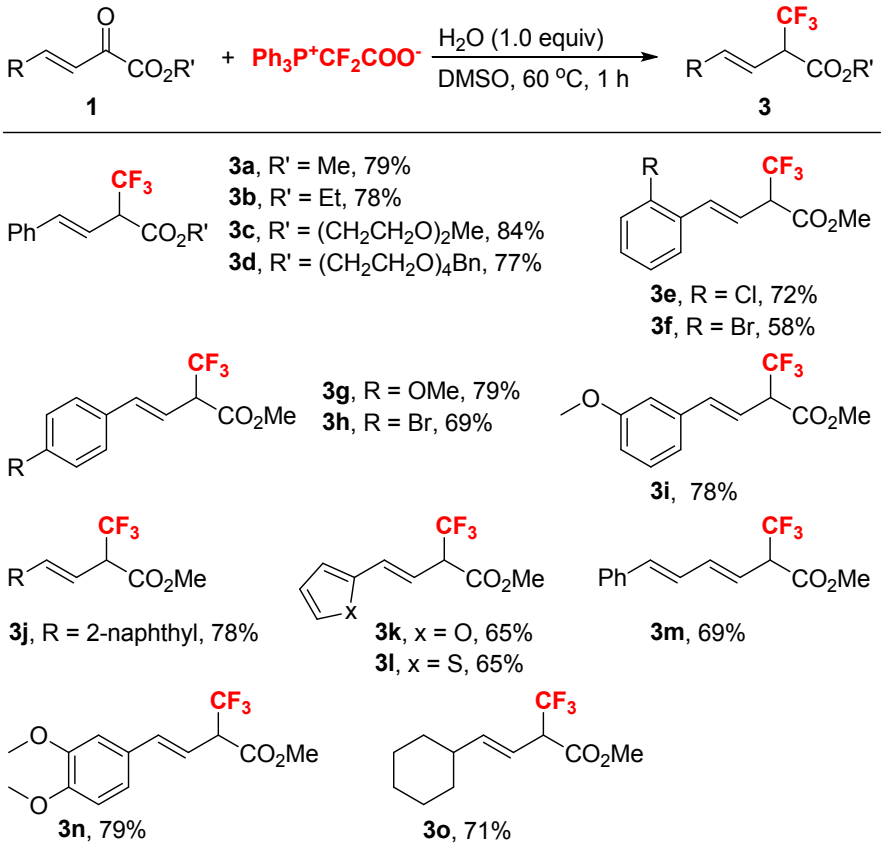

| entry | deviation from the standard conditions | yield (%)[b] |
|---|---|---|
| **1** | **none** | **98 (85)**[c] |
| 2 | 0.5 equiv $H_2O$ | 78 |
| 3 | 3.0 equiv $H_2O$ | 86 |
| 4 | MeOH instead of $H_2O$ | 56 |
| 5 | EtOH instead of $H_2O$ | 73 |
| 6 | *i*PrOH instead of $H_2O$ | 82 |
| 7 | AcOH instead of $H_2O$ | 12 |
| 8 | toluene as the solvent | <5 |
| 9 | MeCN as the solvent | 51 |
| 10 | THF as the solvent | 27 |
| 11 | $CH_2Cl_2$ as the solvent | 18 |
| 12 | EtOAc as the solvent | 44 |
| 13 | DMF as the solvent | 62 |
| 14 | the reaction was carried out at rt | <5 |

[a]Reaction conditions: **1a** (0.1 mmol), $Ph_3P^+CF_2CO_2^-$ (2.0 equiv) and $H_2O$ (1.0 equiv) in DMSO (1.0 mL) at 60 °C (oil bath) for 1 h. [b]Yields determined by $^{19}F$ NMR spectroscopy using trifluorotoluene as an internal standard. [c]The yield is for the isolated and purified product **3a**.

With the optimized conditions in hand (Table 1, entry 1), the generality of the transformation was examined with respect to different alkenyl-substituted α-keto esters (Scheme 3). This reaction system was not sensitive to the steric hindrance of the ester group adjacent to the ketone carbon, and changing from the methyl to ethyl and even functional polyethylene glycol (PEG) esters caused no drop in the yields of the corresponding products (**3a-d**, 77-84%). Subsequently, α-keto esters substrates bearing aromatic rings substituted with an electron-donating (OMe) or electron-withdrawing group (Cl, Br) on the *ortho*-, *para*-, or *meta*-position were investigated, leading to the expected pruducts **3e-i** in good yields. Substrate with a fused ring (**1j**, R = 2-naphthyl) worked smoothly, providing product **3j** in 78% yield. For furan and thiophene-derived α-keto esters, desired products **3k-l** were obtained in 65% yields.

It is worth noting that substrate containing a diene moiety was compatible with the current reaction protocol (**3m**). Substrate bearing two substituents at the aromatic ring of the styrene (**1n**) was also converted into α-$CF_3$ ester efficiently. Significantly, when an aliphatic alkene was combined in the α-keto ester and subjected to the standard reaction conditions, a high yield was provided (**3o**).

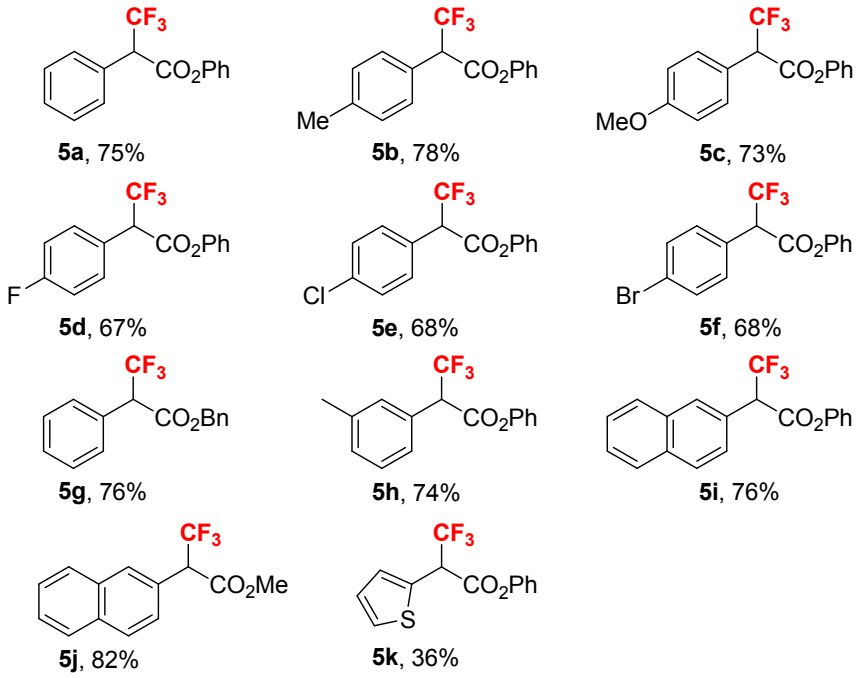
**Scheme 3. Substrate Scope of Alkenyl-substituted α-Keto Esters**[a]



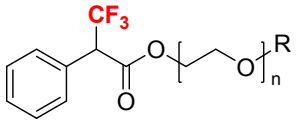

[a]Reaction conditions: **1** (0.5 mmol), $Ph_3P^+CF_2CO_2^-$ (2.0 equiv) and $H_2O$ (1.0 equiv) in DMSO (5.0 mL) at 60 °C (oil bath) for 1 h. Yields are for the isolated products **3**. Yield of the isolated and purified product

Inspired by the above results, we turned our attention to the unique reactivity of α-keto esters and performed some further experiments by utilizing different aryl-substituted α-keto esters (Scheme 4). The electronic property, positional change (*para*- or *meta*-) of the aromatic ring, and steric bulk of the esters did not have much impact on reaction efficiency, the products **5a-h** were afforded in good yields. It should be noted that substrates **4i-j** bearing fused ring moiety were tolerable with the reaction procedure. Heteroaryl α-keto ester **4k** is tolerated under the similar reaction conditions, albeit in a lower yield (36%). When an alkyl α-keto ester methyl 2-oxopropanoate was examined, the corresponding product was observed in 47% yield by $^{19}F$ NMR spectroscopy. Unfortunately, the product is difficult to isolate from relatively complicated reaction system, even purification of it 4 times through the silica gel column. The synthetic utility of this protocol was further investigated by late-stage

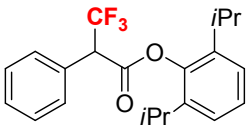
**Scheme 4. Substrate Scope of Aryl-substituted α-Keto Esters**[a]

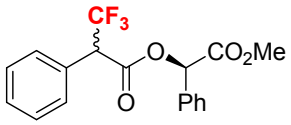

Late-stage deoxyhydrotrifluoromethylation of complex molecules



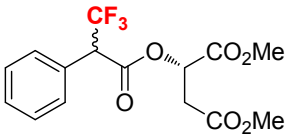
**5l**, n = 2 , R = Me, 67%
**5m**, n = 4 , R = Bn, 72%
(from polyethylene glycol)



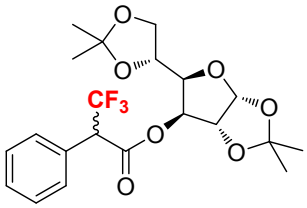

**5n**, 75%
(from propofol)



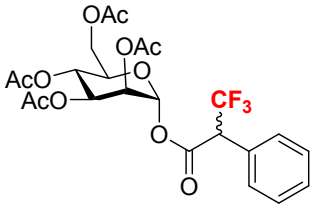

**5o**, 71%, *d.r.* = 1:1
(from mandelic acid)




**5p**, 59%, *d.r.* = 1:1
(from malic acid)




**5q**, 52%, *d.r.* = 1:1
(from glucose)



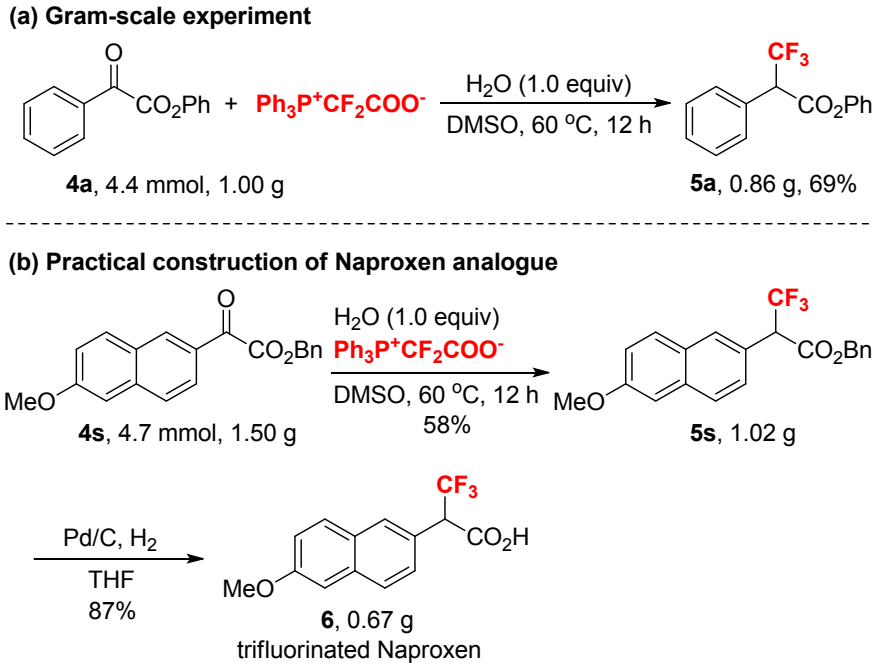

**5r**, 72%, *d.r.* = 56:44
(from mannose)

[a]Reaction conditions: **4** (0.5 mmol), $Ph_3P^+CF_2CO_2^-$ (3.0 equiv) and $H_2O$ (1.0 equiv) in DMSO (5.0 mL) at 60 °C (oil bath) for 12 h. Yields are for the isolated products **5**. Diastereomeric ratio was determined by $^1H$ NMR and $^{19}F$ NMR analysis of the crude product.

deoxyhydrotrifluoromethylation of complex molecules. Polyethylene glycols (PEGs),[17] which are water-soluble, nontoxic, and biocompatible polymers with widely applications, were included to subsrates and subjected to the deoxyhydrotrifluoromethylation, the reactions proceeded smoothly to generate desired products **5l-m** in 67-72% yields. Substrate **4n** derivatived from propofol,[18] a widely used intravenous anesthetic in clinical practice, gave the resulting product **5n** in 75% yield. Mandelic acid[19] and malic acid[20] derivatives **4o-p** were readily transformed to the corresponding functionalized α-$CF_3$ ester **5o-p** in moderate to good yields. Lastly, glycosyl containing α-keto esters **4q-r** prepared from glucose[21] and mannose,[22] respectively, could successfully react with $Ph_3P^+CF_2CO_2^-$, led to the glycosylated products **5q-r** in 52-72% yields and approximate 1:1 dr. However, probably because of high volatility of some products, relatively low yields were obtained in these cases.

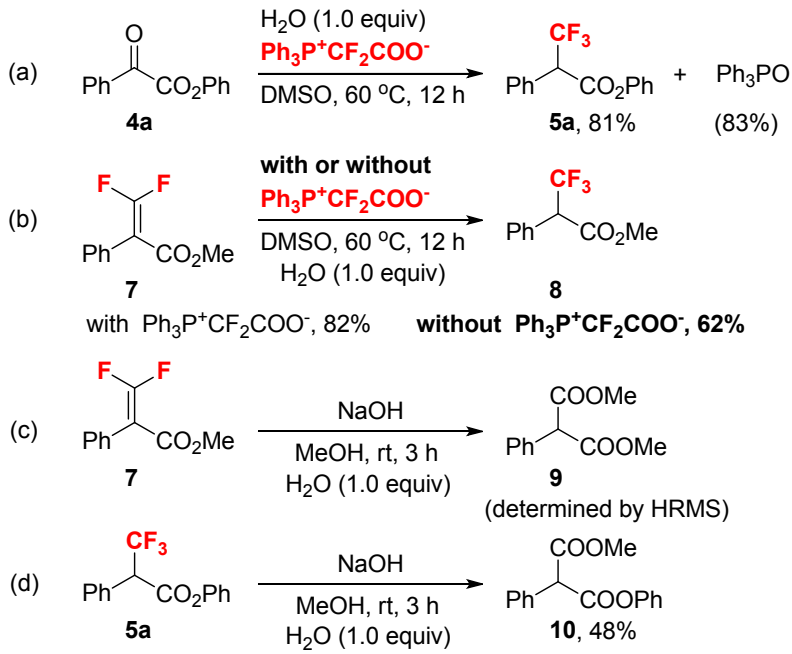
To further demonstrate the practical advantage of the current deoxyhydrotrifluoromethylation, a gram-scale reaction for the preparation of **5a** was conducted. The reaction proceeded smoothly under the optimal reaction conditions, the resulting product was achieved without significant drop in the yield (69%, Scheme 5a). Encouraged by this result, we intended to apply this methodology to construct the trifluorinated analogue of Naproxen, which is a regularly used drug for the treatment of joint swelling, pain, and inflammation through inhibiting the action of cyclooxygenase involved in the production of prostaglandins. With this impression in mind, conducting the deoxyhydrotrifluoromethylation of α-keto ester **4s** on larger scale, 1.02 g of the desired α-$CF_3$ ester **5s** was furnished. Subsequently, the trifluorinated Naproxen **6** was formed in 87% yield by reduction of **5s** with Pd/C (Scheme 5b).

**Scheme 5. Gram-scale Synthesis and Construction of Trifluoromethylated Naproxen**



A series of additional experiments were conducted to gain insights into the reaction mechanism (Scheme 6). Interestingly, we analysed the reaction of **4a** with $Ph_3P^+CF_2CO_2^-$ under standard reaction conditions and found that a large amount of $Ph_3PO$ was observed (Scheme 6a). It indicates that a Wittig reaction may be occuring during the trifluoromethylation process and produced a *gem*-difluoroalkene as the key intermediate. Then, a *gem*-difluoroalkene **7** was synthesized and subjected to standard conditions, providing the corresponding α-$CF_3$ ester **8** in 82% yield, which confirms our speculation. In the meantime, the resulting α-$CF_3$ ester **8** was also detected in 62% yield in the absence of $Ph_3P^+CF_2CO_2^-$ (Scheme 6b). These results clearly show that the $CF_3$ group on the products may come from the hydrolysis of *gem*-difluoroalkenes. Treatment of *gem*-difluoroalkene **7** with NaOH in methanol at room temperature, malonate **9** was detected in the reaction mixture by HRMS (Scheme 6c). A similar malonate **10** was also afforded when the product **5a** was used under the same conditions, demonstrating that the $CF_3$ group of alkyl is unstable under strongly basic conditions (Scheme 6d).

**Scheme 6. Preliminary Mechanistic Exploration**



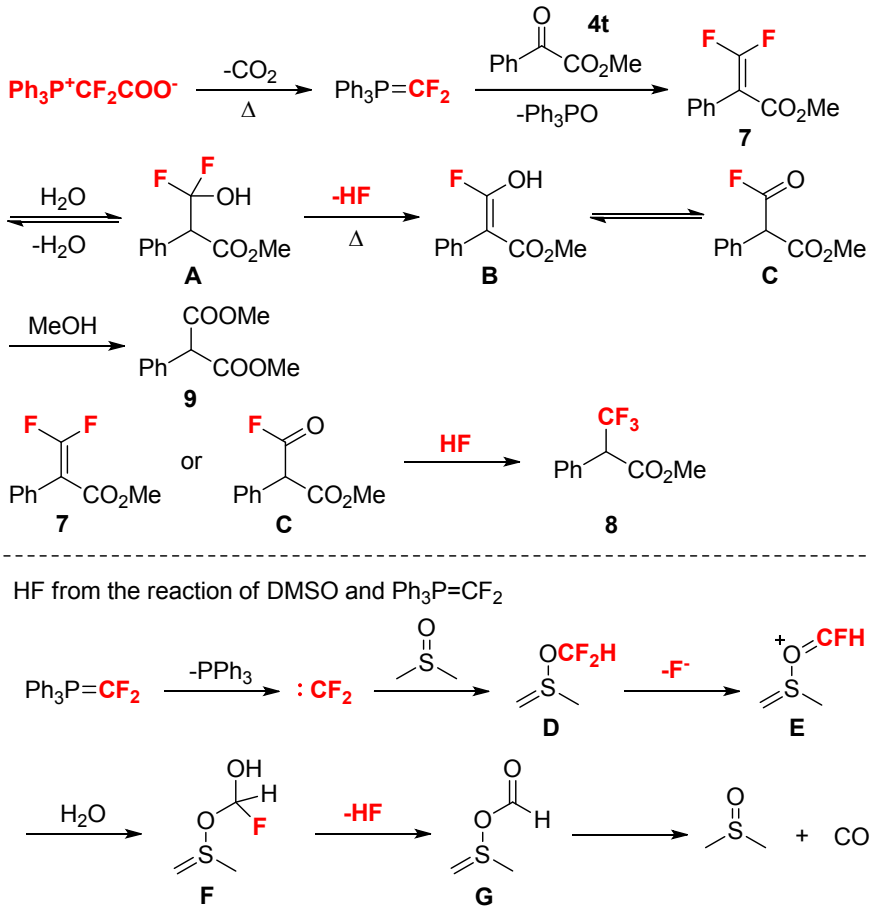

In light of above experimental results and literature reports,[14] a possible mechanism is described (Scheme 7). Initially, $Ph_3P^+CF_2CO_2^-$ can easily undergo a thermal decarboxylation to furnish the phosphonium ylide ($Ph_3P{=}CF_2$), which further reacts with α-keto ester **4t** results in the formation of *gem*-difluoroalkene **7** via a Wittig reaction. The species **A** could be obtained after the hydrolysis of *gem*-difluoroalkene. Subsequently, the elimination of HF from species **A** generated the enolate intermediate **B**, which could be further converted to the species **C** through the equilibrium between ketone and enol. Alternatively, a side product malonate **9** was furnished in the presence of methanol. Finally, the nucleophilic addition of *gem*-difluoroalkene **7** or intermediate **C** with HF delivered the α-$CF_3$ ester **8**. Moreover, the difluorocarbene intermediate (:$CF_2$), which could be easily formed by dissociation of the

phosphonium ylide, was captured by dimethyl sulfoxide, followed by thermal decomposition of the difluoromethylated intermediate in the presence of water, gives rise to CO and HF.[2d,14d] The *gem*-difluoroalkene was not detected in the reaction system owing to a rapid reaction process in which the fluoride ion ($F^-$) nucleophilic attacked the double bond ($C=CF_2$).

## CONCLUSION

In summary, a facile procedure for the efficient deoxyhydrotrifluoromethylation of a wide range of α-keto esters has been demonstrated, using $Ph_3P^+CF_2CO_2^-$ as the powerful trifluoromethylating reagent without an extra fluoride anion reagent. Water acts as essential role in promotion of the reaction to generate the trifluoromethyl moiety by decomposing the difluoromethylated intermediate. The employment of this protocol as a late-stage functionalization tool has also been developed through the successful deoxyhydrotrifluoromethylation of bioactive compounds. Owing to readily available and bench-stable starting materials as well as step-economy, this transformation is efficient and easy to scale up. Further development of other kinds of trifluoromethylation reactions using difluoromethylating reagents are currently underway in our laboratory.

**Scheme 7. Suggested Mechanism**



## EXPERIMENTAL SECTION

### General

Unless otherwise noted, proton ($^1$H), proton-decoupled carbon [$^{13}$C{1H}] and proton-decoupled fluorine [$^{19}$F{1H}] NMR spectra were recorded on Bruker Avance 400 MHz spectrometers. $^1$H NMR spectra were referenced to tetramethylsilane (s, 0.00 ppm) using $CDCl_3$ as solvent, $^{13}$C NMR spectra were referenced to solvent carbons (77.16 ppm for $CDCl_3$). $^{19}$F NMR spectra were referenced to 2% perfluorobenzene (s, -164.90 ppm) in $CDCl_3$. THF, $Et_2O$, toluene, EtOAc, DMF, MeCN and DMSO were dried and freshly distilled prior to use. Flash chromatography was performed on silica gel (200 - 300 mesh) with either EtOAc/petroleum ether (PE, 60 - 90 $^o$C). High-resolution mass spectrometry (HRMS) were recorded on a LTQ Orbitrap Elite or Agilent 1100-MSD spectrometers.

The known compounds **1a-1b**[23], **1e**[24], **1f-1n**[23], **1o**[24], **4a**[28], **4e**[29], **4g**[28], **4j**[25a], **4k**[25b] and **4s**[30] were prepared according to reported procedures, and all the spectra data are in agreement with the reports.

Synthesis of substrates

Preparation of compound **1c**, **1d**.[26]

To a solution of potassium (*E*)-2-oxo-4-phenylbut-3-enoate (2.1 g, 10.0 mmol, 1.0 equiv) in water (10 mL), 1 N HCl (15 mL) was added dropwise under magnetic stirring. The reaction mixture was stirred at rt for 12 h. A precipitate was generally formed and ethyl acetate (20 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). Organic layers were combined and dried on sodium sulfate. After filtration, solvent was removed under reduced pressure. The resulting residue was used for the next reaction without further purification.

To a solution of above residue in $CH_2Cl_2$ (20 mL) at 0 °C, were added successively DMAP (0.1 g, 12.0 mmol, 0.2 equiv), phenol or alcohol (5.9 mmol, 1.0 equiv), and DCC (1.8 g, 8.8 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 15 h, filtered through a short pad of celite and concentrated under reduced pressure. The crude material was purified by flash chromatography to afford the desired product.

***2-(2-Methoxyethoxy)ethyl (E)-2-oxo-4-phenylbut-3-enoate (1c).*** The product (1.33 g, 81% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 5/1) as a yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 16.2 Hz, 1H), 7.63 (dd, *J* = 7.6, 1.5 Hz, 2H), 7.48 – 7.40 (m, 3H), 7.33 (d, *J* = 16.2 Hz, 1H), 4.50 (dd, *J* = 5.5, 4.2 Hz, 2H), 3.84 (dd, *J* = 5.5, 4.2 Hz, 2H), 3.69 (dd, *J* = 5.6, 3.6 Hz, 2H), 3.56 (dd, *J* = 5.6, 3.6 Hz, 2H), 3.38 (s, 3H) ppm; $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) δ 182.7, 162.2, 148.6, 134.0, 131.6, 129.1, 129.0, 120.7, 71.8, 70.5, 68.6, 65.2, 59.0 ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{15}H_{18}NaO_5^+$ 301.1046, found 301.1052.

***Phenyl-2,5,8,11-tetraoxatridecan-13-yl (E)-2-oxo-4-phenylbut-3-enoate (1d).*** The product (2.14 g, 82% yield) was purified with silica gel chromatography (dichloromethane/methanol = 50/1) as a yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 16.2 Hz, 1H), 7.61 (d, *J* = 6.5 Hz, 2H), 7.43 – 7.25 (m, 9H), 4.54 (s, 2H), 4.47 – 4.45 (m, 2H), 3.82 – 3.80 (m, 2H), 3.69 – 3.60 (m, 12H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 182.6, 162.1, 148.5, 138.2, 133.9, 131.6 128.99, 128.94, 128.2, 127.6, 127.5, 120.6, 73.1, 70.54, 70.50, 70.49, 70.47, 69.3 68.4, 65.1 ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{25}H_{30}NaO_7^+$ 465.1884, found 465.1894.

Preparation of compound **4b-4d**, **4f**, **4h-4i**[26, 27]

To a solution of functionalized acetophenone (10 mmol, 1.0 equiv) in pyridine (15 mL) was added selenium dioxide (1.3 g, 12 mmol, 1.2 equiv.) at room temperature and the mixture was stirred at 110 °C (oil bath) for 20 h. After filtration of the reaction mixture, the residue was washed with $CH_2Cl_2$ and the filtrate was concentrated in vacuo. The resulting residue was used for the next reaction without further purification.

To a solution of above residue in $CH_2Cl_2$ (20 mL), at 0 °C, were added successively DMAP (0.1 g, 12 mmol, 0.2 equiv), phenol or alcohol (5.9 mmol, 1.0 equiv), and DCC (1.8 g, 8.8 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 15 h, filtered through a short pad of celite and concentrated under reduced pressure. The crude material was purified by flash chromatography to afford the desired product.

***Phenyl 2-oxo-2-(p-tolyl)acetate (4b).*** The product (1.06 g, 75% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 50/1) as a white solid, mp = 80–83 °C;. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.2 Hz, 2H), 7.46 (dd, *J* = 10.8, 5.0 Hz, 2H), 7.37 – 7.26 (m, 5H), 2.47 (s, 3H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 185.0, 162.1, 150.0, 146.8, 130.4, 130.0, 129.9, 129.8, 126.8, 121.4, 22.1 ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{15}H_{12}NaO_3^+$ 263.0679, found 263.0683.

***Phenyl 2-(4-methoxyphenyl)-2-oxoacetate (4c).*** The product (0.95 g, 63% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 30/1) as a white solid, mp = 56–59 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.9 Hz, 2H), 7.46 (t, *J* = 7.9 Hz, 2H), 7.34 – 7.26 (m, 3H), 7.02 (d, *J* = 8.9 Hz, 2H), 3.92 (s, 3H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 183.7, 165.4, 162.2, 150.1, 132.9, 129.8, 126.8, 125.4, 121.4, 114.5, 55.8 ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{15}H_{12}NaO_4^+$ 279.0628, found 279.0634.

***Phenyl 2-(4-fluorophenyl)-2-oxoacetate (4d).*** The product (1.28 g, 89% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 50/1) as a white solid, mp = 41–43 °C;. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.16 (m, 2H), 7.44 (dd, *J* = 11.2, 4.4 Hz, 2H), 7.33 – 7.20 (m, 5H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 183.5, 167.1 (d, *J* = 258.9 Hz), 161.5, 150.0, 133.2 (d, *J* = 9.9

Hz), 129.8, 128.9 (d, $J$ = 2.8 Hz), 126.9, 121.3, 116.5 (d, $J$ = 22.3 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -103.6 (s, 1F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{14}H_9FNaO_3^+$ 267.0428, found 267.0433.

***Phenyl 2-(4-bromophenyl)-2-oxoacetate (4f).*** The product (1.31 g, 73% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 50/1) as a white solid, mp = 62–65 °C;. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.00 (d, $J$ = 8.6 Hz, 2H), 7.70 (d, $J$ = 8.6 Hz, 2H), 7.46 (t, $J$ = 7.9 Hz, 2H), 7.34 – 7.25 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 184.0, 161.2, 149.9, 132.6 131.7, 131.2, 131.0, 129.9, 126.9, 121.3 ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{14}H_9BrNaO_3^+$ 326.9627, found 326.9647.

***Phenyl 2-oxo-2-(m-tolyl)acetate (4h).*** The product (1.01 g, 71% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 30/1) as a white solid, mp = 46–49 °C;. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.90 (d, $J$ = 6.2 Hz, 2H), 7.51 – 7.41 (m, 4H), 7.33 – 7.25 (m, 3H), 2.43 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 185.6, 162.1, 150.0, 139.1, 136.2, 132.3, 130.5, 129.8, 129.0, 127.6, 126.8, 121.3, 21.4 ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{15}H_{12}NaO_3^+$ 263.0679, found 263.0685.

***Phenyl 2-(naphthalen-2-yl)-2-oxoacetate (4i).*** The product (1.35 g, 83% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 30/1) as a yellow solid, mp = 65–67 °C;. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.09 (dd, $J$ = 8.6, 1.7 Hz, 1H), 7.95 – 7.84 (m, 3H), 7.64 – 7.60 (m, 1H), 7.56 – 7.52 (m, 1H), 7.47 – 7.43 (m, 2H), 7.30 (dd, $J$ = 10.7, 4.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 185.2, 162.0, 150.1, 136.5, 133.8, 132.3, 130.2, 129.9, 129.8, 129.7, 129.2, 128.0, 127.4, 126.8, 124.0, 121.4 ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{18}H_{12}NaO_3^+$ 299.0679, found 299.0685.

Preparation of compound **4l-4r**.[26]

A solution of 2.5 N NaOH (0.8 g, 20.0 mmol, 2.0 equiv) was added to methyl 2-oxo-2-phenylacetate (1.6 g, 10.0 mmol, 1.0 equiv.) and the mixture was stirred for 2 hours at room temperature. After the reaction was finished, 1 N HCl (20 mL) was added to the mixture until the pH was lower than 7.0, which was then extracted with ethyl acetate (3 x 30 mL). Organic phases were combined and dried over sodium sulfate. The solvent was then removed under vacuum to afford the α-keto acids without further purification.

To a solution of above residue in $CH_2Cl_2$ (20 mL), at 0 °C, were added successively DMAP (0.1 g, 12 mmol, 0.2 equiv), phenol or alcohol (5.9 mmol, 1.0 equiv), and DCC (1.8 g, 8.8 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 15 h, filtered through a short pad of celite and concentrated

under reduced pressure. The crude material was purified by flash chromatography to afford the desired product.

***2-(2-Methoxyethoxy)ethyl 2-oxo-2-phenylacetate (4l).*** The product (1.27 g, 85% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 5/1) as a pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.65 (dd, *J* = 9.3, 5.5 Hz, 1H), 7.50 (dd, *J* = 10.1, 5.4 Hz, 2H), 4.58 – 4.55 (m, 2H), 3.85 – 3.82 (m, 2H), 3.68 – 3.66 (m, 2H), 3.57 – 3.54 (m, 2H), 3.36 (d, *J* = 4.0 Hz, 3H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 186.1, 163.6, 134.8, 132.1, 129.9, 128.7, 71.6, 70.3, 68.4, 64.7, 58.8 ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{13}H_{16}NaO_5^+$ 275.0890, found 275.0893.

***Phenyl-2,5,8,11-tetraoxatridecan-13-yl 2-oxo-2-phenylacetate (4m).*** The product (2.11 g, 86% yield) was purified with silica gel chromatography (dichloromethane/methanol = 50/1) as a pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.34 – 7.26 (m, 5H), 4.55 – 4.52 (m, 4H), 3.83 – 3.81 (m, 2H), 3.69 – 3.61 (m, 12H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 186.3, 163.8, 138.3, 135.0, 132.4, 130.1, 128.9, 128.4, 127.8, 127.6, 73.2, 70.7, 70.6, 69.4, 68.6, 65.0 ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{23}H_{28}NaO_7^+$ 439.1727, found 439.1735.

***2,6-Diisopropylphenyl 2-oxo-2-phenylacetate (4n).*** The product (1.36 g, 74% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 100/1) as a yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.13 (m, 2H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 2H), 7.32 – 7.22 (m, 3H), 3.14 – 3.05 (m, 2H), 1.26 (d, *J* = 6.8 Hz, 12H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 185.7, 162.5, 144.8, 140.5, 135.4, 132.5, 130.2, 129.3, 127.4, 124.4, 27.6, 22.9 ppm; HRMS-ESI m/z : $[M+H]^+$ calcd for $C_{20}H_{23}O_3^+$ 311.1642, found 311.1649.

***(R)-2-Methoxy-2-oxo-1-phenylethyl 2-oxo-2-phenylacetate (4o).*** The product (1.30 g, 74% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 30/1) as a pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.14 (m, 2H), 7.71 – 7.66 (m, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.50 – 7.40 (m, 5H), 6.16 (s, 1H), 3.81 (s, 3H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 185.8, 168.6, 163.4, 135.3, 132.6, 132.4, 130.4 129.8, 129.12, 129.07, 127.9, 75.9, 53.2 ppm; HRMS-ESI m/z : $[M+K]^+$ calcd for $C_{17}H_{14}KO_5^+$ 337.0473, found 337.0477.

***Dimethyl (S)-2-(2-oxo-2-phenylacetoxy)succinate (4p).*** The product (1.67 g, 96% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 5/1) as a pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.6 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 5.78 (dd, *J* = 7.1, 5.0 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 3.05 – 3.03 (m, 2H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 185.6, 169.3, 168.4, 162.9, 135.3, 132.3, 130.4, 129.1, 69.5, 53.2, 52.5, 35.7 ppm; HRMS-ESI m/z : $[M+Br]^-$ calcd for $C_{14}H_{14}BrO_7^-$ 372.9923, found 372.9914.

***(3aR,5R,6S,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl 2-oxo-2-phenylacetate (4q).*** The product (1.83 g, 79% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 5/1) as a colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 5.95 (d, *J* = 3.7 Hz, 1H), 5.67 (d, *J* = 3.0 Hz, 1H), 4.66 (d, *J* = 3.7 Hz, 1H), 4.28 (dd, *J* = 8.6, 3.0 Hz, 1H), 4.20 – 4.16 (m, 1H), 4.11 (dt, *J* = 8.7, 5.0 Hz, 1H), 4.02 (dd, *J* = 8.8, 4.4 Hz, 1H), 1.56 (s, 3H), 1.47 (s, 3H), 1.34 (s, 6H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 185.8, 162.6, 135.3, 132.3, 130.2, 129.0, 112.7, 109.6, 105.4, 83.3, 80.2, 77.3, 72.4, 67.6, 27.0, 26.8, 26.3, 25.3 ppm; HRMS-ESI m/z : $[M+H]^+$ calcd for $C_{20}H_{25}O_8^+$ 393.1544, found 393.1551.

***(2R,3R,4S,5S,6R)-2-(Acetoxymethyl)-6-(2-oxo-2-phenylacetoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (4r).*** The product (2.72 g, 96% yield) was purified with silica gel chromatography (dichloromethane/methanol = 50/1) as a white solid, mp = 93–96 °C;. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 2H), 6.36 (d, *J* = 1.6 Hz, 1H), 5.43 – 5.35 (m, 3H), 4.32 (dd, *J* = 12.4, 5.0 Hz, 1H), 4.19 – 4.11 (m, 2H), 2.23 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 184.6, 170.6, 169.9, 169.8, 169.6, 160.9, 135.6, 131.9, 130.2, 129.3, 92.2, 71.3, 68.6, 68.0, 65.3, 62.0, 20.82, 20.77, 20.7, 20.6 ppm; HRMS-ESI m/z : $[M+K]^+$ calcd for $C_{22}H_{24}KO_{12}^+$ 519.0899, found 519.0924.

General procedure for deoxyhydrotrifluoromethylation of alkenyl-substituted α-keto esters with $Ph_3P^+CF_2\ COO^-$

In an argon-filled glovebox, a dry reaction tube was charged with methyl (*E*)-2-oxo-4-phenyl- but-3-enoate **1a** (0.5 mmol, 1.0 equiv), 2,2-difluoro-2-(triphenylphosphonio)acetate (1.0 mmol, 2.0 equiv), and DMSO (5.0 mL). $H_2O$ (0.5 mmol, 1.0 equiv) was added to the reaction mixture at the room temperature in the end. The mixture kept stirring at 60 °C (oil bath) for 1 hour. The residue was directly subjected to silica gel flash chromatography to afford the desired product **3a** in 79% yield.

***Methyl (E)-4-phenyl-2-(trifluoromethyl)but-3-enoate (3a).***[11] The product (96.0 mg, 79% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 5/1) as a pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 6.70 (d, *J* = 15.8 Hz, 1H), 6.22 (dd, *J* = 15.8 Hz, 9.4Hz, 1H), 3.99 – 3.89 (m, 1H), 3.80 (s, 3H) ppm; $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) δ -71.4 (s, 3F) ppm.

***Ethyl (E)-4-phenyl-2-(trifluoromethyl)but-3-enoate (3b).*** The product (106.2 mg, 78% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 5/1) as a colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H), 6.70 (d, *J* = 15.9 Hz, 1H), 6.23 (dd, *J* = 15.9, 9.3 Hz, 1H), 4.26 (qd, *J* = 7.1, 1.3 Hz, 2H), 3.91 (p, *J* = 8.5 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}$C{$^1$H}

NMR (101 MHz, $CDCl_3$) δ 166.2 (q, *J* = 2.8 Hz), 138.2, 135.6, 128.8, 126.9, 123.9 (q, *J* = 280.2 Hz), 116.9 (d, *J* = 2.5 Hz), 62.3, 54.3 (q, *J* = 29.0 Hz), 14.1 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -71.3 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{13}H_{13}F_3NaO_2^+$ 281.0760, found 281.0759.

***2-(2-Methoxyethoxy)ethyl (E)-4-phenyl-2-(trifluoromethyl)but-3-enoate (3c).*** The product (139.1 mg, 84% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 5/1) as a yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 6.71 (d, *J* = 15.9 Hz, 1H), 6.23 (dd, *J* = 15.9, 9.2 Hz, 1H), 4.36 (dd, *J* = 5.5, 3.8 Hz, 2H), 3.98 (p, *J* = 8.4 Hz, 1H), 3.73 – 3.70 (m, 2H), 3.61 (dd, *J* = 5.6, 3.5 Hz, 2H), 3.49 (dd, *J* = 5.5, 3.6 Hz, 2H), 3.33 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.0 (d, *J* = 2.6 Hz), 138.2, 135.4, 128.7, 126.8, 123.8 (q, *J* = 280.3 Hz), 116.5 (d, *J* = 2.3 Hz), 71.8, 70.5, 68.7, 65.0, 58.9, 53.9 (q, *J* = 29.0 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -71.2 (s, 3F) ppm; HRMS-ESI m/z : $[M-H]^-$ calcd for $C_{16}H_{18}F_3O_4^-$ 331.1163, found 331.1160.

***Phenyl-2,5,8,11-tetraoxatridecan-13-yl(E)-4-phenyl-2-(trifluoromethyl)but-3-enoate (3d).*** The product (191.2 mg, 77% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 3/1) as a yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 10H), 6.70 (d, *J* = 15.9 Hz, 1H), 6.22 (dd, *J* = 15.9, 9.2 Hz, 1H), 4.55 (s, 2H), 4.33 (dd, *J* = 5.4, 3.3 Hz, 2H), 3.97 (p, *J* = 8.4 Hz, 1H), 3.71 – 3.61 (m, 14H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.8 (d, *J* = 2.6 Hz), 138.13, 138.07, 135.2, 128.5, 128.2, 127.5, 127.4, 126.6, 123.7 (q, *J* = 280.3 Hz), 116.4 (d, *J* = 2.3 Hz), 73.0, 70.43, 70.40, 70.35, 69.3, 68.5, 64.9, 53.7 (q, *J* = 28.9 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -71.2 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{26}H_{31}F_3NaO_6^+$ 519.1965, found 519.1963.

***Methyl (E)-4-(2-chlorophenyl)-2-(trifluoromethyl)but-3-enoate (3e).*** The product (100.0 mg, 72% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 5/1) as a colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 1H), 7.36 (dt, *J* = 6.3, 2.9 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.12 (d, *J* = 15.8 Hz, 1H), 6.23 (dd, *J* = 15.8, 9.4 Hz, 1H), 4.01 (p, *J* = 8.4 Hz, 1H), 3.82 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4 (q, *J* = 2.6 Hz), 134.5, 133.6, 133.5, 129.90, 129.83, 127.2, 127.1, 123.7 (q, *J* = 280.4 Hz), 119.5 (d, *J* = 2.4 Hz), 54.1 (q, *J* = 29.2 Hz), 53.1 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -71.1 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{12}H_{10}ClF_3NaO_2^+$ 301.0214, found 301.0207.

***Methyl (E)-4-(2-bromophenyl)-2-(trifluoromethyl)but-3-enoate (3f).*** The product (86.8 mg, 58% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 5/1) as a yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.55 (t, *J* = 7.1 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 15.8 Hz, 1H), 6.18 (dd, *J* = 15.8, 9.3 Hz, 1H), 4.06 – 3.97 (m, 1H), 3.83 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.3 (d, *J* = 2.8 Hz), 137.1, 135.4, 133.1, 130.1, 127.8, 127.4, 123.9, 123.7 (q, *J* = 280.3 Hz), 119.7 (d, *J* = 2.5 Hz), 54.0 (q, *J* = 29.2 Hz), 53.1 ppm; $^{19}F\{^1H\}$ NMR

(376 MHz, $CDCl_3$) δ -71.2 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{12}H_{10}BrF_3NaO_2^+$ 344.9708, found 344.9701.

***Methyl (E)-4-(4-methoxyphenyl)-2-(trifluoromethyl)but-3-enoate (3g).*** The product (108.7 mg, 79% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 30/1) as a pale yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.07 (dd, *J* = 15.8, 9.3 Hz, 1H), 3.90 (dt, *J* = 16.9, 8.4 Hz, 1H), 3.80 (d, *J* = 4.5 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.8 (d, *J* = 2.8 Hz), 160.2, 137.8, 128.3, 128.2, 123.9 (q, *J* = 280.2 Hz), 114.3 (d, *J* = 2.5 Hz), 114.2, 55.4, 54.2 (q, *J* = 29.2 Hz), 53.0 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -71.3 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{13}H_{13}F_3NaO_3^+$ 297.0709, found 297.0707.

***Methyl (E)-4-(4-bromophenyl)-2-(trifluoromethyl)but-3-enoate (3h).*** The product (111.8 mg, 69% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 7/1) as a white solid, mp = 38–40 °C;. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.21 (dd, *J* = 15.9, 9.3 Hz, 1H), 3.99 – 3.86 (m, 1H), 3.80 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.3 (d, *J* = 2.6 Hz), 137.1, 134.4, 131.9, 128.4, 123.7 (q, *J* = 280.2 Hz), 122.8, 117.5 (d, *J* = 2.4 Hz), 53.9 (q, *J* = 29.2 Hz), 53.1 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -71.2 (s, 3F) ppm; HRMS-ESI m/z : $[M+K]^+$ calcd for $C_{12}H_{10}BrF_3KO_2^+$ 360.9448, found 360.9439.

***Methyl (E)-4-(3-methoxyphenyl)-2-(trifluoromethyl)but-3-enoate (3i).*** The product (107.4 mg, 78% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 30/1) as a yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.9 Hz, 1H), 6.96 (dd, *J* = 22.2Hz, 4.8 Hz 2H), 6.85 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.67 (d, *J* = 15.8 Hz, 1H), 6.21 (dd, *J* = 15.8, 9.3 Hz, 1H), 3.98 – 3.89 (m, 1H), 3.80 (d, *J* = 3.7 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.54 (q, *J* = 2.7 Hz), 160.0, 138.3, 136.8, 129.8, 123.8 (q, *J* = 280.2 Hz), 119.5, 116.9 (d, *J* = 2.5 Hz), 114.6, 112.0, 55.3, 54.0 (q, *J* = 29.1 Hz), 53.0 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -71.1 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{13}H_{13}F_3NaO_3^+$ 297.0709, found 297.0707.

***Methyl (E)-4-(naphthalen-2-yl)-2-(trifluoromethyl)but-3-enoate (3j).*** The product (115.4 mg, 78% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 4/1) as a white solid, mp = 83–86 °C;. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 12.5, 7.8 Hz, 1H), 7.60 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.50 – 7.45 (m, 2H), 6.86 (d, *J* = 15.8 Hz, 1H), 6.34 (dd, *J* = 15.8, 9.3 Hz, 1H), 4.03 – 3.95 (m, 1H), 3.83 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.6 (d, *J* = 2.7 Hz), 138.4, 133.5, 133.4, 132.9, 128.5, 128.2, 127.8, 127.5, 126.6, 126.5, 123.9 (q, *J* = 280.3 Hz), 123.3, 116.9 (d, *J* = 2.4

Hz), 54.1 (q, *J* = 29.1 Hz), 53.0 ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -71.0 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{16}H_{13}F_3NaO_2^+$ 317.0760, found 317.0756.

***Methyl (E)-4-(furan-2-yl)-2-(trifluoromethyl)but-3-enoate (3k).*** The product (75.6 mg, 65% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 5/1) as a yellow oil; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 1.3 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.40 – 6.34 (m, 2H), 6.14 (dd, *J* = 15.8, 9.4 Hz, 1H), 3.87 (dt, *J* = 11.2, 8.5 Hz, 1H), 3.80 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.5 (q, *J* = 3.1 Hz), 151.1, 143.1, 126.0, 123.8 (q, *J* = 280.3 Hz), 114.9 (d, *J* = 2.9 Hz), 111.6, 110.3, 53.8 (q, *J* = 29.3 Hz), 53.1 ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -71.3 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{10}H_9F_3NaO_3^+$ 257.0396, found 257.0395.

***Methyl (E)-4-(thiophen-2-yl)-2-(trifluoromethyl)but-3-enoate (3l).*** The product (81.6 mg, 65% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 5/1) as a pale yellow oil; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 5.0 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.82 (d, *J* = 15.7 Hz, 1H), 6.02 (dd, *J* = 15.7, 9.3 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.80 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4 (d, *J* = 2.7 Hz), 140.2, 131.2, 127.61, 127.56, 125.9, 123.8 (q, *J* = 280.2 Hz), 115.7 (d, *J* = 2.4 Hz), 53.9 (q, *J* = 29.3 Hz), 53.1 ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -71.3 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{10}H_9F_3NaO_2S^+$ 273.0168, found 273.0174.

***Methyl (3E,5E)-6-phenyl-2-(trifluoromethyl)hexa-3,5-dienoate (3m).*** The product (93.8 mg, 69% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 5/1) as a white solid, mp = 44–48 $^{o}$C;. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.77 (m, 4H), 7.61 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.51 – 7.46 (m, 2H), 6.87 (d, *J* = 15.8 Hz, 1H), 6.34 (dd, *J* = 15.8, 9.3 Hz, 1H), 3.99 (p, *J* = 8.3 Hz, 1H), 3.83 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.5 (d, *J* = 2.6 Hz), 138.4, 136.6, 135.4, 128.8, 128.3, 127.0, 126.7, 123.8 (q, *J* = 280.1 Hz), 119.8 (d, *J* = 2.5 Hz), 53.8 (q, *J* = 29.2 Hz), 53.0 ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -71.3 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{14}H_{13}F_3NaO_2^+$ 293.0760, found 293.0757.

***Methyl (E)-4-(3,4-dimethoxyphenyl)-2-(trifluoromethyl)but-3-enoate (3n).*** The product (120.1 mg, 79% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 5/1) as a colorless oil; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 6.96 – 6.93 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.07 (dd, *J* = 15.8, 9.3 Hz, 1H), 3.94 – 3.89 (m, 7H), 3.81 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.8 (d, *J* = 2.8 Hz), 149.8, 149.2, 138.0, 128.5, 123.9 (q, *J* = 280.2 Hz), 120.5, 114.4 (d, *J* = 2.4 Hz), 111.1, 108.9, 55.96, 55.94, 54.0 (q, *J* = 29.1 Hz), 53.0 ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -71.4 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{14}H_{15}F_3NaO_4^+$ 327.0815, found 327.0813.

***Methyl (E)-4-cyclohexyl-2-(trifluoromethyl)but-3-enoate (3o).*** The product (89.1 mg, 71% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 30/1) as a colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 5.78 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.47 (dd, *J* = 15.5, 9.2 Hz, 1H), 3.77 (s, 3H), 3.70 (p, *J* = 8.5 Hz, 1H), 2.02 (dt, *J* = 10.3, 6.8 Hz, 1H), 1.75 – 1.64 (m, 5H) , 1.32 – 1.05 (m, 5H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 167.1 (d, *J* = 2.8 Hz), 146.1, 124.0 (q, *J* = 279.9 Hz), 115.4 (d, *J* = 2.3 Hz), 54.0 (q, *J* = 28.8 Hz), 52.8, 40.7, 32.3, 26.1, 25.9 ppm; $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) δ -71.8 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{12}H_{17}F_3NaO_2^+$ 273.1073, found 273.1072.

General procedure for deoxyhydrotrifluoromethylation of aryl-substituted α-keto esters with $Ph_3P^+CF_2COO^-$

In an argon-filled glovebox, a dry reaction tube was charged with phenyl 2-oxo-2-phenyl- acetate **4a** (0.5 mmol, 1.0 equiv), 2,2-difluoro-2-(triphenylphosphonio)acetate (1.5 mmol, 3.0 equiv), and DMSO (5.0 mL). $H_2O$ (0.5 mmol, 1.0 equiv) was added to the reaction mixture at the room temperature in the end. The mixture kept stirring at 60 °C (oil bath) for 12 hours. The residue was directly subjected to silica gel flash chromatography (petroleum ether/dichloromethane = 10/1) to afford the desired product **5a** in 75% yield.

***Phenyl 3,3,3-trifluoro-2-phenylpropanoate (5a).*** The product (104.8 mg, 75% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 10/1) as a pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.9 Hz, 2H), 7.44 – 7.43 (m, 3H), 7.35 (t, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.05 – 7.03 (m, 2H), 4.57 (q, *J* = 8.4 Hz, 1H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 164.8 (q, *J* = 2.7 Hz), 150.2, 129.64, 129.60, 129.2, 129.0 (d, *J* = 1.6 Hz), 126.6, 123.8 (q, *J* = 279.8 Hz), 121.2, 55.6 (q, *J* = 29.1 Hz) ppm; $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) δ -70.6 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{15}H_{11}F_3NaO_2^+$ 303.0603, found 303.0600.

***Phenyl 3,3,3-trifluoro-2-(p-tolyl)propanoate (5b).*** The product (115.2 mg, 78% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 10/1) as a pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.19 (dd, *J* = 12.1, 7.7 Hz, 3H), 7.02 (d, *J* = 8.0 Hz, 2H), 4.52 (q, *J* = 8.3 Hz, 1H), 2.33 (s, 3H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 165.0 (q, *J* = 2.7 Hz), 150.3, 139.6, 130.0, 129.6, 129.5, 126.5, 126.0 (d, *J* = 1.5 Hz), 123.8 (q, *J* = 279.8 Hz), 121.2, 55.3 (q, *J* = 29.1 Hz), 21.2 ppm; $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) δ -70.8 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{16}H_{13}F_3NaO_2^+$ 317.0760, found 317.0757.

***Phenyl 3,3,3-trifluoro-2-(4-methoxyphenyl)propanoate (5c).*** The product (113.0 mg, 73% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 50/1) as a yellow solid, mp = 46–48 °C;. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.6 Hz, 2H), 7.35 (t, *J* = 7.9 Hz, 2H), 7.22 (t, *J*

= 7.4 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 4.51 (q, *J* = 8.4 Hz, 1H), 3.79 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 165.1 (d, *J* = 2.7 Hz), 160.6, 150.2, 130.8, 129.6, 126.5, 123.8 (q, *J* = 279.7 Hz), 121.2, 120.9 (d, *J* = 1.6 Hz), 114.6, 55.3, 54.8 (q, *J* = 29.5 Hz) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -71.0 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{16}H_{13}F_3NaO_3^+$ 333.0709, found 333.0705.

***Phenyl 3,3,3-trifluoro-2-(4-fluorophenyl)propanoate (5d).*** The product (100.6 mg, 67% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 15/1) as a pale yellow oil; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.5, 5.2 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.26 – 7.22 (m, 1H), 7.15 – 7.03 (m, 4H), 4.56 (q, *J* = 8.3 Hz, 1H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 164.7 (d, *J* = 2.4 Hz), 163.6 (d, *J* = 249.3 Hz), 150.2, 131.5 (d, *J* = 8.4 Hz), 129.7, 126.7, 124.9 (q, *J* = 1.7 Hz), 123.6 (qd, *J* = 279.8 Hz), 121.2, 116.4 (d, *J* = 21.9 Hz), 54.9 (q, *J* = 29.4 Hz) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -70.9 (s, 3F), -114.7 (s, 1F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{15}H_{10}F_4NaO_2^+$ 321.0509, found 321.0517.

***Phenyl 2-(4-chlorophenyl)-3,3,3-trifluoropropanoate (5e).*** The product (107.7 mg, 68% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 15/1) as a pale yellow oil; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.36 (m, 6H), 7.26 (dd, *J* = 8.4, 6.4 Hz, 1H), 7.06 – 7.03 (m, 2H), 4.55 (q, *J* = 8.3 Hz, 1H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 164.5 (d, *J* = 2.9 Hz), 150.1, 136.0, 131.0, 129.7, 129.6, 127.5 (d, *J* = 1.4 Hz), 126.7, 123.5 (q, *J* = 280.0 Hz), 121.2, 55.0 (q, *J* = 29.5 Hz) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -70.8 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{15}H_{10}ClF_3NaO_2^+$ 337.0214, found 337.0220.

***Phenyl 2-(4-bromophenyl)-3,3,3-trifluoropropanoate (5f).*** The product (122.6 mg, 68% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 15/1) as a white solid, mp = 51–53 °C;. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.5 Hz, 2H), 7.41 – 7.34 (m, 4H), 7.23 (dd, *J* = 10.6, 4.2 Hz, 1H), 7.04 (d, *J* = 7.7 Hz, 2H), 4.53 (q, *J* = 8.3 Hz, 1H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 164.4 (d, *J* = 2.7 Hz), 150.1, 132.5, 131.3, 129.7, 128.0 (d, *J* = 1.5 Hz), 126.7, 124.2, 123.4 (q, *J* = 280.0 Hz), 121.1, 55.1(q, *J* = 29.5 Hz) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -70.7 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{15}H_{10}BrF_3NaO_2^+$ 380.9708, found 380.9718.

***Benzyl 3,3,3-trifluoro-2-phenylpropanoate (5g).*** The product (112.1 mg, 76% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 10/1) as a pale yellow oil; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 10H), 5.16 (dd, *J* = 33.0, 12.3 Hz, 2H), 4.36 (q, *J* = 7.6 Hz, 1H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1 (q, *J* = 2.6 Hz), 135.0, 129.6, 129.3, 129.0, 128.7, 128.6, 128.2, 123.8 (q, *J* = 279.8 Hz), 67.7, 55.6 (q, *J* = 28.9 Hz) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz,

$CDCl_3$) δ -70.4 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{16}H_{13}F_3NaO_2^+$ 317.0760, found 317.0757.

***Phenyl 3,3,3-trifluoro-2-(m-tolyl)propanoate (5h).*** The product (109.3 mg, 74% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 15/1) as a pale yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.19 (m, 7H), 7.04 – 7.02 (m, 2H), 4.52 (q, *J* = 8.4 Hz, 1H), 2.37 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.9 (d, *J* = 2.7 Hz), 150.2, 139.1, 130.4, 130.3, 129.7, 129.1, 128.9 (d, *J* = 1.5 Hz), 126.6, 126.5, 123.8 (q, *J* = 279.9 Hz), 121.3, 55.6 (q, *J* = 29.1 Hz), 21.5 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -70.7 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{16}H_{13}F_3NaO_2^+$ 317.0760, found 317.0758.

***Phenyl 3,3,3-trifluoro-2-(naphthalen-2-yl)propanoate (5i).*** The product (124.7 mg, 76% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 15/1) as a pale yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.89 – 7.82 (m, 3H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.18 (dd, *J* = 12.8, 5.3 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 2H), 4.73 (q, *J* = 8.3 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.9 (d, *J* = 2.5 Hz), 150.2, 133.6, 133.3, 129.7, 129.6, 129.2, 128.3, 127.8, 127.2, 126.9, 126.6, 126.4 (d, *J* = 1.2 Hz), 126.2, 123.9 (q, *J* = 280.0 Hz), 121.2, 55.7 (q, *J* = 29.2 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -70.3 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{19}H_{13}F_3NaO_2^+$ 353.0760, found 353.0755.

***Methyl 3,3,3-trifluoro-2-(naphthalen-2-yl)propanoate (5j).*** The product (110.0 mg, 82% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 15/1) as a white solid, mp = 56–59 °C;. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.83 – 7.78 (m, 3H), 7.53 – 7.45 (m, 3H), 4.50 (q, *J* = 8.5 Hz, 1H), 3.72 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.8 (q, *J* = 2.6 Hz), 133.5, 133.2, 129.5, 128.9, 128.2, 127.8, 127.0, 126.8, 126.3, 124.0 (q, *J* = 279.8 Hz), 55.5 (q, *J* = 28.9 Hz), 53.0 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -70.5 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{14}H_{11}F_3NaO_2^+$ 291.0603, found 291.0600.

***Phenyl 3,3,3-trifluoro-2-(thiophen-2-yl)propanoate (5k).*** The product (51.5 mg, 36% yield) was purified with silica gel chromatography (petroleum ether/ dichloromethane = 15/1) as a colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 5H), 7.10 – 7.06 (m, 3H), 4.86 (q, *J* = 8.0 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.0 (d, *J* = 2.6 Hz), 150.2, 129.7, 128.9 (d, *J* = 1.9 Hz), 127.8, 127.4, 126.7, 123.1 (q, *J* = 280.6 Hz), 121.2, 51.3 (q, *J* = 30.8 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -71.5 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{13}H_9F_3NaO_2S^+$ 309.0168, found 309.0172.

***2-(2-Methoxyethoxy)ethyl 3,3,3-trifluoro-2-phenylpropanoate (5l).*** The product (102.3 mg, 67% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 5/1) as a pale yellow

oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 5H), 4.41 – 4.34 (m, 2H), 4.32 – 4.27 (m, 1H),3.68 – 3.66 (m, 2H), 3.55 (dd, *J* = 5.5, 2.9 Hz, 2H), 3.47 (td, *J* = 6.1, 3.2 Hz, 2H), 3.35 (d, J = 2.3 Hz, 3H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 166.1 (q, *J* = 2.6 Hz), 129.5, 129.3 (d, *J* = 1.5 Hz), 129.2, 128.9, 123.7 (q, *J* = 279.7 Hz), 71.8, 70.5, 68.7, 65.0, 59.0, 55.4 (q, *J* = 28.8 Hz) ppm; $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) δ -70.7 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{14}H_{17}F_3NaO_4^+$ 329.0971, found 329.0967.

***Phenyl-2,5,8,11-tetraoxatridecan-13-yl 3,3,3-trifluoro-2-phenylpropanoate (5m).*** The product (168.1 mg, 72% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 4/1) as a pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.24 (m, 10H), 4.56 (s, 2H), 4.40 – 4.33 (m, 2H), 4.29 – 4.23 (m, 1H), 3.68 – 3.53 (m, 14H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 166.2 (q, *J* = 2.9 Hz), 138.3, 129.6, 129.32 (d, *J* = 1.7 Hz), 129.27, 129.0, 128.4, 127.8, 127.7, 123.7 (q, *J* = 279.8 Hz), 73.3, 70.69, 70.68, 70.64, 70.60, 69.5, 68.7, 65.0, 55.4 (q, *J* = 28.9 Hz) ppm; $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) δ -70.8 (s, 3F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{24}H_{29}F_3NaO_6^+$ 493.1808, found 493.1801.

***2,6-Diisopropylphenyl 3,3,3-trifluoro-2-phenylpropanoate (5n).*** The product (116.3 mg, 75% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 100/1) as a white solid, mp = 80–82 $^o$C;. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.41 (m, 5H), 7.18 (dd, *J* = 24.3, 16.7 Hz, 3H), 4.64 (q, *J* = 8.5 Hz, 1H), 2.86 (s, 1H), 2.40 (s, 1H), 1.27 – 0.86 (m, 12H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 164.9 (q, *J* = 2.5 Hz), 145.0, 140.5, 129.74, 129.71, 129.2, 128.9 (d, *J* = 1.4 Hz), 127.2, 124.1, 123.9 (q, *J* = 279.6 Hz), 55.7 (q, *J* = 29.4 Hz), 27.5, 22.9 ppm; $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) δ -70.5 (s, 3F) ppm; HRMS-ESI m/z : $[M-H]^-$ calcd for $C_{21}H_{22}F_3O_2^-$ 363.1577, found 363.1577.

***(R)-2-Methoxy-2-oxo-1-phenylethyl 3,3,3-trifluoro-2-phenylpropanoate (5o).*** The product (106.1 mg, 71% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 30/1) as a pale yellow oil and as an inseparable mixture of diastereoisomers (*d. r.* = 1:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 10H), 6.00 (s, 1H), 4.49 (dq, *J* = 16.8, 8.4 Hz, 1H), 3.72 (s, 1.5H), 3.64 (s, 1.5H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 168.4, 168.3, 165.60 (d, *J* = 2.5 Hz), 165.57 (d, *J* = 2.5 Hz), 133.0, 132.9, 129.8, 129.7, 129.6, 129.5, 129.4, 129.02, 128.95, 128.9, 128.8 (d, *J* = 1.2 Hz), 127.7, 127.5, 123.7 (q, *J* = 280.1 Hz), 123.7 (q, *J* = 280.1 Hz), 75.7, 75.6, 55.4 (q, *J* = 29.3 Hz), 55.3 (q, *J* = 28.9 Hz), 52.8, 52.7 ppm; $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) δ -70.62 (s, 1.5F), -70.63 (s, 1.5F) ppm; HRMS-ESI m/z : $[M+K]^+$ calcd for $C_{18}H_{15}F_3KO_4^+$ 391.0554, found 391.0557.

***Dimethyl (2S)-2-((3,3,3-trifluoro-2-phenylpropanoyl)oxy)succinate (5p).*** The product (102.9 mg, 59% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 7/1) as a pale

yellow oil and as an inseparable mixture of diastereoisomers (*d. r.* = 1:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 5H), 5.59 (ddd, *J* = 12.7, 7.9, 4.6 Hz, 1H), 4.42 (qd, *J* = 8.4, 6.2 Hz, 1H), 3.77 (s, 1.5H), 3.67 (d, *J* = 12.5 Hz, 3H), 3.53 (s, 1.5H), 2.98 – 2.81 (m, 2H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 169.3, 169.0, 168.5, 168.4, 165.2 (d, *J* = 3.0 Hz), 165.1 (d, *J* = 2.8 Hz), 129.7, 129.6, 129.4, 129.0, 128.9, 128.7 (d, *J* = 0.9 Hz), 123.6 (q, *J* = 279.5 Hz), 123.5 (q, *J* = 279.7 Hz), 69.5, 69.4, 55.3 (q, *J* = 29.3 Hz), 55.2 (q, *J* = 29.2 Hz), 52.9, 52.8, 52.3, 52.1, 35.7 ppm; $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) δ -70.7 (s, 1.5F), -70.8 (s, 1.5F) ppm; HRMS-ESI m/z : $[M-H]^-$ calcd for $C_{15}H_{14}F_3O_6^-$ 347.0748, found 347.0749.

***(3aR,5R,6S,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl 3,3,3-trifluoro-2-phenylpropanoate (5q).*** The product (115.5 mg, 52% yield) was purified with silica gel chromatography (petroleum ether/dichloromethane = 1/1) as a colorless oil and as an inseparable mixture of diastereoisomers (*d. r.* = 1:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 5H), 5.88 (d, *J* = 3.5 Hz, 0.5H), 5.74 (d, *J* = 3.6 Hz, 0.5H), 5.40 – 5.39 (m, 1H), 4.50 (d, *J* = 3.6 Hz, 0.5H), 4.40 – 4.32 (m, 1.5H), 4.19 (s, 1H), 4.13 (dd, *J* = 8.2, 2.7 Hz, 1H), 3.99 – 3.96 (m, 0.5H), 3.91 – 3.82 (m, 1H), 3.78 (dt, *J* = 8.2, 5.5 Hz, 0.5H), 1.51 (s, 3H), 1.41 (s, 1.5H), 1.31 (dd, *J* = 14.2, 10.2 Hz, 6H), 1.10 (s, 1.5H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 164.9 (d, *J* = 2.8 Hz), 164.7 (d, *J* = 2.6 Hz), 129.6, 129.53, 129.50, 129.14, 129.09, 128.9 (d, *J* = 1.0 Hz), 123.6 (q, *J* = 280.0 Hz), 112.7, 109.6, 109.4, 105.21, 105.18, 83.2, 83.0, 80.1, 77.6, 77.3, 72.3, 71.9, 67.7, 67.4, 55.7 (q, *J* = 29.3 Hz), 55.6 (q, *J* = 28.9 Hz) 26.9, 26.83, 26.78, 26.3, 25.1, 24.9 ppm; $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) δ -70.6 (s, 1.5F), -70.7 (s, 1.5F) ppm; HRMS-ESI m/z : $[M+Cl]^-$ calcd for $C_{21}H_{25}ClF_3O_7^-$ 481.1246, found 481.1240.

***(2R,3R,4S,5S,6R)-2-(Acetoxymethyl)-6-((3,3,3-trifluoro-2-phenylpropanoyl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (5r).*** The product (192.1 mg, 72% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 4/1) as a yellow oil and as an inseparable mixture of diastereoisomers (*d. r.* = 56:44); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 5H), 6.15 (dd, *J* = 13.7, 1.5 Hz, 1H), 5.32 – 5.13 (m, 3H), 4.45 (qd, *J* = 8.3, 4.0 Hz, 1H), 4.25 (dd, *J* = 12.4, 5.7 Hz, 0.44H), 4.11 (ddd, *J* = 17.4, 12.4, 3.5 Hz, 1H), 4.00 (ddd, *J* = 9.8, 5.6, 2.0 Hz, 0.44H), 3.85 (dd, *J* = 12.5, 2.1 Hz, 0.56H), 3.34 (ddd, *J* = 10.1, 4.7, 2.1 Hz, 0.56H), 2.07 (ddd, *J* = 26.4, 20.7, 2.9 Hz, 12H) ppm; $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 170.4, 170.3, 169.7, 169.6, 169.51, 169.47, 169.3, 163.5 (d, *J* = 2.7 Hz), 163.3 (d, *J* = 2.5 Hz), 129.54, 129.50, 129.4, 129.3, 129.2, 129.1, 128.7, 128.3, 123.4 (q, *J* = 280.3 Hz), 123.3 (q, *J* = 279.7 Hz), 91.9, 91.2, 71.2, 70.7, 68.5, 68.4, 67.7, 65.2, 64.7, 61.9, 61.5, 55.1 (q, *J* = 29.2 Hz), 55.0 (q, *J* = 29.4 Hz), 20.50, 20.45, 20.4 ppm; $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) δ -70.0 (s, 1.32F), -70.5 (s, 1.68F) ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{23}H_{25}F_3NaO_{11}^+$ 557.1241, found 557.1248.

***Benzyl 3,3,3-trifluoro-2-(6-methoxynaphthalen-2-yl)propanoate (5s).*** In an argon-filled glovebox, a dry flask was charged with phenyl benzyl 2-(6-methoxynaphthalen-2-yl)-2-oxoacetate **4s** (1.50 g, 4.7 mmol, 1.0 equiv), 2,2-difluoro- 2-(triphenylphosphonio)acetate (5.00 g, 14.1 mmol, 3.0 equiv), and DMSO (40 mL). $H_2O$ (0.08 g, 4.7 mmol, 1.0 equiv) was added to the reaction mixture at the room temperature in the end. The mixture kept stirring at 60 $^oC$ (oil bath) for 12 hours. Water (50 mL) was added, and the mixture was extracted with ethyl acetate (3 x 30 mL). Organic layers were combined and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 5/1) to afford the desired product **5s** (1.02 g, 2.7 mmol) in 58% yield as a yellow solid, mp = 84–87 $^oC$;. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.69 (m, 3H), 7.46 (d, $J$ = 8.5 Hz, 1H), 7.32 – 7.25 (m, 5H), 7.19 – 7.13 (m, 2H), 5.26 (d, $J$ = 12.3 Hz, 1H), 5.17 (d, $J$ = 12.3 Hz, 1H), 4.50 (q, $J$ = 8.5 Hz, 1H), 3.92 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.3 (q, $J$ =2.3 Hz), 158.6 135.0, 134.8, 129.8, 129.2, 128.72, 128.65, 128.3, 127.7, 127.0, 124.3 (d, $J$ = 1.5 Hz), 124.0 (q, $J$ = 280.0 Hz), 119.7, 105.6, 67.8, 55.54 (q, $J$ = 28.9 Hz), 55.47 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -70.6 (s, 3F) ppm; HRMS-ESI m/z : $[M+H]^+$ calcd for $C_{21}H_{18}F_3O_3^+$ 375.1203, found 375.1218.

***3,3,3-Trifluoro-2-(6-methoxynaphthalen-2-yl)propanoic acid (6).***[11] To a solution of **5s** in THF (20 mL) were added Pd/C (10% on carbon, 0.85 g, 0.8 mmol, 0.3 equiv). The reaction mixture was stirred under $H_2$ atmosphere (balloon) at rt for 3 h, filtered through a short pad of celite and concentrated under reduced pressure. The crude material was purified by flash chromatography (dichloromethane/methanol = 10/1) to afford the desired product **6** (0.67 g, 2.4 mmol) in 87% yield as a yellow solid, mp = 131–133 $^oC$;. $^1H$ NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.74 (dd, $J$ = 15.5, 8.8 Hz, 2H), 7.51 (d, $J$ = 8.5 Hz, 1H), 7.19 – 7.11 (m, 2H), 4.67 (q, $J$ = 8.9 Hz, 1H), 3.86 (s, 3H) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -70.6 (s, 3F) ppm.

***Methyl 3,3,3-trifluoro-2-phenylpropanoate (8).***[7b] In an argon-filled glovebox, a dry reaction tube was charged with phenyl methyl 3,3-difluoro -2-phenylacrylate **7** (0.1 mmol, 1.0 equiv), 2,2-difluoro-2-(triphenylphosphonio)acetate (0.3 mmol, 3.0 equiv), and DMSO (1 mL). $H_2O$ (0.1 mmol, 1.0 equiv) was added to the reaction mixture at the room temperature in the end. The mixture kept stirring at 60 $^oC$ (oil bath) for 12 hours. Yields of product **8** were determined by $^{19}F$ NMR spectroscopy using trifluorotoluene as an internal standard. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 5H), 4.33 (q, $J$ = 8.6 Hz, 1H), 3.74 (s, 3H) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -70.8 (s, 3F) ppm.

***Methyl 3-phenyl 2-phenylmalonate (10).*** A dry reaction tube was charged with phenyl 3,3,3-trifluoro-2-phenylpropanoate **5a** (0.3 mmol, 1.0 equiv), NaOH (0.6 mmol, 2.0 equiv), and MeOH (2 mL). $H_2O$ (0.3 mmol, 1.0 equiv) was added to the reaction mixture at the room temperature in the end. The mixture kept stirring at rt for 3 hours. The resulting mixture was directly subjected to silica gel flash chromatography (petroleum ether/dichloromethane = 10/1) to afford the desired product **10** (38.9 mg,

0.14 mmol) in 48% yield as a pale yellow oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.43 – 7.35 (m, 5H), 7.24 (dd, *J* = 12.2, 4.7 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 2H), 4.88 (s, 1H), 3.82 (s, 3H) ppm; $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 168.5, 166.8, 150.7, 132.3, 129.6, 129.5, 129.0, 128.7, 126.3, 121.4, 57.9, 53.2 ppm; HRMS-ESI m/z : $[M+Na]^+$ calcd for $C_{16}H_{14}NaO_4^+$ 293.0784, found 293.0788.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Screening of reaction conditions and copies of $^{1}$H, $^{13}$C, $^{19}$F NMR (PDF)

## AUTHOR INFORMATION

### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) (a) Harper, D. B.; O'Hagan, D. The Fluorinated Natural Products. *Nat. Prod. Rep.* **1994**, *11*, 123-133. (b) O'Hagan, D.; Harper, D. B. Fluorine-containing Natural Products. *J. Fluorine Chem.* **1999**, *100*, 127-133.

(2) (a) Furuya, T.; Kamlet, A. S.; Ritter, T. Catalysis for Fluorination and Trifluoromethylation. *Nature* **2011**, *473*, 470-477. (b) Charpentier, J.; Früh, N.; Togni, A. Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents. *Chem. Rev.* **2015**, *115*, 650-682. (c) Yang, C.; Hassanpour, A.; Ghorbanpour, K.; Abdolmohammadi, S.; Vessally, E. Recent Advances in Direct Trifluoromethylation of Olefinic C–H Bonds. *RSC Adv.* **2019**, *9*, 27625-27639 and references cited therein.

(3) (a) Hiyama, T. *Organo-fluorine Compounds, Chemistry and Applications,* Springer-Verlag: Berlin Heidelberg, **2000**. (b) Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking

Beyond Intuition. *Science* **2007**, *317*, 1881-1886. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in Medicinal Chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320-330. (d) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, **2009**. (e) Fujiwara, T.; O'Hagan, D. Successful Fluorine-containing Herbicide Agrochemicals. *J. Fluorine Chem.* **2014**, *167*, 16-29. (f) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II−III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422-518. (g) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822-5880. (h) Mei, H.; Han, J.; Fustero, S.; Medio-Simon, M.; Sedgwick, D. M.; Santi, C.; Ruzziconi, R.; Soloshonok, V. A. Fluorine-Containing Drugs Approved by the FDA in 2018. *Chem. - Eur. J.* **2019**, *25*, 11797-11819. (i) Moschner, J.; Stulberg, V.; Fernandes, R.; Huhmann, S.; Leppkes, J.; Koksch, B. Approaches to Obtaining Fluorinated α‑Amino Acids. *Chem. Rev.* **2019**, *119*, 10718-10801.

(4) (a) Middleton, W. J.; Bingham, E. M. The Synthesis of Antiinflammatory α-(trifluoromethyl) Arylacetic Acids. *J. Fluorine Chem.* **1983**, *22*, 561-574. (b) Butovich, I. A.; Soloshonok, V. A.; Kukhar, V. P. The Unusual Action of (*R,S*)-2-Hydroxy-2-trifluoromethyl-*trans*-*n*-*octadec*-4-enoic Acid on 5-Lipoxygenase from Potato Tubers. *Eur. J. Biochem.* **1991**, *199*, 153-155. (c) Sculptoreanu, A.; Yoshimura, N.; de Groat, W. C. KW-7158 [(2*S*)-(+)-3,3,3-Trifluoro-2-hydroxy-2-methyl-*N*-(5,5,10-trioxo-4,10-dihydrothieno[3,2-c][1]benzothiepin-9-yl)propanamide] Enhances A-Type $K^+$ Currents in Neurons of the Dorsal Root Ganglion of the Adult Rat. *J. Pharmacol. Exp. Ther.* **2004**, *310*, 159-168. (d) Parker, J. S.; Bower, J. F.; Murray, P. M.; Patel, B.; Talavera, P. Kepner-Tregoe Decision Analysis as a Tool To Aid Route Selection. Part 3. Application to a Back-Up Series of Compounds in the PDK Project. *Org. Process Res. Dev.* **2008**, *12*, 1060-1077. (e) Combs, A. P. Recent Advances in the Discovery of Competitive Protein Tyrosine Phosphatase 1B Inhibitors for the Treatment of Diabetes, Obesity, and Cancer. *J. Med. Chem.* **2010**, *53*, 2333-2344. (f) Vorobyeva, D. V.; Peregudov, A. S.; Röschenthaler, G.-V.; Osipov, S. N. Synthesis of α-$CF_3$-Containing Triazolyl Amino Acids as Potential Neurotransmitters via Click-reaction. *J. Fluorine Chem.* **2015**, *175*, 60-67.

(5) (a) Carnell, A. J.; Hale, I.; Denis, S.; Wanders, R. J. A.; Isaacs, W. B.; Wilson, B. A.; Ferdinandusse, S. Design, Synthesis, and In Vitro Testing of α-Methylacyl-CoA Racemase Inhibitors. *J. Med. Chem.* **2007**, *50*, 2700-2707. (b) Wang, X.; Buchwald, S. L. Synthesis of Optically Pure 2‑Trifluoromethyl Lactic Acid by Asymmetric Hydroformylation. *J. Org. Chem.* **2013**, *78*, 3429-3433. (c) Dong, K.; Li, Y.; Wang, Z.; Ding, K. Catalytic Asymmetric Hydrogenation of α-$CF_3$- or β-$CF_3$-Substituted Acrylic Acids using Rhodium(I) Complexes with a Combination of Chiral and Achiral Ligands. *Angew. Chem. Int. Ed.* **2013**, *52*, 14191-14195. (d) Han, X.; Wu, H.; Wang, W.; Dong, C.;

Tien, P.; Wu, S.; Zhou, H.-B. Synthesis and SARs of Indole-based α-Amino Acids as Potent HIV-1 Non-nucleoside Reverse Transcriptase Inhibitors. *Org. Biomol. Chem.* **2014**, *12*, 8308-8317. (e) Chen, M. Z.; Sach, N. W.; Nuhant, P.; Fadeyi, O. O.; Trujillo, J.; Lombardo, V.; Bernier, L.; Unwalla, R.; Flick, A. C. Synthesis of (*R*)- and (*S*)-α-Trifluoromethyl Propanoic Acids via Asymmetric Hydrogenation followed by Salt Resolution. *Tetrahedron: Asymmetry* **2016**, *27*, 882-887. (f) Banerjee, S.; Schmidt, J.; Talmon, Y.; Hori, H.; Asaid, T.; Ameduri, B. A Degradable Fluorinated Surfactant for Emulsion Polymerization of Vinylidene Fluoride. *Chem. Commun.* **2018**, *54*, 11399-11402. (g) Bhakta, U.; Kattamuri, P. V.; Siitonen, J. H.; Alemany, L. B.; Kürti, L. Enantioselective Catalytic Allylation of Acyclic Ketiminoesters: Synthesis of α‐Fully-Substituted Amino Esters. *Org. Lett.* **2019**, *21*, 9208-9211.

(6) (a) Umemoto, T.; Ishihara, S. Power-Variable Electrophilic Trifluoromethylating Agents. *S*-, *Se*-, and *Te*-(Trifluoromethyl)dibenzothio-, -seleno-, and -tellurophenium Salt System. *J. Am. Chem. Soc.* **1993**, *115*, 2156-2164. (b) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. Highly Enantioselective Copper-Catalyzed Electrophilic Trifluoromethylation of β-Ketoesters. *J. Am. Chem. Soc.* **2012**, *134*, 10769-10772. (c) Gelat, F.; Patra, A.; Pannecoucke, X.; Biju, A. T.; Poisson, T.; Besset, T. N‐Heterocyclic Carbene-Catalyzed Synthesis of α‐Trifluoromethyl Esters. *Org. Lett.* **2018**, *20*, 3897-3901 and references cited therein.

(7) (a) Hu, M.; Ni, C.; Hu, J. Copper-Mediated Trifluoromethylation of α‐Diazo Esters with $TMSCF_3$: The Important Role of Water as a Promoter. *J. Am. Chem. Soc.* **2012**, *134*, 15257-15260. (b) Hu, X.-Q.; Han, J.-B.; Zhang, C.-P. Cu-Mediated Trifluoromethylation of Aromatic α-Diazo Esters with the Yagupolskii–Umemoto Reagent. *Eur. J. Org. Chem.* **2017**, 324-331.

(8) (a) Miura, K.; Takeyama, Y.; Oshima, K.; Utimoto, K. Triethylborane Induced Perfluoroalkylation of Silyl Enol Ethers and Ketene Silyl Acetals with Perfluoroalkyl Iodides. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542-1553. (b) Sato, K.; Yuki, T.; Yamaguchi, R.; Hamano, T.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. Mechanistic Studies on α-Trifluoromethylation of Ketones via Silyl Enol Ethers and Its Application to Other Carbonyl Compounds. *J. Org. Chem.* **2009**, *74*, 3815-3819. (c) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. Photoredox Catalysis: A Mild, Operationally Simple Approach to the Synthesis of α-Trifluoromethyl Carbonyl Compounds. *Angew. Chem. Int. Ed.* **2011**, *50*, 6119-6122. (d) Katayev, D.; Matoušek, V.; Koller, R.; Togni, A. Lewis Acid Catalyzed Synthesis of α‐Trifluoromethyl Esters and Lactones by Electrophilic Trifluoromethylation. *Org. Lett.* **2015**, *17*, 5898-5901. (e) Katayev, D.; Václavík, J.; Brüning, F.; Commare, B.; Togni, A. Synthesis of Quaternary α-Perfluoroalkyl Lactams via Electrophilic Perfluoroalkylation. *Chem. Commun.* **2016**, *52*, 4049-4052.

(9) Eisenberger, P.; Gischig, S.; Togni, A. Novel 10-I-3 Hypervalent Iodine-Based Compounds for Electrophilic Trifluoromethylation. *Chem. - Eur. J.* **2006**, *12*, 2579-2586.

(10) Umemoto, T.; Ishihara, S. Power-variable Trifluoromethylating Agents, (Trifluoromethyl) dibenzothio- and -Selenophenium Salt System. *Tetrahedron Lett.* **1990**, *31*, 3579-3582.

(11) Yoo, W.-J.; Kondo, J.; Rodríguez-Santamaría, J. A.; Nguyen, T. V. Q.; Kobayashi, S. Efficient Synthesis of a-Trifluoromethyl Carboxylic Acids and Esters through Fluorocarboxylation of *gem*-Difluoroalkenes. *Angew. Chem. Int. Ed.* **2019**, *58*, 6772-6775.

(12) (a) Nguyen, B. V.; Burton, D. J. A New Route for the Preparation of Substituted 2,2-Difluorostyrenes and a Convenient Route to Substituted (2,2,2-Trifluoroethyl)benzenes. *J. Org. Chem.* **1997**, *62*, 7758-7764. (b) Qiao, Y.; Si, T.; Yang, M.-H.; Altman, R. A. Metal-Free Trifluoromethylation of Aromatic and Heteroaromatic Aldehydes and Ketones. *J. Org. Chem.* **2014**, *79*, 7122-7131. (c) Deng, X.; Lin, J.; Zheng, J.; Xiao, J. Cu-Promoted Oxidative Trifluoromethylation of Terminal Alkynes with Difluoromethylene Phosphobetaine. *Chin. J. Chem.* **2014**, *32*, 689-693. (d) Gao, B.; Zhao, Y.; Ni, C.; Hu, J. AgF-Mediated Fluorinative Homocoupling of *gem*-Difluoroalkenes. *Org. Lett.* **2014**, *16*, 102-105. (e) Gao, B.; Zhao, Y.; Hu, J. AgF-Mediated Fluorinative Cross-Coupling of Two Olefins: Facile Access to α-$CF_3$ Alkenes and β-$CF_3$ Ketones. *Angew. Chem. Int. Ed.* **2015**, *54*, 638-642. (f) Tian, P.; Wang, C.-Q.; Cai, S.-H.; Song, S.; Ye, L.; Feng, C.; Loh, T.-P. $F^-$ Nucleophilic-Addition-Induced Allylic Alkylation. *J. Am. Chem. Soc.* **2016**, *138*, 15869-15872. (g) Tang, H.-J.; Lin, L.-Z.; Feng, C.; Loh, T.-P. Palladium-Catalyzed Fluoroarylation of *gem*-Difluoroalkenes. *Angew. Chem. Int. Ed.* **2017**, *56*, 9872-9876. (h) Tang, H.-J.; Zhang, Y.-F.; Jiang, Y.-W.; Feng, C. $F^-$ Nucleophilic-Addition-Induced [3+2] Annulation: Direct Access to $CF_3$ ‐Substituted Indenes. *Org. Lett.* **2018**, *20*, 5190-5193. (i) Liu, H.; Ge, L.; Wang, D.-X.; Chen, N.; Feng, C. Photoredox-Coupled F-Nucleophilic Addition: Allylation of *gem*-Difluoroalkenes. *Angew. Chem. Int. Ed.* **2019**, *58*, 3918-3922.

(13) (a) Hu, J.; Zhang, W.; Wang, F. Selective Difluoromethylation and Monofluoromethylation Reactions. *Chem. Commun.* **2009**, 7465-7478. (b) Zhang, C.-P.; Chen, Q.-Y. Guo, Y.; Xiao, J.-C.; Gu, Y.-C. Progress in Fluoroalkylation of Organic Compounds via Sulfinatodehalogenation Initiation System. *Chem. Soc. Rev.* **2012**, *41*, 4536-4559. (c) Ni, C.; Hu, J. Recent Advances in the Synthetic Application of Difluorocarbene. *Synthesis* **2014**, *46*, 842-863. (d) Ni, C.; Hu, M.; Hu, J. Good Partnership between Sulfur and Fluorine: Sulfur-Based Fluorination and Fluoroalkylation Reagents for Organic Synthesis. *Chem. Rev.* **2015**, *115*, 765-825. (e) Pan, X.; Xia, H.; Wu, J. Recent Advances in Photoinduced Trifluoromethylation and Difluoroalkylation. *Org. Chem. Front.* **2016**, *3*, 1163-1185. (f) Dilman, A. D.; Levin, V. V. Difluorocarbene as a Building Block for Consecutive Bond-Forming Reactions. *Acc. Chem. Res.* **2018**, *51*, 1272-1280. (g) Feng, Z.; Xiao, Y.-L.; Zhang, X. Transition-Metal

(Cu, Pd, Ni)-Catalyzed Difluoroalkylation via Cross-Coupling with Difluoroalkyl Halides. *Acc. Chem. Res.* **2018**, *51*, 2264-2278.

(14) (a) Zheng, J.; Cai, J.; Lin, J.-H.; Guo, Y.; Xiao, J.-C. Synthesis and Decarboxylative Wittig Reaction of Difluoromethylene Phosphobetaine. *Chem. Commun.* **2013**, *49*, 7513-7515. (b) Zheng, J.; Lin, J.-H.; Cai, J.; Xiao, J.-C. Conversion between Difluorocarbene and Difluoromethylene Ylide. *Chem. - Eur. J.* **2013**, *19*, 15261-15266. (c) Zheng, J.; Lin, J.-H.; Yu, L.-Y.; Wei, Y.; Zheng, X.; Xiao, J.-C. Cross-Coupling between Difluorocarbene and Carbene-Derived Intermediates Generated from Diazocompounds for the Synthesis of *gem*-Difluoroolefins. *Org. Lett.* **2015**, *17*, 6150-6153. (d) Zheng, J.; Lin, J.-H.; Deng, X.-Y.; Xiao, J.-C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)-Promoted Decomposition of Difluorocarbene and the Subsequent Trifluoromethylation. *Org. Lett.* **2015**, *17*, 532-535. (e) Liu, Y.; Zhang, K.; Huang, Y.; Pan, S.; Liu, X.-Q.; Yang, Y.; Jiang ,Y.; Xu, X.-H. Synthesis of 3-Fluoroalkenyl-3-trifluoromethyl-2-oxindoles by the Reaction of Indoline-2,3-diones with Difluoromethylene Phosphabetaine. *Chem. Commun.* **2016**, *52*, 5969-5972. (f) Zheng, J.; Cheng, R.; Lin, J.-H.; Yu, D.-H.; Ma, L.; Jia, L.; Zhang, L.; Wang, L.; Xiao, J.-C.; Liang, S. H. An Unconventional Mechanistic Insight into $SCF_3$ Formation from Difluorocarbene: Preparation of $^{18}F$-Labeled α-$SCF_3$ Carbonyl Compounds. *Angew. Chem. Int. Ed.* **2017**, *56*, 3196-3200. (g) Yu, J.; Lin, J.-H.; Xiao, J.-C. Reaction of Thiocarbonyl Fluoride Generated from Difluorocarbene with Amines. *Angew. Chem. Int. Ed.* **2017**, *56*, 16669-16673.

(15) (a) Fu, M.; Chen, L.; Jiang, Y.; Jiang, Z.-X.; Yang, Z. Copper-Catalyzed Intermolecular Chloro- and Bromotrifluoromethylation of Alkenes. *Org. Lett.* **2016**, *18*, 348-351. (b) Jia, Y.; Qin, H.; Wang, N.; Jiang, Z.-X.; Yang, Z. $Fe_2O_3$ ‑Promoted Intermolecular Chlorotrifluoromethylthiolation of Alkenes. *J. Org. Chem.* **2018**, *83*, 2808-2817.

(16) Fuqua, S. A.; Duncan, W. G.; Silverstein, R. M. A One-Step Synthesis of 1,1-Difluoro Olefins from Aldehydes. *J. Org. Chem.* **1965**, *30*, 1027-1029.

(17) Harris, J. M.; Chess, R. B. Effect of Pegylation on Pharmaceuticals. *Nat. Rev. Drug Discovery* **2003**, *2*, 214-221.

(18) Baker, M. T.; Naguib, M. Propofol: The Challenges of Formulation. *Anesthesiology* **2005**, *103*, 860-876.

(19) Van Patten, P. L. Mandelic Acid and Urinary Tract Infections. *Antonie van Leeuwenhoek* **1979**, *45*, 622-623.

(20) Goldberg, I.; Rokem, J. S.; Pines, O. Organic Acids: Old Metabolites, New Themes. *J. Chem. Technol. Biotechnol.* **2006**, *81*, 1601-1611.

(21) Adeva-Andany, M. M.; Pérez-Felpete, N.; Fernández-Fernández, C.; Donapetry-García, C.; Pazos-García, C. Liver Glucose Metabolism in Humans. *Biosci. Rep.* **2016**, *36*, e00416.

(22) Hu, X.; Shi, Y.; Zhang, P.; Miao, M.; Zhang, T.; Jiang, B. D-Mannose: Properties, Production, and Applications: An Overview. *Comp. Rev. Food Sci. Food Safety*, **2016** *15*, 773-785.

(23) Tang, X.-Z.; Tong, L.; Liang, H.-J.; Liang, J.; Zou, Y.; Zhang, X.-J.; Yan, M.; Chan, A. S. C. Facile Synthesis of Substituted Diaryl sulfones via a [3 + 3] Benzannulation Strategy. *Org. Biomol. Chem.* **2018**, *16*, 3560-3563.

(24) Feng, J.; Fu, X.; Chen, Z.; Lin, L.; Liu, X.; Feng, X. Efficient Enantioselective Synthesis of Dihydropyrans Using a Chiral *N,N′*-Dioxide as Organocatalyst. *Org. Lett.* **2013**, *15*, 2640-2643.

(25) (a) Zhuang, J.; Wang, C.; Xie, F.; Zhang, W. One-pot Efficient Synthesis of Aryl α-Keto Esters from Aryl-ketones. *Tetrahedron.* **2009**, *65*, 9797-9800. (b) Harada, K.; Imbe, Y.; Nishihira, K.; Tanaka, S.; Fujitsu, S.; Sugise, R.; Kashiwagi, K.; Sumida, T.; Doi, T.; Nishio, M. Phosphorus Catalysts for Decarbonylation Reaction. US Patent US005892091A, 1999.

(26) Hameury, T.; Guillemont, J.; Hijfte, L. V.; Bellosta, V.; Cossy, J. Diastereodivergent Addition of Allenylzincs to Aryl Glyoxylates. *Org. Lett.* **2009**, *11*, 2397-2400.

(27) Karasawa, T.; Oriez, R.; Kumagai, N.; Shibasaki, M. *anti*-Selective Catalytic Asymmetric Nitroaldol Reaction of α-Keto Esters: Intriguing Solvent Effect, Flow Reaction, and Synthesis of Active Pharmaceutical Ingredients. *J. Am. Chem. Soc.* **2018**, *140*, 12290-12295.

(28) Jin, Z.; Jiang, K.; Fu, Z.; Torres, J.; Zheng, P.; Yang, S.; Song, B.-A.; Chi, Y. R. Nucleophilic β-Carbon Activation of Propionic Acid as a 3-Carbon Synthon by Carbene Organocatalysis. *Chem. - Eur. J.* **2015**, *21*, 9360-9363.

(29) Duan, H.-F.; Xie, J.-H.; Qiao, X.-C.; Wang, L.-X.; Zhou, Q.-L. Enantioselective Rhodium-Catalyzed Addition of Arylboronic Acids to α-Ketoesters. *Angew. Chem. Int. Ed.* **2008**, *47*, 4351-4353.

(30) Chen, J.; Li, F.; Wang, F.; Hu, Y.; Zhang, Z.; Zhao, M.; Zhang, W. $Pd(OAc)_2$-Catalyzed Asymmetric Hydrogenation of α-Iminoesters. *Org. Lett.* **2019**, *21*, 9060-9065.