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A new finding in selective Baeyer–Villiger oxidation of α-fluorinated ketones; a new and practical route for the synthesis of α-fluorinated esters

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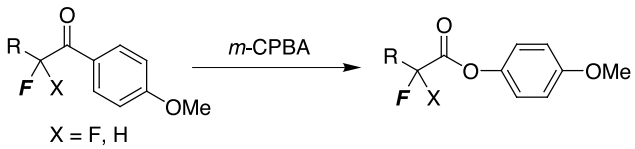
Abstract—α-Fluorinated esters were effectively prepared by the Baeyer–Villiger oxidation of α-fluorinated ketones with *m*-chloroperbenzoic acid (*m*-CPBA) under mild conditions. The yield of the esters was influenced by the choice of solvent, base, and substituent on the aryl group of the ketones. 4-Methoxyphenyl substituted fluoroketones were oxidized almost quantitatively with *m*-CPBA within 10 min to 12 h at room temperature using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a cosolvent with CH_2Cl_2 (1:1, v/v) and aqueous buffer (KH_2PO_4–NaOH, pH 7.6) as an additive base. The oxidation reaction rates of α-fluorinated ketones were higher than those of the corresponding non-fluorinated ketones. The fluorine atom at α-position of fluoromethyl aryl ketones enhanced the reactivity in the Baeyer–Villiger oxidation.

1. Introduction

Esters containing fluorine atoms at the α-position have been especially focused as inhibitors or bioactive compounds as their carboxylic acid derivatives.[1] Those fluoroesters have been synthesized by direct fluorination of corresponding esters,[2] the Reformatsky reactions of fluorine and other halogen containing esters,[1c,d,3] and the aldol condensation reactions of ketene silyl acetals,[4] lithium enolate,[5] or α-siliylated esters.[6] The Baeyer–Villiger oxidation of fluorinated ketone to obtain α-monofluoroester was also reported by Shiozaki.[7] Unfortunately, the yield of α-monofluoro *tert*-butyl ester with 5 equiv. of magnesium monoperphthalate was rather low (57%) even though the corresponding ketone was oxidized at 50°C for 18 h.

The Baeyer–Villiger oxidation is an archetype of synthetic transformations and has been commonly employed for ester synthesis from many kinds of ketones.[8] Special effects of fluorine atom(s) on Baeyer–Villiger oxidation are worth investigating. There have been some reports about the interesting stereoelectronic effects on Baeyer–Villiger oxidation of fluorinated ketones.[9] To our best knowledge, however, little has been known regarding relationship between the substitution mode of the substrates (not only fluoromethyl groups but also the migrating groups) and their reactivities in detail. Furthermore, much less attention has been paid to the synthetic applications of Baeyer–Villiger oxidation of α-fluorinated ketones, that could be straightforward to the α-fluorinated esters. In this paper, we report on an effective synthetic approach to α-fluorinated esters by the Baeyer–Villiger oxidation under mild conditions (Scheme 1). Moreover, the effect of the α-fluorine atom of ketones in this oxidation is also discussed.



Scheme 1.

2. Results and discussion

2.1. The Baeyer–Villiger oxidation of fluorinated acetophenones

m-Chloroperbenzoic acid (*m*-CPBA) has been widely used as an oxidant for the Baeyer–Villiger oxidation. First, the oxidation of several fluorinated and non-fluorinated ketones with *m*-CPBA was examined (Table 1).

Yields of esters were strongly affected by a kind of base, solvent, and aryl substituents. Trifluoromethyl phenyl ketone **1** was converted 47% under the conventional Baeyer–Villiger oxidation conditions (entry 1, dispersed

Keywords: fluorine and compounds; Baeyer–Villiger reactions; oxidation; esters.

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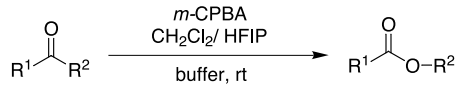
Table 1. Baeyer–Villiger oxidation of ketones



Entry	Ketone	R^1	R^2	Time	% yield of ester[a]
1[b]	**1**	CF_3	Ph	10 min	53
2	**1**	CF_3	Ph	10 min	87
3	**2**	CF_3	4-MeO-C_6H_4	10 min	>99
4	**3**	CF_3	4-Mc-C_6H_4	10 min	95
5	**4**	CF_3	4-Cl-C_6H_4	10 min	76
6	**5**	CF_3	*n*-C_6H_{13}	10 min	57
7	**6**	CF_2H	Ph	10 min	48
8	**7**	CFH_2	Ph	10 min	25
9	**8**	CH_3	Ph	10 min	6
10	**8**	CH_3	Ph	3 h	20
11[b]	**8**	CH_3	Ph	3 h	7
12	**9**	CH_3	4-MeO-C_6H_4	10 min	>98
13	**10**	CH_3	*n*-C_6H_{13}	10 min	4

Reaction conditions: ketone: 0.2 mmol, *m*-CPBA: 0.25 mmol, CH_2Cl_2: 0.5 mL, HFIP: 0.5 mL, buffer (phosphate buffer, pH 7.6): 0.2 mL.

[a] Determined by ^{19}F or ^1H NMR (the yields are based on conversions of ketones because of easily hydrolytic decomposition of the fluorinated esters to fluorinated acetic acids. The acetates were detected by ^{19}F NMR).

[b] Anhydrous CH_2Cl_2 (1 mL) was used as a solvent and $NaHCO_3$ (0.25 mmol) was used as a base instead of aqueous buffer.

sodium bicarbonate ($NaHCO_3$) in anhydrous dichloromethane[9c,10]). After extensive experimental survey, it was found that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and the aqueous buffer[11] instead of $NaHCO_3$ were clearly effective for the conversion of **1** (entry 2). Since 10 mol% of KH_2PO_4 and NaOH to ketone were contained in the buffer solution, they had to work as a catalyst in the reaction. The aqueous base likely enhances the removal of the hydroxyl proton from the adduct of *m*-CPBA to ketones (Criegee intermediate) and then accelerates the rearrangement, and would not work for the ionization of peracid as described by Krow[8d] and Renz.[8a] The combination of HFIP and aqueous buffer also accelerated the reaction for non-fluorinated acetophenone (entries 10–13).

In general, the migratory preference of the substituted aryl group depends on its electron-releasing ability.[8a] The results from the substituted aryl and alkyl ketones were consistent with the rule; 4-methoxyphenyl (**2**)>4-methylphenyl (**3**)> phenyl (**1**) and 4-chlorophenyl (**4**)>*n*-hexyl (**5**) (entries 2–6).

Here, the effect of fluorine atoms on the reactivity was clearly observed. The reaction rate and the yield of esters were increased, depending on the number of α-fluorine atoms of fluoromethyl phenyl ketones; 87% for CF_3 (**1**) (entry 2), 48% for CF_2H (**6**) (entry 7), 25% for CFH_2 (**7**) (entry 8), and 6% for CH_3 (**8**) (entry 9). Competitive experiments were carried out for 4-methoxyphenyl trifluoromethyl (**2**) and methyl (**9**) ketones. On treating the 1:1 mixture of **2** (0.22 mmol) and **9** (0.22 mmol) with *m*-CPBA (0.19 mmol, 0.43 equiv.), 80% of **2** and 3% of **9** were converted to the corresponding esters, respectively. These results obviously demonstrated that the trifluoromethyl ketone reacted much faster than the corresponding non-fluoromethyl ketone under the conditions employed.

To elucidate the reactivity difference of each ketone, IR absorptions of C=O stretching bands are exemplified (Table 2). The results reveal the effect of α-fluorine atoms, both to the CO stretching frequencies ν_{CO} and the reactivities of ketones.

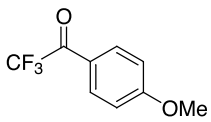
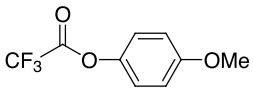
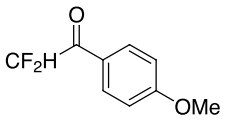
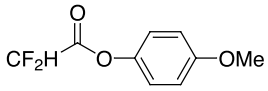
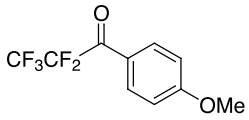
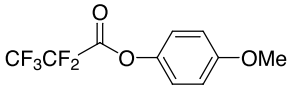
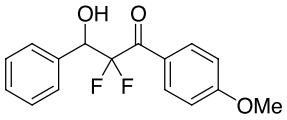
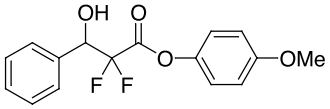
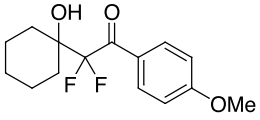
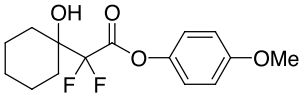
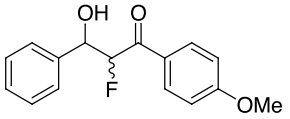
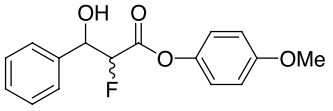
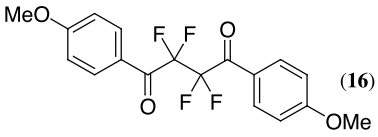
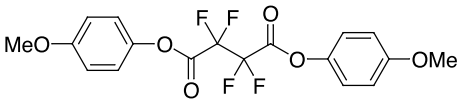
For aryl ketones (R^2=Ar), the substitution of fluorine atoms on the methyl group makes the absorption peaks shift higher in wavenumber (results shown on the third row in Table 2 for R^2=C_6H_5, R^1=CF_3, CF_2H, CFH_2, CH_3, and R^2=4-MeO-C_6H_4, R^1=CF_3, CH_3 in Table 2). These data suggest that fluoromethyl groups activate carbonyl carbon electronically, and make the nucleophilic addition of peracid to the carbonyl carbon easier. Kitazume et al. reported on the negative effect of the fluorinated alkyl group on the Baeyer–Villiger oxidation under their conditions,[9a,12] and explained that fluorine atoms might destabilize the Criegee intermediate due to the electronic repulsion between the oxygen atom of the hydroxy group and the fluorine atom(s) of the fluoroalkyl group. In contrast to this fact, the present experimental results show that the electron-withdrawing property of the fluorine atom apparently promotes the Baeyer–Villiger oxidation of both fluoromethyl aryl and trifluoromethyl hexyl ketones (**1**–**7**) in slightly basic biphase solution. In a series of methyl and fluoromethyl phenyl ketones (third row in Table 2), the reactivities are dependent on the electrophilic nature of the carbonyl groups, as observed in the higher C=O stretching absorption of the more highly fluorinated methyl ketones. The same reactivity dependency was observed for 4-methoxyphenyl ketones. The nucleophilic addition of the peracid to the carbonyl groups would play an important role for the reaction rates of this series of substrates, where the migrating groups are fixed to one of the aryl groups. However, the reverse trend was observed in a series of trifluoromethyl hexyl and substituted phenyl ketones (first column in Table 2).[13] In these cases, the intramolecular nucleophilic attack of the electron-rich migrating group on the peroxide oxygen in the Criegee intermediate would

Table 2. IR absorptions of C=O bond in ketones (R^1COR^2) and yields of the Baeyer–Villiger oxidation products

R^1COR^2	CF_3	CF_2H	CFH_2	CH_3	CF_3CF_2
4-MeO-C_6H_4	1707 [>99]	1698 [97]		1676 [>98]	1698 [94]
4-MeO-C_6H_4	1716 [95]				
C_6H_5	1719 [87]	1712 [48]	1705 [25]	1683 [6]	
4-Cl-C_6H_4	1722 [76]				
n-C_6H_{13}	1765 [57]			1722 [4]	

Wavenumbers of C=O stretching (cm^{-1}), and the numbers in parentheses are % conversion with *m*-CPBA in 10 min.

Table 3. Baeyer–Villiger oxidation of ketones

Entry	Ketone (mol%)		*m*-CPBA (mol%)	Conditions	Ester		Isolated yield (%)
1		(**2**)	125	rt, 10 min		(**17**)	99[a,b]
2		(**11**)	125	rt, 10 min		(**18**)	97
3		(**12**)	125	rt, 10 min		(**19**)	94[a]
4		(**13**)	250	rt, 1 h		(**20**)	99
5		(**14**)	250	rt, 12 h		(**21**)	98
6		(**15**)	250	rt, 12 h		(**22**)	98
7		(**16**)	250	rt, 10 min		(**23**)	82

Reaction conditions: ketone: 0.2 mmol, CH_2Cl_2 1 mL, HFIP 1 mL, buffer (phosphate buffer, pH 7.6) 0.2 mL.
[a] Determined by ^{19}F NMR.
[b] % conversion of ketone.

control the total conversion of the Baeyer–Villiger oxidation, since the nucleophilic addition of the peracid to the carbonyl groups must occur quickly due to the strong electron-withdrawing nature of trifluoromethyl group, and may not be a rate-determining step.

2.2. The Baeyer–Villiger oxidation of fluorinated 4-methoxyphenyl substituted ketones

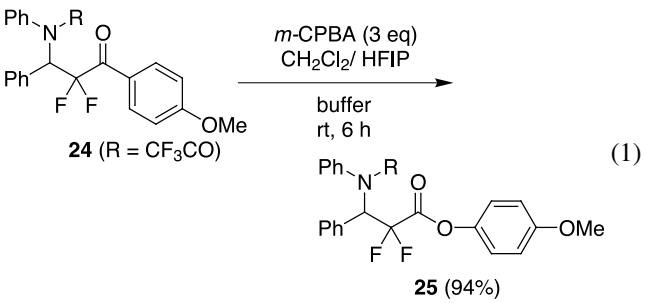
The experimental results described above clearly demonstrate that fluoroalkyl ketones with 4-methoxyphenyl group undergo very smooth esterification by the Baeyer–Villiger oxidation in an HFIP-buffer system and the present protocol can be used for an effective preparation of fluoroesters. Application of the methodology to other substrates was examined (Table 3).

Not only trifluoromethyl ketone **2**, but also difluoromethyl and pentafluoroethyl ketones (**11** and **12**) were successfully transformed within 10 min to the corresponding esters (**18** and **19**) in excellent yields.

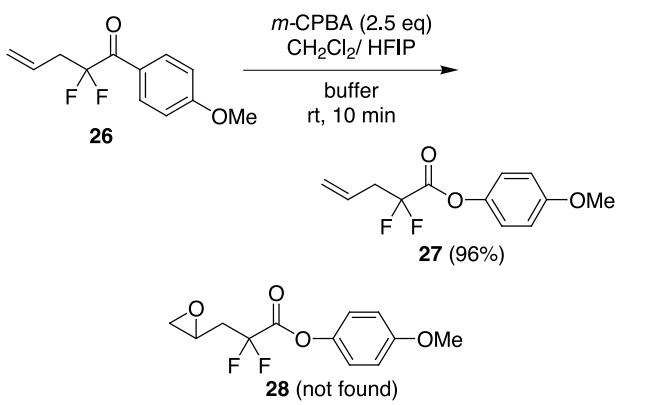
Ketones **13**–**15** are the Mukaiyama-aldol products[14] obtained from 2,2-difluoro- and 2-fluoroenol silyl ethers.[15,16] Corresponding esters **20**–**22** were obtained almost quantitatively. Higher amount of *m*-CPBA and longer reaction time are required for the hydroxy ketones (entries 4–6) as compared with non-hydroxy ketones (entries 1, 2, 3 and 7). Lower wavenumbers for the hydroxy ketones **13**–**15** of C=O absorption (**13**: ν_{CO} 1668 cm^{-1}) than those of ketones **2**, **11** and **12** (**11**: ν_{CO} 1698 cm^{-1}) also suggest the less reactivity. The diketone **16**[17] was also converted smoothly to diester **23** (2,2,3,3-tetrafluorosuccinate) under the same condition (entry 7).

The potential applications of the new Baeyer–Villiger oxidation system, *m*-CPBA–HFIP/KH_2PO_4–NaOH buffer are shown in Eqs. (1) and (2). β-Aminoketone **24** was oxidized at room temperature for 6 h, forming difluorinated β-amino acid derivative **25** in 94% yield (Eq. (1)). Interestingly, an alkene functionality in **26** was compatible under the present oxidative conditions; no formation of

epoxide **28** was detected and chemoselective Baeyer–Villiger oxidation was achieved to afford the desired ester **27** in 96% yield (Eq. (2)).



(1)



(2)

In summary, 4-methoxyphenyl substituted α-fluorinated esters were efficiently prepared by the Baeyer–Villiger oxidation with *m*-CPBA of the corresponding fluoroketones. Despite their synthetic potential, the Baeyer–Villiger reactions of fluorinated ketones have been little attention. For the Baeyer–Villiger oxidation, the α-fluorine atoms of the ketones enhance the reactivity, and the use of a catalytic amount of aqueous buffer and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a cosolvent favorably affected the yield of the esters, and the reaction rate. This finding clearly demonstrates the versatility and high potential of these chemoselective transformations in synthetic organic chemistry.

3. Experimental

3.1. General

Unless otherwise noted, all manipulations were carried out under an inert atmosphere (nitrogen or argon) in flame-dried glassware and using syringe-cannula/septa techniques. THF was distilled from sodium/benzophenone ketyl. CH_2Cl_2 was freshly distilled from phosphorus pentoxide. HFIP was stored over molecular sieves 4 Å. *m*-CPBA was washed with phosphate buffer and distilled water, then dried under reduced pressure.[18] All other reagents and solvents were employed without further purification. 2,2-Difluoro-1-(*p*-methoxyphenyl)enol silyl ether (**29**) was prepared from the corresponding trifluoromethyl ketone by means of Mg(0)-promoted defluorination.[15a] Unless otherwise stated, ^1H and ^{19}F NMR spectra were recorded at 200 and 188 MHz, respectively, using $CDCl_3$ as a solvent. The chemical shifts are reported in δ (ppm) value relative to Me_4Si (δ 0 ppm for ^1H NMR) and C_6F_6 (δ 0 ppm for ^{19}F NMR). Coupling constants are reported in hertz (Hz). NMR yields were calculated by ^{19}F NMR integration of products relative to the 1,3-bis(trifluoromethyl)benzene internal standard.

3.2. Synthesis of the starting ketones

3.2.1. 2,2-Difluoro-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one (13). To an anhydrous CH_2Cl_2 solution (4 mL) of $TiCl_4$ (455 mg, 2.4 mmol) was added a dichloromethane solution (1.5 mL) of benzaldehyde (509 mg, 4.8 mmol) at −78°C under a nitrogen atmosphere. The mixture was stirred for 10 min, a solution of the difluoroenol silyl ether **29** (517 mg, 2 mmol) in dry CH_2Cl_2 (1.5 mL) was added dropwise at −78°C. After stirring for additional 15 min, the reaction was quenched with water. The mixture was extracted with ether, and the organic phase was washed with brine, dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by column chromatography on silica gel afforded 368 mg (63%) of the aldol **13** as colorless crystals: IR (KBr) colorless crystals; mp 118–119°C; IR (KBr) 3448, 1668, 1594 cm^{-1}; ^1H NMR δ 3.19 (d, *J*=4.2 Hz, 1H), 3.89 (s, 3H), 5.37 (ddd, *J*=19, 5.1, 4.2 Hz, 1H), 6.34 (d, *J*=9.0 Hz, 2H), 7.36–7.54 (m, 5H), 8.07 (d, *J*=9.0 Hz, 2H); ^{19}F NMR δ 45.6 (dd, *J*=294, 19 Hz, 1F), 57.8 (dd, *J*=294, 5.1 Hz, 1F); MS *m*/*z* (%) 292 (M^+, 1), 186 (49), 135 (100), 77 (50). Anal. calcd for $C_{16}H_{14}O_3F_2$: C, 65.75; H, 4.83. Found: C, 65.50; H, 4.99.

3.2.2. 2,2-Difluoro-2-(1-hydroxycyclohexyl)-1-(4-methoxyphenyl)ethan-1-one (14). Using the procedure described above for the synthesis of **13**, the title compound was obtained as colorless crystals (75%); mp 72–73°C; IR (KBr) 3536, 1664, 1610 cm^{-1}; ^1H NMR δ 1.59–1.90 (m, 10H), 2.70 (s, 1H), 3.89 (s, 3H), 6.95 (d, *J*=9.1 Hz, 2H), 8.12 (d, *J*=9.1 Hz, 2H); ^{19}F NMR δ 49.5 (s, 2F); MS *m*/*z* (%) 284 (M^+, 2), 266 (6), 186 (47), 135 (100), 107 (19), 92 (20), 77 (47). Anal. calcd for $C_{15}H_{18}O_3F_2$: C, 63.37; H, 6.38. Found: C, 63.06; H, 6.43.

3.2.3. 2-Fluoro-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one (15). By a procedure similar to that for **13**, the title compound (488 mg, 89%) was obtained from 2-fluoro-1-(*p*-methoxyphenyl)enol silyl ether (**30**)[16] and benzaldehyde. Colorless crystals, as a mixture of diastereomers. A diastereomer ratio of 2:1 was determined by comparing the intensities of the indicated ^{19}F NMR peaks (∗=major isomer; ∗∗=minor isomer); mp 71°C (decomposition); IR (KBr) 3404, 1674, 1602 cm^{-1}; ^1H NMR δ ∗∗2.87 (d, *J*=3.5 Hz, 1H), ∗3.16 (d, *J*=3.8 Hz, 1H), 3.87 (s, 3H), ∗5.23 (ddd, *J*=10, 6.8, 3.8 Hz, 1H), ∗∗5.2–5.4 (m, 1H), ∗5.50 (dd, *J*=48, 6.8 Hz, 1H), ∗∗5.56 (dd, *J*=48, 3.8 Hz, 1H), 6.90 (d, *J*=9.2 Hz, 2H), 7.3–7.5 (m, 5H), ∗7.90 (d, *J*=9.2 Hz, 2H), ∗∗7.92 (d, *J*=9.2 Hz, 2H); ^{19}F NMR δ ∗∗−35.6 (dd, *J*=48, 22 Hz, 1F), ∗−26.7 (dd, *J*=48, 10 Hz, 1F); MS *m*/*z* (%) 168 (32), 135 (100), 107 (31), 92 (38), 77 (73). Anal. calcd for $C_{16}H_{15}O_3F$: C, 70.06; H, 5.51. Found: C, 70.15; H, 5.57.

3.2.4. 2,2-Difluoro-1-(4-methoxyphenyl)-3-[*N*-phenyl-*N*-(trifluoroacetyl)amino]-3-phenylpropan-1-one (24). To an anhydrous CH_2Cl_2 solution (10 mL) of $BF_3{\cdot}OEt_2$

(679 mg, 5.5 mmol) was added a mixture of *N*-phenylbenzaldimine (977 mg, 5.5 mmol) and difluoroenol silyl ether **29** (1.02 g, 5.0 mmol) in dry CH_2Cl_2 (2 mL) at −78°C under an argon atmosphere. After stirring for additional 15 min at 0°C, the reaction was quenched with water. The mixture was extracted with ether, and the organic phase was washed with brine, dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by column chromatography on silica gel (hexane/ethyl acetate, 10/1) afforded 1.27 g (70%) of the β-amino ketone **31** (R=H) as colorless crystals: IR (KBr) colorless crystals; mp 96°C; IR (KBr) 3408, 1698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.59 (d, *J*=9.0 Hz, 1H), 5.28 (ddd, *J*=17, 9.0, 8.5 Hz, 1H), 6.60 (d, *J*=8.5 Hz, 2H), 6.70 (t, *J*=7.5 Hz, 1H), 6.92 (d, *J*=8.5 Hz, 2H), 7.10 (t, *J*=7.5 Hz, 2H), 7.3–7.4 (m, 3H), 7.45 (d, *J*=7.5 Hz, 2H), 7.98 (d, *J*=8.5 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ 50.7 (dd, *J*=269, 17 Hz, 1F), 58.5 (dd, *J*=269, 8.5 Hz 1F); MS *m/z* (%) 367 (M^+, 3), 182 (100), 135 (8), 104 (15), 92 (6), 77 (31). Anal. calcd for $C_{22}H_{19}NO_2F_2$: C, 71.92; H, 5.21; N, 3.81. Found: C, 71.94; H, 4.93; N, 3.66. Upon treatment with trifluoroacetic anhydride (56 μL, 0.4 mmol) and pyridine (31 μL, 0.4 mmol) in Et_2O (1 mL), β-amino ketone **31** (146 mg, 0.4 mmol) was readily converted into the title compound **24** (R=CF_3CO). After evaporation of the solvent, the residue was filtered through a short pad of silica gel to give 439 mg (95%) of crude **24**, suitable for use in the next step without further purification.

3.2.5. 2,2-Difluoro-1-(4-methoxyphenyl)-4-penten-1-one (26). To a stirred suspension of anhydrous powder KF (finely ground and activated by heating with a heat gun under vacuum) (696 mg, 1.2 mmol) and CuI (274 mg, 1.44 mmol) in 1 mL of anhydrous DMF was added a solution of the difluoroenol silyl ether **29** (310 mg, 1.2 mmol) in dry DMF (1 mL). The reaction mixture was allowed to warm to 40°C, followed by addition of 0.42 mL (4.8 mmol) of allyl bromide. After stirring for 3 h, the reaction was quenched with water. The mixture was extracted with ether, and the organic phase was washed with brine, dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by column chromatography on silica gel (hexane/ethyl acetate, 10/1) afforded 141 mg (52%) of **26** as a colorless oil: IR 1692, 1610 cm^{-1}; ^1H NMR δ 2.95 (dt, *J*=7.0, 17.6 Hz, 2H), 3.89 (s, 3H), 5.25 (d, *J*=11.2 Hz, 1H), 5.26 (d, *J*=14.4 Hz, 1H), 5.85 (ddt, *J*=14.4, 11.2 Hz, 7.0, 1H), 6.96 (d, *J*=9.1 Hz, 2H), 8.10 (d, *J*=9.1 Hz, 2H); ^{19}F NMR δ 62.8 (t, *J*=17.6 Hz, 2F); MS *m/z* (%) 226 (M^+, 4), 135 (100), 107 (11), 92 (14), 77 (21). Anal. calcd for $C_{12}H_{12}O_2F_2$: C, 63.71; H, 5.35. Found: C, 63.64; H, 5.20.

3.3. Typical procedure for the synthesis of esters by the Baeyer–Villiger oxidation

To a mixture of ketone (0.2 mmol) and *m*-CPBA (0.25 mmol) in CH_2Cl_2/HFIP (1 mL/1 mL) was added phosphate buffer (0.2 mL) at ambient temperature. After stirring for additional 10 min, the reaction mixture was concentrated under reduced pressure. The residue was dissolved with Et_2O/THF=10:1. The solution was washed with ice-cooled 2% aqueous Na_2SO_3, ice-cooled 1% aqueous $NaHCO_3$, and ice-cooled brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Yields were calculated by ^{19}F NMR integration of products relative to the 1,3-bis(trifluoromethyl)benzene internal standard.

3.3.1. 4-Methoxyphenyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate (20). Colorless crystals; mp 98–99°C; IR (KBr) 3452, 1784, 1508 cm^{-1}; ^1H NMR δ 2.72 (d, *J*=4.2 Hz, 1H), 3.80 (s, 3H), 5.30 (ddd, *J*=15, 8.3, 4.2 Hz, 1H), 6.86–6.99 (m, 4H), 7.40–7.55 (m, 5H); ^{19}F NMR δ 42.2 (dd, *J*=260, 15 Hz, 1F), 47.6 (dd, *J*=260, 8.3 Hz, 1F); MS *m/z* (%) 308 (M^+, 25), 204 (3), 124 (100), 109 (46), 77 (16). Anal. calcd for $C_{16}H_{14}O_4F_2$: C, 62.33; H, 4.58. Found: C, 62.29; H, 4.77.

3.3.2. 4-Methoxyphenyl 2,2-difluoro-2-(1-hydroxycyclohexyl)ethanoate (21). Colorless crystals; mp 54–55°C; IR (KBr) 3496, 2944, 1778, 1506 cm^{-1}; ^1H NMR δ 1.65–1.95 (m, 10H), 2.27 (s, 1H), 3.81 (s, 3H), 6.89–7.12 (m, 4H); ^{19}F NMR δ 42.1 (s, 2F); MS *m/z* (%) 300 (M^+, 18), 202 (2), 124 (100), 109 (53), 81 (48). Anal. calcd for $C_{15}H_{18}O_4F_2$: C, 59.99; H, 6.04. Found: C, 59.81; H, 6.09.

3.3.3. 4-Methoxyphenyl 2-fluoro-3-hydroxy-3-phenylpropanoate (22). Colorless crystals, as a mixture of diastereomers. A diastereomer ratio of 2:1 was determined by comparing the intensities of the indicated ^{19}F NMR peaks (* =major isomer; * * =minor isomer); mp 71°C (decomposition); IR (KBr) 3452, 1780, 1754, 1506 cm^{-1}; ^1H NMR δ 2.7–2.8 (m, 1H), *3.78 (s, 3H), * * 3.79 (s, 3H), 5.1–5.5 (m, 2H), 6.8–6.9 (m, 4H), 7.3–7.6 (m, 5H); ^{19}F NMR δ * * −39.6 (dd, *J*=49, 21 Hz, 1F), *−36.1 (dd, *J*=49, 17 Hz, 1F); MS *m/z* (%) 290 (M^+, 10), 184 (2), 124 (100), 109 (41), 77 (17). Anal. calcd for $C_{16}H_{15}O_4F$: C, 66.20; H, 5.21. Found: C, 66.12; H, 5.13.

3.3.4. Bis(4-methoxyphenyl) 2,2,3,3-tetrafluorosuccinate (23). Colorless crystals; mp 61–62°C; IR (KBr) 1790, 1600 cm^{-1}; ^1H NMR δ 3.81 (s, 6H), 6.87–6.95 (m, 4H), 7.07–7.15 (m, 4H); ^{19}F NMR δ 41.9 (s, 4F); MS *m/z* (%) 402 (M^+, 51), 279 (2), 251 (11), 223 (35), 123 (100), 107 (25), 95 (32). Anal. calcd for $C_{18}H_{14}O_6F_4$: C, 53.74; H, 3.51. Found: C, 53.64; H, 3.76.

3.3.5. 4-Methoxyphenyl 2,2-difluoro-3-[*N*-phenyl-*N*-(trifluoroacetyl)amino]-3-phenylpropanoate (25). The crude product was purified by silica gel column chromatography (hexane/Et_2O=10:1) to afford **25** as a colorless oil; IR (NaCl) 1784, 1714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.19 (d, *J*=8.0 Hz, 1H), 6.80 (dd, *J*=13.8, 16.4 Hz, 1H), 6.86 (d, *J*=9.0 Hz, 2H), 6.89 (d, *J*=9.0 Hz, 2H), 7.01 (t, *J*=8.0 Hz, 1H), 7.16 (d, *J*=7.5 Hz, 2H), 7.28 (dd, *J*=7.5, 8.0 Hz, 2H), 7.36 (t, *J*=7.5 Hz, 1H), 7.38 (t, *J*=7.5 Hz, 1H), 7.44 (t, *J*=7.5 Hz, 1H), 7.66 (d, *J*=8.0 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ 53.5 (dd, *J*=256, 13.8 Hz, 1F), 54.9 (dd, *J*=256, 16.4 Hz, 1F), 94.3 (s, 3F); MS *m/z* (%) 479 (M^+, 3), 356 (100), 328 (29), 172 (48), 167 (36), 77 (71). Anal. calcd for $C_{24}H_{18}NO_4F_5$: C, 60.13; H, 3.78; N, 2.92. Found: C, 60.10; H, 3.99; N, 2.77.

3.3.6. 4-Methoxyphenyl 2,2-difluoro-4-pentenoate (27). Colorless oil; bp 90°C (1.0 mm Hg); IR (NaCl) 1788, 1602, 1508 cm^{-1}; ^1H NMR δ 2.98 (dt, *J*=7.1, 15.6 Hz, 2H), 3.81

(s, 3H), 5.35 (d, J=10.1 Hz, 1H), 5.36 (d, J=17.1 Hz, 1H), 5.85 (ddt, J=17.1, 10.1, 7.1 Hz, 1H), 6.96 (d, J=9.2 Hz, 2H), 7.06 (d, J=9.2 Hz, 2H); ^{19}F NMR δ 56.6 (t, J=15.6 Hz, 2F); MS m/z (%) 242 (M^+, 35), 135 (19), 124 (100), 109 (51), 91 (14). Anal. calcd for $C_{12}H_{12}O_3F_2$: C, 59.50; H, 4.99. Found: C, 59.80; H, 5.26.

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