A solvent-free, base-catalyzed domino reaction towards trifluoromethylated benzenes from bio-based methyl coumalate

Liang Chang, Nadja Klipfel, Luc Dechoux, Serge Thorimbert

A solvent-free, base-catalyzed domino reaction towards trifluoromethylated benzenes from bio-based methyl coumalate

Liang Chang, Nadja Klipfel, Luc Dechoux * and Serge Thorimbert *

A novel, efficient, and environmentally compatible method for CF_3-substituted benzene production is reported. It sources a bio-based feedstock, employs *t*BuOK as catalyst, and is solvent-free. This regioselective approach provides various trifluoromethyl benzenes in good to excellent yields, without extra oxidant or special care. CO_2 and water are the only byproducts of this process, and reaction conditions can scale up to gram quantities. The transformation involves an unprecedented *t*BuOK-catalyzed domino process, and features Michael addition / 6π-electrocyclic ring opening / [1,5]-H shift / carba-6π-electrocyclic ring closure / decarboxylative aromatization reactions.

Introduction

CF_3-functionalized aromatic and heterocyclic compounds play an essential role in medicinal chemistry, due to their unique pharmacokinetic properties.[1] The increased lipophilicity and stability, brought by the CF_3 group, improve bioavailability of the therapeutic compounds. Steric bulk introduced by the CF_3 group may allow a better binding to target proteins.[2] Thus, a wide range of methods have been described to introduce CF_3 groups to aromatics. For instance, the metal-mediated coupling of Ar-H,[3] ArX or $ArBX_2$,[4] with Si-CF_3 or the TMG.ICF_3 complex,[5,6] hypervalent iodine,[7] and by photoredox catalysis.[8] The use of metals, large quantities of byproducts, and waste are major drawbacks to these approaches. There are atom-economical alternatives for synthesis of trifluoromethyl-benzenes. Namely, Cycloaddition (CA) reactions and formal-CA reactions which employ a "trifluoromethylated building block approach". For example, Co- and Rh-mediated [2+2+2] cycloaddition reactions with fluoroalkylated alkynes[9], formal [4+2]-CA, and [3+3]-CA have been reported[10]. The formal [3+3]-CA between bis-silyl enol ethers and β-dimethyl thiounsaturated trifluoromethyl-ketones give tetrasubstituted arenes (Figure 1, a).[10b] The Diels-Alder (DA) cycloadditions between 1-ethoxy-3-trifluoromethyl-1, 3-butadiene, and electron-poor dienophiles yield trifluoromethyl-substituted benzenes (Figure 1, b).[10a] However, the number of studies reporting cycloadditions based on CF_3 substrates is rather limited.

On the other hand, *α*-pyrones[11] (e.g. methyl coumalate, **MC**) with dienophiles like alkynes,[12] enolethers,[13] or even simple alkenes[14], give substituted aromatics (methylbenzoates from **MC**). This happens through the Diels-Alder process after decarboxylation[15] and eventually releases an alcohol molecule. As shown by Haufe and co-workers, CF_3-substituted α-pyrones react with electron-rich alkynes in an inverse electron-demand Diels-Alder (IEDDA) reaction. This occurs under microwave irradiation, providing CF_3-benzene in good yield (figure 1, c).[12c]

Figure 1. Approaches to trifluoromethylated benzene by cycloaddition reactions

Although the Diels–Alder reaction remains exceptional in its scope and versatility for the methods of aromatic six-membered rings architecture, the development of thermal carba-6π-electrocyclization-aromatization process has come to complement [4+2] cycloadditions, when synthesizing poly-substituted benzene analogues. Funk and co-workers reported a streamlined electrocyclization-aromatization reaction of 2-acyl-3-amino-hexatrienes.[16] Anderson *et al*. developed a cascade cyclization of ynamides to azabicycles.[17] Chuang *et al*. reported approaches to isatin derivatives, which utilize three-component reactions of phosphines, enynedioates, and cinnamaldimine.[18] Recently, Huang *et al.* developed a new path to diaminobenzenes *via* highly electron-rich triene intermediates[19]; however, the aromatization step of these procedures often required extra oxidizers. Furthermore, 6π-electrocyclization aromatization reactions for

Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, IPCM, F-75005 Paris, France.
† serge.thorimbert@sorbonne-universite.fr; luc.dechoux@sorbonne-universite.fr
http://www.ipcm.fr/presentation-682?lang=en
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

polyfunctionalized benzenes remain challenging.[19] To the best of our knowledge, the synthesis of trifluoromethylated benzene *via* 6π-electrocyclization reaction has not been reported in previous literature.

Thus, considering the pharmacokinetic and pharmaceutical values of CF_3-functionalized compounds we launched a program in devising an environmentally friendly synthetic method for the preparation of trifluoromethylated benzenes. In order to reach the key intermediate CF_3-hexatriene (Figure 1, d), **MC** has been selected as an electrophilic pro-diene synthon based on our recent finding that **MC** can be readily converted to diene in the presence of certain nucleophiles.[20] Arising from dimerization of biorenewable malic acid, **MC** provides a basis for sustainable synthesis leading to novel bio-based product. We report herein a novel, environmentally compatible method towards CF_3-substituted benzenes in solvent-free conditions.

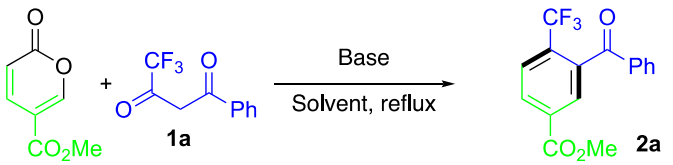
Results and discussion

We began our study, by treating **MC** and trifluoroaceto-acetophenone **1a** with 1 equiv. of Et_3N in DCM at reflux for 30 h. It provided the expected arene **2a** in 54% yield (Table 1, entry 1).

Optimization of the reaction conditions to obtain trifluoromethyl-arene **2a** is presented in Table 1. The solvent plays an important role in this type of transformation. Low conversions were observed in THF, EtOH, and water. This is due to trimerization of the starting diketone **1a,** giving 1,3,6-trifluoromethyl-2,4,5-triphenylbenzene (entries 2-4). Comparatively, toluene is the solvent of choice. It yields benzene **2a** at 81% after 30 h at reflux, in the presence of stoichiometric amounts of Et_3N (entry 5). We found that simpler amines, such as the cyclic amidine 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), are highly efficient and output **2a** in 70% yields within an hour (entry 6).

To improve sustainability of the reaction conditions, we tested catalytic amounts of base. The quantity of DBU was successfully decreased to 10 mol%, providing product in 85% yield after 8 h (entry 7). However, separation of the expected product **2a** and the starting diketone **1a** was difficult. The reaction was extended to reach complete conversion and facilitate purification. After 15 h refluxing with 0.1 equiv. of DBU, trifluoromethyl benzophenone **2a** was isolated in 89% yield (entry 8). No improvement in this transformation was observed when 10 mol% *t*BuOK was employed (entry 9). Other bases such as Quinuclidine, DMAP, Imidazole, Et_3N, or even DBN were not as efficient as DBU (see SI Table S1). Solvent-free conditions led to the formation of expected compound **2a** in 1.5 h, but a moderate 67% yield (entry 10). Interestingly, the replacement of DBU by *t*BuOK (10 mol%) gave **2a** in excellent yield (entry 11). Lowering the catalytic loading down to 5 mol% resulted in a longer reaction time to reach similar yield (entry 12). Finally, a slight decrease in reaction temperature to 80 °C enhance the isolated yield up to 95% (entry 13). No amelioration was observed with the inorganic bases K_2CO_3 or KOH (entry 14-15).

Table 1. Optimization of the Reaction Conditions[a]

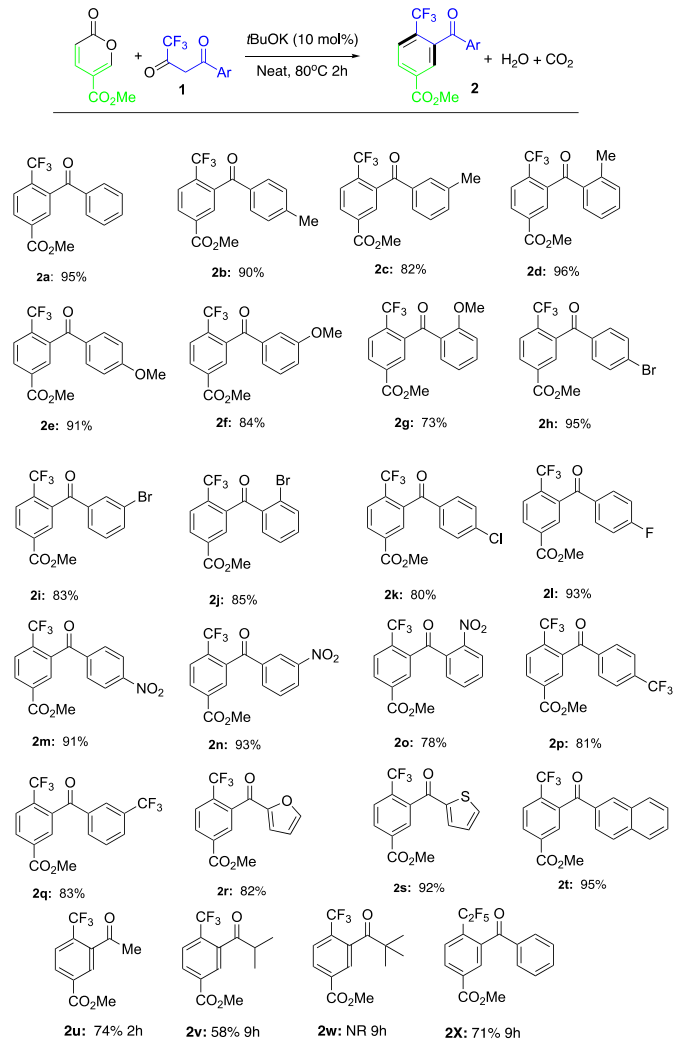


Entry	Base (equiv.)	Solvent	Time (h)	Yield(%)[b]
1	Et_3N (1)	DCM	30	54
2	Et_3N (1)	THF	30	29
3	Et_3N (1)	EtOH	30	28
4	Et_3N (1)	H_2O	30	ND
5	Et_3N (1)	toluene	30	81
6	DBU (1)	toluene	1	70
7	DBU (0.1)	toluene	8	85
8	DBU (0.1)	toluene	15	89
9	*t*BuOK (0.1)	toluene	15	80
10	DBU (0.1)	neat[c]	1.5	67
11	*t*BuOK (0.1)	neat[c]	1.5	90
12	*t*BuOK (0.05)	neat[c]	4	93
13	*t*BuOK (0.1)	neat[d]	2	95
14	K_2CO_3 (0.1)	neat[c]	1.5	74
15	KOH (0.1)	neat[c]	1.5	70

[a]Reaction conditions: All reactions were performed with **MC** (1 mmol) and trifluoroaceto-acetophenone **1a** (1 mmol). [b] isolated yields. [c]At 110°C .[d]At 80°C.

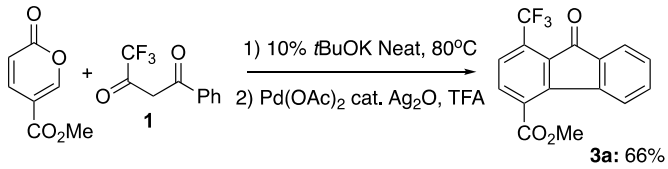
With the optimal conditions established, we prepared various trifluoromethyl-β-diketones **1a-t**, according to known procedures.[21] We then subjected each to the reaction conditions (**MC**, *t*BuOK 10 mol%, neat, 80°C) (Table 2). Excellent regioselectivity is observed in the crude. ^{19}F NMR spectroscopy shows 100% selectivity in favor of the benzophenone type product **2** *vs* its trifluoro-acetophenone regioisomer (ArCOCF3). Careful examination of the different spectra (See SI) shows the CF_3 group signal at around –60 ppm. This is consistent with an aromatic CF_3 moiety.[22] The putative trifluoro-acetophenone regioisomer derivative would have its $COCF_3$ signal shifted up-field at around –70, –80 ppm. The effect of the substituent on the aromatic ring was investigated. Electron-neutral, electron-poor and electron-rich-groups were tolerated at the ortho-, meta- and para-positions. With the Methyl electron-donating groups, the corresponding benzenes **2b-d** were formed in yields ranging from 90 to 96%. Similarly, the methoxy p-electron-donating group provided expected trifluoromethyl arenes (**2e-g**) in yields up to 91%. Halogen-substituted benzenes were obtained in 80-95% yields, no matter the halogen and its position on the aromatic ring (**2h-l**). The ortho substituted nitro compound **2o** was formed in 78% yield, whereas meta- and para- isomers (**2m-n**) were successfully isolated in 91-93% yield.

Table 2. Synthesis of a variety of trifluoromethyl benzenes **2**.



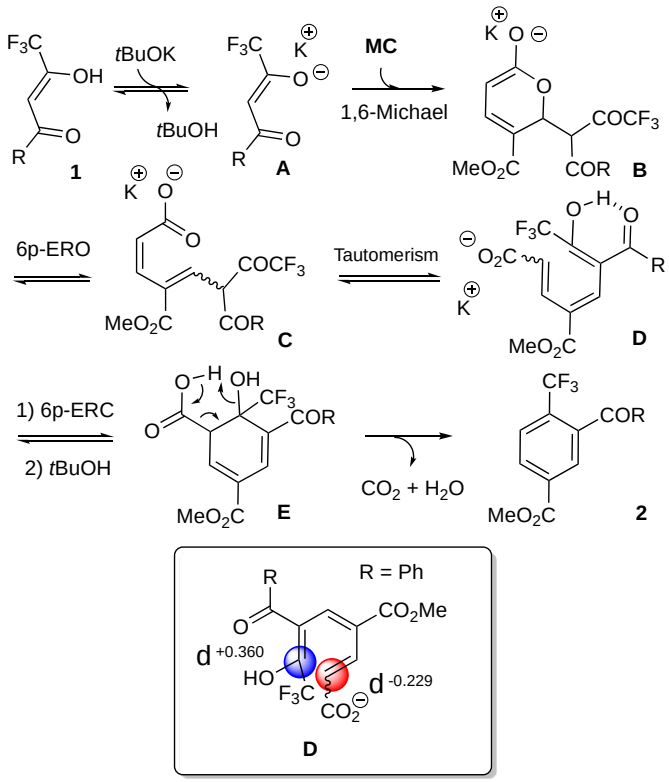
The strongly electron-withdrawing trifluoromethyl group did not alter the efficiency of this domino reaction. It rendered the corresponding bis-trifluoromethyl derivatives **2p-q**, in yields up to 83%. The reaction tolerates other aromatic rings like furan (**2r**, 82%), thiophene (**2s**, 92%), and naphthalene (**2t**, 95%). In contrast to the previous results, reaction outcome is more erratic with trifluoro-alkyl diketones. Trifluoroaceto-acetone **1u** gave the expected arene **2u** in 76% yield, while the hindered diketone (**1v**; R=*i*-Pr) reacts slowly, and gives the product **2v** in 58% yield after 9 h. It is noteworthy that the more hindered diketone (**1w**; R=*t*-Bu) did not react in these conditions. The reaction could be extended to the pentafluoroethyl-acetophenone **1x**, which gave arene **2x** in 84% yield. With the developed protocol in hand, trifluoromethyl acetophenone synthesis could be readily scaled up to gram quantities without difficulty, providing 1.87 g (89%) of compound **2b** after simple crystallization in EtOH.

Figure 2. One-pot synthesis of CF_3-functionalized fluorenone.



We also demonstrate that this reaction could incorporate with Pd-catalyzed dehydrogenative cyclization,[24] leading to CF_3-functionalized fluorenone (**3a,** 66%) in an efficient one-pot sequence.

Scheme 1. Plausible mechanism for the domino reaction leading to trifluoromethyl benzenes **2**.



To account for the generality of this method, a possible mechanism is presented in Scheme 1. The base promoted the deprotonation of trifluoromethyl keto-enol **1** to release enolate **A**. This enolate **A** adds to **MC** following a 1,6-Michael addition process, to generate the cyclic enolate **B**.[20] We propose that rapid 6π-electrocyclic ring opening (6π-ERO) of **B** leads to dienoate **C**.[20] The presence of the strong electron withdrawing CF_3 group should favor the tauto-isomerization to carba-hexatriene **D**. Carba-6π-ERC of hexatrienes is considered relatively disfavored; however, it is documented.[23,26] The presence of an electron withdrawing group on the C2 position, as in intermediate **D**, decreases the activation barrier energy by about 25 kcal mol^{-1}. Moreover, the present case of 6π-ERC might be facilitated by a push/pull type mechanism, between the hydrogen bonded enol and the proximal carbonyl (RCO).[27] ChemDraw® calculation of CF_3-triene intermediate **D**, applying the extended Hückel method, suggested both large partial positive and negative charges at C-1 and C-6. Carba-6π-electrocyclic ring closure would therefore be favored.[23] Finally,

the last step of the catalytic cycle involves a Doebner type[28] decarboxylation-dehydration of intermediate **E** to give trifluoromethyl benzenes **2**.

Conclusions

We have reported an efficient, solvent-free, and environmentally friendly reaction of methyl coumalate with trifluoromethyl-β-diketones, in a *t*BuOK-catalyzed domino Michael – 6π-ERO – tautomerization – 6π-ERC – aromatization sequence. This procedure is a practical and sustainable approach, sourced from bio-renewable molecules (**MC**), for easy synthesis of myriad trifluoromethyl-benzene derivatives. Most bear the benzophenone core structure,[29] which act on the biological targets of many diseases (e.g. cancer, Alzheimers, anti-viral and anti-bacterial drugs, prostatic hyperplasia, cardiovascular disease).[30] In addition to broad substrate scope, this unprecedented synthetic approach has the advantages of readily available starting materials, lack of oxidizers, proceeds without a metallic catalyst, and releases only water and CO_2. These soft experimental conditions do not need additive or special care (anhydrous or oxygen free conditions), and is applicable on the multi-gram scale.

Experimental section

Materials and general methods

All reactions were carried out under air with magnetic stirring. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz for ^{1}H nuclei, 100 MHz for ^{13}C nuclei. Chemical shifts are reported in δ units, parts per million (ppm) using, for ^{1}H and ^{13}C, solvent residual peak as internal standard references: chloroform (7.26 ppm for ^{1}H NMR and 77.16 ppm). Coupling constants (*J*) are given in Hz, multiplicities are abbreviated as: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), m (multiplet). High resolution mass spectra (HR-MS) were recorded on a LTQ-Orbitrap Mass Spectrometer [Thermo Scientific]. IR: Shimadzu IRAffinity-1CE spectrometer, wavenumbers in cm^{-1} .

Typical experimental procedure for the synthesis of compound 2 (a-w).

Methyl coumalate (154 mg, 1 mmol, 1 equiv), trifluoromethyl-β-diketone **1** (1 mmol, 1 equiv) and *t*BuOK (11 mg, 0.1 mmol, 0.1 equiv) were mixed in a scklenk tube and stirred at 80 °C for 2 hours. The reaction mixture was cooled to room temperature, directly loaded to a plug of silica gel and eluted with cyclohexane/EtOAc (5/1 V/V). Evaporation of the solvent under vacuum delivered the expected products **2**.

New compound characterization data

Methyl 3-benzoyl-4-(trifluoromethyl) benzoate (2a): colorless oil (293 mg, 95%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.2 Hz, 1H), 8.05 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 3.94 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.4, 165.1, 138.8 (q, *J* = 2.0 Hz), 136.0, 134.2, 133.1, 131.9 (q, *J* = 24.7 Hz), 130.7, 130.2 (2C), 129.1, 128.7 (2C), 127.1 (q, *J* = 4.6 Hz), 123.1 (q, *J* = 275.7 Hz), 52.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.5; **IR** (film, cm^{-1}): 2957, 1730, 1678, 1495, 1450, 1244, 988, 947, 754; **HRMS** (ESI) *m/z* calcd for [M+Na^+] $C_{16}H_{11}F_3NaO_3$ 331.0552, found 331.0543.

Methyl 3-(4-methylbenzoyl)-4-(trifluoromethyl) benzoate (2b): yellow solid (291 mg, 90 %); mp: 106-107 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 – 8.22 (m, 1H), 8.06 (d, *J* = 0.6 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 3.95 (s, 3H), 2.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.0, 165.1, 145.3, 139.0 (q, *J* = 2.0 Hz), 133.5, 133.0, 131.8 (q, *J* = 32.7 Hz), 130.6, 130.3, 129.4, 129.1, 127.03 (q, *J* = 4.6 Hz), 123.14 (q, *J* = 274.6 Hz). 52.7, 21.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.5; **IR** (film, cm^{-1}): 2957, 1300, 1170, 1140, 1108; **HRMS** (ESI) *m/z* calcd for [M+Li^+] $C_{17}H_{13}F_3LiO_3$ 329.0972, found 329.0976.

Methyl 3-(3-methylbenzoyl)-4-(trifluoromethyl) benzoate (2c): yellow solid (263 mg, 82 %); mp: 78-79 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 – 8.21 (m, 1H), 8.08 (d, *J* = 0.6 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.65 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 3.97 (s, 3H), 2.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)) δ 194.6, 165.1, 139.0 (q, *J* = 2.0 Hz), 138.7, 137.7, 136.0, 135.0, 133.1, 131.8 (q, *J* = 32.7 Hz), 130.7, 130.4, 129.1, 128.5, 127.7, 127.1 (q, *J* = 4.6 Hz), 123.2 (q, *J* = 274.5 Hz), 52.7, 21.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.5; **IR** (film, cm^{-1}): 1696, 1638, 1580, 1305, 1064,; **HRMS** (ESI) *m/z* calcd for [M+Na^+] $C_{17}H_{13}F_3NaO_3$ 345.0709, 345.0721.

Methyl 3-(2-methylbenzoyl)-4-(trifluoromethyl) benzoate (2d): yellow solid (309 mg, 96 %); mp: 99-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.2 Hz, 1H), 8.01 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 6.8 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 2.61 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)) δ 195.8, 164.7, 140.3, 140.1 (q, *J* = 1.8 Hz), 135.1, 132.8, 132.5, 132.4, 131.9, 131.4 (q, *J* = 32.0 Hz), 130.5, 129.3, 126.8 (q, *J* = 4.7 Hz), 125.2, 122.9 (q, *J* = 274.5 Hz), 52.3, 21.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.5; **IR** (film, cm^{-1}): 1702, 1623, 1371, 1263, 1193, 1124, 1026; **HRMS** (ESI) *m/z* calcd for [M+Na^+] $C_{11}H_{19}F_3NaO_3$ 345.0709, found 345.0708.

Methyl 3-(4-methoxybenzoyl)-4-(trifluoromethyl) benzoate (2e): yellow solid (308 mg, 91 %); mp: 108-109 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.2 Hz, 1H), 8.02 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H), 3.82 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.9, 165.1, 164.4, 133.0, 132.6 (2C), 139.1 (q, *J* = 2.0 Hz), 131.6 (q, *J* = 32.6 Hz), 130.5, 129.0, 129.0, 127.0 (q, *J* = 4.5 Hz), 123.2 (q, *J* = 274.6 Hz), 113.9 (2C), 55.5, 52.6; **^{19}F NMR** (376 MHz, $CDCl_3$): δ—58.6; **IR** (film, cm^{-1}): 1690, 1637, 1587, 1525, 1287, 1212, 1183, 1146; **HRMS** (ESI) *m/z* calcd for [M+Na^+] $C_{17}H_{13}F_3NaO_4$ 361.0658, found 361.0664.

Methyl 3-(3-methoxybenzoyl)-4-(trifluoromethyl) benzoate (2f): yellow solid (284 mg, 84 %); mp: 100-101 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.2 Hz, 1H), 8.06 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.14 (dd, *J* = 8.2, 2.6 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.5, 165.3, 160.2, 139.1 (q, *J* = 1.9 Hz), 137.6, 133.4, 132.1 (q, *J* = 32.7 Hz), 131.1, 129.9, 129.4, 127.4 (q, *J* = 4.5 Hz), 123.8, 123.5 (q, *J* = 274.6 Hz), 121.0, 114.1, 55.7, 53.0; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.6; **IR** (film, cm^{-1}): 1693, 1638, 1589, 1542, 1378, 1312, 1289,

1258, 1214, 1183; **HRMS** (ESI): *m/z* calcd for [M+K$^+$] $C_{17}H_{13}F_3KO_4$ 377.0398, found 377.0388.

Methyl 3-(2-methoxybenzoyl)-4-(trifluoromethyl) benzoate (2g): yellow solid (247 mg, 73 %); mp: 100-101 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.2 Hz, 1H), 7.95 (s, 1H), 7.85 – 7.74 (m, 2H), 7.54 (ddd, *J* = 8.5, 7.4, 1.8 Hz, 1H), 7.05 (td, J = 7.4, 0.8 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 3.91 (s, 3H), 3.51 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.5, 165.2, 159.4, 142.0 (q, *J* = 2.0 Hz), 135.2, 132.7, 131.6, 130.5 (q, *J* = 32.6 Hz), 129.8, 127.9, 126.4 (q, *J* = 4.7 Hz), 125.8, 123.1 (CF_3, q, *J* = 274.4 Hz), 120.5, 111.9, 55.2, 52.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.6; **IR** (film, cm^{-1}): 1693, 1626, 1543, 1318, 1295, 1271, 1208, 1162, 1143, 1067, 1028; **HRMS** (ESI) *m/z* calcd for [M+Na$^+$] $C_{17}H_{13}F_3NaO_4$ 361.0658, found 361.0665.

Methyl 3-(4-bromobenzoyl)-4-(trifluoromethyl) benzoate (2h): yellow solid (366 mg, 95 %); mp: 76-77 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.2 Hz, 1H), 8.02 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.62 (m, 4H), 3.90 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.0, 164.6, 137.8 (q, *J* = 2.0 Hz), 133.7, 134.5, 132.9, 131.8, 131.5 (q, *J* = 32.7 Hz), 131.2, 130.7, 129.4, 128.7, 126.9 (q, *J* = 4.6 Hz), 122.8 (q, *J* = 273.0 Hz), 52.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.4; **IR** (film, cm^{-1}): 1707, 1628, 1522, 1260, 1211, 1185, 1159, 1127, 1083 ; **HRMS** (ESI): *m/z* calcd for [M+Na$^+$] $C_{16}H_{10}BrF_3NaO_3$ 408.9658, found 408.9641.

Methyl 3-(3-bromobenzoyl)-4-(trifluoromethyl) benzoate (2i): yellow solid (320 mg, 83 %); mp: 76-77 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.2 Hz, 1H), 8.03 (s, 1H), 7.92 (t, *J* = 1.8 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.75 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.64 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 3.95 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.3, 165.2, 138.2 (q, *J* = 1.9 Hz), 138.1, 137.3, 133.6, 132.9, 132.1 (q, *J* = 32.7 Hz), 131.4, 130.6, 129.3, 129.2, 127.6 (q, *J* = 4.5 Hz), 123.4, 123.4 (q, *J* = 274.6 Hz), 53.1; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.4; **IR** (film, cm^{-1}): 1701, 1607, 1275, 1209, 1162, 1145, 1120, 1075; **HRMS** (ESI): *m/z* calcd for [M+Na$^+$] $C_{16}H_{10}BrF_3NaO_3$ 408.9658, found 408.9622.

Methyl 3-(2-bromobenzoyl)-4-(trifluoromethyl) benzoate (2j): yellow solid (330 mg, 85 %); mp: 97-98 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.2 Hz, 1H), 8.03 (s, 1H), 7.92 (t, *J* = 1.8 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.75 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.64 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 3.95 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.3, 165.2, 138.2 (q, *J* = 1.9 Hz), 138.1, 137.3, 133.6, 132.9, 132.1 (q, *J* = 32.7 Hz), 131.4, 130.6, 129.3, 129.2, 127.6 (q, *J* = 4.5 Hz), 123.4, 123.4 (q, *J* = 274.6 Hz), 53.1; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.4; **IR** (film, cm^{-1}): 1705, 1602, 1380, 1311, 1291, 1268, 1247, 1210, 1189, 1168, 1151, 1133, 1121; **HRMS** (ESI): *m/z* calcd for [M+Na$^+$] $C_{16}H_{10}BrF_3NaO_3$ 408.9658, found 408.9650.

Methyl 3-(4-chlorobenzoyl)-4-(trifluoromethyl) benzoate (2k): yellow solid **(**273mg, 80%**)**; mp: 110-111 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (ddd, *J* = 8.2, 1.6, 0.8 Hz, 1H), 8.08 – 8.02 (m, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.76 – 7.67 (m, 2H), 7.50 – 7.42 (m, 2H), 3.96 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.1, 164.9, 140.8, 138.2 (q, *J* = 2.0 Hz), 134.3, 133.2, 131.9 (q, *J* = 32.8 Hz), 131.5, 131.0 (2C), 127.2 (q, *J* = 4.6 Hz), 129.1 (2C), 129.0, 123.0 (CF_3, q, *J* = 274.6 Hz), 52.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.4; **IR** (film, cm^{-1}): 2955, 1734, 1673, 1587, 1439, 1168, 1043, 1011, 943, 916, 855, 780, 707; **HRMS** (ESI) *m/z* calcd for [M+Na$^+$] $C_{16}H_{10}ClF_3NaO_3$ 365.0163, found 365.0167.

Methyl 3-(4-fluorobenzoyl)-4-(trifluoromethyl) benzoate (2l): yellow solid **(**304mg, 93%**)**; mp: 95-96 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (ddd, *J* = 8.2, 1.6, 0.8 Hz, 1H), 8.10 – 8.02 (m, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.86 – 7.76 (m, 2H), 7.20 – 7.10 (m, 2H), 3.96 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.8, 166.3 (d, *J* = 257.1 Hz), 165.0, 138.4 (q, *J* = 2.0 Hz) 133.2, 132.9 (d, *J* = 9.7 Hz), 131.8 (q, *J* = 32.7 Hz) 130.9, 129.0, 127.16 (q, *J* = 4.6 Hz), 123.1 (q, *J* = 274.6 Hz), 115.96 (d, *J* = 22.1 Hz) 52.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.50, —102.93 (m); **IR** (film, cm^{-1}) : 2955, 1733, 1672, 1598, 1306, 1173, 1158, 1114, 1045, 983, 926, 850, 782, 715; **HRMS** (ESI) *m/z* calcd for [M+Na$^+$] $C_{16}H_{10}F_4NaO_3$ 349.0458, found 349.0465.

Methyl 3-(4-nitrobenzoyl)-4-(trifluoromethyl) benzoate (2m): yellow solid (322 mg, 91%); mp: 108-109 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.32 – 8.30 (m, 3H), 8.05 (s, 1H), 7.96 – 7.89 (m, 3H), 3.91(s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.1, 165.1, 151.2, 140.7, 137.7, 133.9, 132.2 (q, *J* = 32.9 Hz), 131.7 (q, *J* = 1.7 Hz), 131.4, 129.3, 127.8 (q, *J* = 4.5 Hz), 124.2 (2C), 123.3 (q, *J* = 274.5 Hz), 53.2; **^{19}F NMR** (376 MHz, CDCl3): δ —58.3; **IR** (film, cm^{-1}): 1732, 1681, 1530, 1306, 1270, 1252, 1171, 1148, 1115, 1044; **HRMS** (ESI): m/z calcd for [M+Na$^+$] $C_{16}H_{10}F_3NNaO_5$ 376.0403, found 376.0393.

Methyl 3-(3-nitrobenzoyl)-4-(trifluoromethyl) benzoate (2n): yellow solid (327 mg, 93%); mp: 130-131 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.54 (t, *J* = 1.8 Hz, 1H), 8.48 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.33 (dd, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 7.7 Hz, 1H), 8.06 (s, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 3.93 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 191.9, 164.5, 148.1, 137.1, 136.9 (q, *J* = 1.9 Hz), 135.1, 133.3, 131.6 (q, *J* = 32.8 Hz), 131.2, 129.9, 128.6, 128.0, 127.2 (q, *J* = 4.5 Hz), 124.3, 122.7 (q, *J* = 274.5 Hz), 52.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.33; **IR** (film, cm^{-1}): 1732, 1608, 1581, 1438, 1350, 1304, 1269, 1197, 1158; **HRMS** (ESI): *m/z*, calcd for [M+Na$^+$] $C_{16}H_{10}F_3NNaO_5$ 376.0409, found 376.0403.

Methyl 3-(2-nitrobenzoyl)-4-(trifluoromethyl) benzoate (2o): yellow solid (275 mg, 78 %); mp: 97-98 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.2 Hz, 1H), 8.09 – 8.03 (m, 1H), 8.01 (s, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.79 – 7.67 (m, 2H), 7.57 – 7.50 (m, 1H), 3.90 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ190.8, 164.4, 147.7, 136.3 (q, *J* = 1.4 Hz), 134.0, 133.4, 133.1, 132.6, 132.5 (q, *J* = 33.3 Hz), 132.1, 130.7, 130.2, 127.9 (q, *J* = 5.6 Hz), 124.4, 122.6 (q, *J* = 274.5 Hz), 52.6; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —59.0; **IR** (film, cm^{-1}): 1715, 1630, 1561, 1488, 1333, 1305, 1285, 1211, 1121, 1070; **HRMS** (ESI): *m/z* calcd for [M+Na$^+$] $C_{16}H_{10}F_3NNaO_5$ 376.0403, found 376.0415.

Methyl 3-(4-(trifluoromethyl)benzoyl)-4-(trifluoromethyl) benzoate (2p): yellow solid (304 mg, 81 %); mp: 78-79 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.2 Hz, 1H), 8.09 – 8.03 (m, 1H), 8.01 (s, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.79 – 7.67 (m, 2H), 7.57 – 7.50 (m, 1H), 3.90 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.7, 165.3, 139.1, 138.3 (q, *J* = 2.0 Hz), 135.8, 135.7 (q, *J* = 32.8 Hz), 135.5, 133.8, 132.3 (q, *J* = 32.8 Hz), 131.7, 130.8, 129.4, 127.7 (q, *J* = 4.5 Hz), 126.2 (q, *J* = 3.7 Hz), 123.9 (CF_3, q, *J* = 272.9 Hz), 123.5 (q, *J* = 274.5 Hz), 53.2; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.48, —63.40; **IR** (film, cm^{-1}): 1732, 1706, 1602, 1390, 1284, 1262, 1214, 1129, 1085,

1054, 1027; **HRMS (ESI)**: *m/z* calcd for [M+Na$^+$] $C_{17}H_{10}F_6NaO_3$ 399.0426, found 399.0427.

Methyl 3-(3-(trifluoromethyl)benzoyl)-4-(trifluoromethyl) benzoate (2q): yellow solid (312 mg, 83 %); mp: 71-72 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ8.29 (d, *J* = 8.9 Hz, 1H), 8.06 (d, *J* = 6.4 Hz, 2H), 7.97 – 7.82 (m, 3H), 7.60 (t, *J* = 7.8 Hz, 1H), 3.93 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ193.5, 165.3, 138.2 (q, *J* = 1.9 Hz), 137.0, 133.9, 133.8,132.7 (q, *J* = 32.8 Hz), 132.3 (q, *J* = 23.2 Hz), 131.7, 130.9 (q, *J* = 3.5 Hz), 129.9, 129.4, 127.8 (q, *J* = 4.5 Hz), 126.9 (q, *J* = 3.8 Hz), 123.5 (CF_3, q, *J* = 274.5 Hz),123.9 (q, *J* = 272.6 Hz), 53.2; **^{19}F NMR** (376 MHz, $CDCl_3$): δ—58.44, —63.01; **IR** (film, cm^{-1}): 1732, 1706, 1602, 1390, 1284, 1262, 1214, 1129, 1085, 1054, 1027; **HRMS (ESI)**: *m/z* calcd for [M+Na$^+$] $C_{17}H_{10}F_6NaO_3$ 399.0426, found 399.0436.

Methyl 3-(furan-2-carbonyl)-4-(trifluoromethyl) benzoate (2r) : yellow solid (245 mg, 82 %); mp: 101-102 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 – 8.25 (m, 1H), 8.18 (d, *J* = 0.6 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.07 (d, *J* = 3.3 Hz, 1H), 6.60 (dd, *J* = 3.3, 1.7 Hz, 1H), 3.97 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.2, 165.0, 151.7, 148.4, 137.4 (q, *J* = 2.0 Hz), 133.1, 132.0 (q, *J* = 32.8 Hz), 131.2, 129.4, 127.2 (q, *J* = 4.7 Hz), 123.0 (q, *J* = 275.1 Hz), 121.7, 112.8, 52.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.6; **IR** (film, cm^{-1}): 2961, 1733, 1659, 1565, 1498, 1305, 1261, 1151, 1132, 1115, 1014, 989, 958, 882, 784, 703; **HRMS** (ESI) *m/z* calcd for [M+Na$^+$] $C_{14}H_9F_3NaO_4$ 321.0345, found 321.0352.

Methyl 3-(thiophene-2-carbonyl)-4-(trifluoromethyl) benzoate: (2s) yellow solid **(**289mg, 92%**)**; mp: 103-104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (ddd, *J* = 8.2, 1.6, 0.8 Hz, 1H), 8.23 – 8.15 (m, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.81 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.34 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.14 (dd, *J* = 4.9, 3.8 Hz, 1H), 3.97 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.3, 165.0, 143.3, 138.2 (q, *J* = 2.0 Hz), 136.2, 136.1, 133.1, 131.7 (q, *J* = 32.8 Hz), 131.0, 129.2, 128.4, 127.2 (q, *J* = 4.6 Hz), 123.0 (q, *J* = 274.6 Hz), 52.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.5; **IR** (film, cm^{-1}): 2957, 1734, 1643, 1513, 1441, 1411, 1304. 1277, 1192, 1139, 1116, 972, 771, 729, 681; **HRMS** (ESI) *m/z* calcd for [M+Li$^+$] $C_{14}H_9F_3LiO_3S$ 321.0379, found 321.0389.

Methyl 3-(2-naphthoyl)-4-(trifluoromethyl) benzoate (2t): yellow solid **(**340mg, 95%**)**; mp: 133-134 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (ddd, *J* = 8.2, 1.6, 0.8 Hz, 1H), 8.03 (d, *J* = 0.6 Hz, 1H), 7.98 (s, 1H), 7.91 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.87 – 7.69 (m, 4H), 7.52 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 3.83 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.4, 165.1, 138.9 (q, *J* = 1.9 Hz), 136.1, 133.5, 133.4, 133.2, 132.2, 132.0 (q, *J* = 32.7 Hz), 130.8, 129.8, 129.2, 129.2, 128.8, 127.9, 127.2 (q, *J* = 4.6 Hz), 127.1, 124.5, 123.2 (q, *J* = 274.6 Hz). 52.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.4. **IR** (film, cm^{-1}): 2977, 1735, 1669, 1436, 1280, 985; **HRMS** (ESI) *m/z* calcd for [M+Li$^+$] $C_{20}H_{13}F_3LiO_3$ 365.0972, found 365.0976.

Methyl 3-acetyl-4-(trifluoromethyl) benzoate (2u) : colorless oil (184mg 74%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (ddd, *J* = 8.2, 1.6, 0.8 Hz, 1H), 8.13 – 8.06 (m, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 3.95 (s, 3H), 2.60 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.6, 165.0, 140.7 (q, *J* = 1.9 Hz), 133.5, 131.0, 130.5 (q, *J* = 32.8 Hz), 128.1, 123.1 (q, *J* = 274.1 Hz), 52.8, 30.4 (q, *J* = 1.7 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.7. **IR** (film, cm^{-1}): 2958, 1730, 1711, 1497, 1439, 1302, 1263, 1172, 1129, 1038, 916, 859, 773, 748; **HRMS** (ESI) *m/z* calcd for [M+Li$^+$] $C_{11}H_9F_3LiO_3$ 253.0659, found 253.0667.

Methyl 3-isobutyryl-4-(trifluoromethyl) benzoate (2v): colorless oil (159mg, 58%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 – 8.14 (m, 1H), 8.08 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 3.98 (s, 3H), 3.33 – 3.11 (m, 1H), 1.22 (s, 3H), 1.20 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.0, 165.1, 140.1 (q, *J* = 2.0 Hz), 131.1 (q, *J* = 32.6 Hz), 133.3, 130.8, 127.3 (q, *J* = 4.9 Hz), 128.1, 123.1 (q, *J* = 274.2 Hz), 52.7, 40.4, 18.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.5. **IR** (film, cm^{-1}): 2977, 2877, 1732, 1709, 1438, 1302, 1258, 1164, 1114, 964, 918, 858, 770; **HRMS** (ESI) *m/z* calcd for [M+Na$^+$] $C_{13}H_{13}F_3NaO_3$ 297.0709, found 297.0720.

Methyl 3-benzoyl-4-(perfluoroethyl) benzoate (2w): yellow oil (255mg, 71%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 – 8.15 (m, 1H), 7.93 (d, *J* = 1.1 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.66 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.57 – 7.45 (m, 1H), 7.45 – 7.31 (m, 2H), 3.84 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.1, 165.0, 136.1, 134.0, 133.2, 130.2, 130.1 (2C), 128.9, 128.6 (2C), 52.72; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —83.48, —108.18. **IR** (film, cm^{-1}): 2957, 1731, 1682, 1450, 1438, 1206, 1163, 1148, 1114, 1080; **HRMS** (ESI) *m/z* calcd for [M+Na$^+$] $C_{17}H_{11}F_5NaO_3$ 381.0521, found 381.0531.

Procedure for the gram scale synthesis of compound 2b

In a 25 mL round-bottom flask equipped with magnetic stir bar, Methyl coumalate (1g, 6.5 mmol, 1 equiv), 4,4,4-trifluoro-1-(p-tolyl)butane-1,3-dione **1b** (1.49g, 6.5 mmol, 1 equiv) and *t*BuOK (73 mg, 6.5 mmol, 0.1 equiv) were added, and the mixture was stirred at 80 °C for 2 hours. When the reaction was completed 10ml absolute EtOH was added and heated to reflex to 5 min, the mixture was cool down to room temperature and gave 1.87 g (89%) of recrystallized **2b**.

Procedure for the one-pot synthesis of compound 3a

To an oven-dried sealed tube equipped with magnetic stir bar was added methyl coumalate (31 mg, 0.2 mmol, 1 equiv), **1a** (43 mg, 0.2 mmol, 1 equiv) and *t*BuOK (2 mg, 0.2 mmol, 0.1 equiv). The reaction was stirred at 80 °C for 2 hours, cool to rt then $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv) followed by Ag_2O (69 mg, 0.3 mmol, 1.5 equiv) were added and the flask purged three times with argon. Trifluoroacetic acid (2 mL) was added to the system and the reaction mixture was stirred at 130 °C for 36 h. After completion of the reaction, the reaction mixture was cooled, filtered through a short pad of Celite® and washed several times with dichloromethane. The combined filtrate was concentrated under vacuum and the residue purified by flash chromatography on silica gel column using cyclohexane/EtOAc as eluent to give the desired product **3a**.

Methyl 9-oxo-1- (trifluoromethyl) -9H- fluorene-4-carboxylate (3a): yellow solid **(**43.4 mg, 66%**); ^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (dt, *J* = 7.8, 0.8 Hz, 1H), 7.95 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.75 (ddd, *J* = 7.4, 1.3, 0.7 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.54 (td, *J* = 7.7, 1.3 Hz, 1H), 7.41 (td, *J* = 7.4, 0.8 Hz, 1H), 4.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.0, 166.6, 145.4, 141.4, 135.3, 135.3, 133.7, 132.5, 130.6, 130.2 (q, *J* = 35.4 Hz), 130.1, 125.7 (q, *J* = 5.9 Hz), 125.4, 124.6, 122.1 (q, *J* = 274.6 Hz), 53.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —61.7; **HRMS** (ESI) *m/z* calcd for [M+Na$^+$] $C_{16}H_9F_3NaO_3$ 329.0396 found 329.0397.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

We thank the University P. et M. Curie (UPMC) and CNRS for funding. The Fédération de Recherche (FR2769) provided technical access for analysis. L.C. thanks the China Scholarship Council (CSC) for a PhD grant. N. K., a master student at Ludwig Maximilian University of Munich, was a 2017 Erasmus+ trainee.

Notes and references

1 For their impact in organic and medicinal chemistry see (*a*) R. Filler, Y. Kobayashi, L. M. Yagupolskii, Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications Elsevier, Amsterdam, **1993**. *(b)* T. Hiyama, Organofluorine Compounds, Chemistry and Applications, Springer-Verlag, Berlin, **2000**. (*c*) R.D. Chambers, Fluorine in Organic Chemistry, Blackwell Publishing/CRC Press, Boca Raton, **2004**. (*d*) W. K. Hagmann, *J. Med. Chem*. 2008, **51**, 4359. (*e*) N. A. Meanwell, *J. Med. Chem.* 2011, **54**, 2529. (*f*) P. Kirsch, Modern Fluoroorganic Chemistry. VCH, Weinheim, **2013**. (*g*) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* 2014, **114,** 2432.

2 For a review see: S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*. 2008, **37**, 320.

3 (*a*) X. Wang, L. Truesdale. J. -Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3648. (*b*) X. Zhang, H. Dai, M. Wasa, J.-Q Yu. *J. Am. Chem. Soc.*, 2012, **134**, 11948. (*c*) L. Hu, X. Chen, Q. Gui, Z. Tan, G. Zhu, *Chem. Commun.*, 2016, **52**, 6845. (d) P. Liu, W. Liu, C.-J. Li, *J. Am. Chem. Soc.*, 2017, **139**, 14315.

4 (*a*) H. Morimoto, T. Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angew. Chem. Int. Ed.* 2011, **50**, 3793. (*b*) Z. Weng, R. Lee, W. Jia, Y. Yuan, W. Wang, X. Feng, K-W. Huang, *Organometallics*, 2011, **30**, 3229. (*c*) L. Chu, F-L. Qing, *Org. Lett*. 2010, **12**, 5060. (*d)* T. D. Senecal, A.T. Parsons, S. L. Buchwald, *J. Org. Chem*. 2011, **76**, 1174. (e) S. L. Clarke, G. P. McGlacken, *Chem. Eur. J.* 2017, **23**, 1219.

5 (*a*) H. Urata, T. Fuchikami, *Tetrahedron Lett.* 1991, **32**, 91. (*b*) G. G. Dubinina, H. Furutachi, D. A. Vicic, *J. Am. Chem. Soc*. 2008, **130**, 8600. *(c*) A. Hafner, S. Bräse, *Angew. Chem. Int. Ed.* 2012, **51**, 3713.

6 F. Sladojevich, E. McNeill, J. Börgel, S-L. Zheng, T. Ritter, *Angew. Chem. Int. Ed.* 2015, **54**, 3712.

7 (*a*) I. Kieltsch, P. Eisenberger, A. Togni, *Angew. Chem. Int. Ed.* 2007, **46**, 754. (*b)* V. Matousek, E. Pietrasiak, R. Schwenk, A. Togni, *J. Org. Chem*. 2013, **78**, 6763. *(c)* Y. Kuninobu, M. Nishi, M. Kanai, *Org. Biomol. Chem*. 2016, **14**, 8092.

8 For trifluoromethylation by photoredox catalysis see: D. A. Nagib, D. MacMillan, *Nature*, 2011, **480,** 224.

9 (*a*)T. Konno, K. Moriyasu, R. Kinugawa, T. Ishihara, *Org. Biomol. Chem*. 2010, **8**, 1718. (*b*) Y. Sakaguchi, Y. Nakazaki, K. Moriyasu, T. Konno, *J. Fluor. Chem.* 2015, **179**, 64.

10 For formal [4+2] CA see: (*a*) J-N. Volle, M. Schlosser, *Eur. J. Org. Chem*. 2002, **9**, 1490. (*b*) D. M. Volochnyuk, A. N. Kostyuk, D. A. Sibgatulin, A. N. Chernega, A.M. Pinchuk, A. Tolmachev, *Tetrahedron* 2004, **60**, 2361. (*c*) V. O. Iaroshenko, A. Bunescu, L. Domke, A. Spannenberg, D. V. Sevenard, A. Villinger, V. Sosnovskikh, P. Langer, *J. Fluor. Chem.* 2011, **132**, 441. For formal [3+3] see: (*d*) C. Mamat, T. Pundt, A. Schmidt, P. Langer,. *Tetrahedron Lett*. 2006, **47**, 2183. (*e*) C. Mamat, T. Pundt, T. Tam Dang, R. Klassen, H. Reinke, M. Köckerling, P. Langer, *Eur. J. Org. Chem*. 2008, **3**, 492.

11 For reviews see: (*a*) K. Afarinkia, V. Vinader, T. Nelson, G. H. Posner, *Tetrahedron*, 1992, **48**, 9111. (*b*) A. Goel, V. J. Ram, *Tetrahedron*, 2009, **65**, 7865.

12 (*a*) J. D. Kirkham, A. G. Leach, E. C. Row, J. Harrity. *Synthesis*, 2012, **44**, 1964. (*b*) I. S. Kondratov, N. A. Tolmachova, V. Dolovanyuk, I. Gerus, K. Bergander, C. G. Daniliuc, G. Haufe, *Eur. J. Org. Chem*. 2014, **12**, 2443. (*c*) I. S. Kondratov, N. A. Tolmachova, V. G. Dolovanyuk, I. I. Gerus, C-G. Daniliuc, G. Haufe, *Eur. J. Org. Chem*. 2015, **11**, 2482.

13 G. A. Kraus, S Riley, T. Cordes, *Green Chem*. 2011, **13**, 2734.

14 (*a*) T. Pfennig, J. M. Carraher, A. Chemburkar, R. L. Johnson, A. T. Anderson, J. P. Tessonnier, M. Neurock, B. H. Shanks, *Green Chem.,* 2017, **19**, 4879. (*b*) T. Pfennig, R. L. Johnson, B. H. Shanks, *Green Chem.*, 2017, **19**, 3263.

15 (*a*) M. Haji Abdullahi, L. M. Thompson, M. J. Bearpark, V. Vinader, K. Afarinkia, *Tetrahedron,* 2016, **72**, 6021. (*b*) J. J. Lee, G. A. Kraus, *Tetrahedron Lett*. 2013, **54**, 2366. (*c*) J. J. Lee, G. R. Pollock III, D. Mitchell, L. Kasuga, G. A. Kraus, *RSC Advances*, 2014, **4**, 45657. (*d*) G. A. Kraus, G. R. Pollock III, C. L. Beck, K. Palmer, A. H. Winter, *RSC. Adv*. 2013, **3**, 12721. (e) J. J. Lee, G. A. Kraus, *Green Chem*. 2014, **16**, 2111. (*f*) T. Guney, J. J. Lee, G. A. Kraus, *Org. Lett*. 2014, **16**, 1124. (*g*) L. R. Domingo, J. A. Saez, S. R. Emamian, *Org. Biomol. Chem*. 2015, **13**, 2034.

16 T. J. Greshock, R. L. Funk, *J. Am. Chem. Soc.* 2006, **128**, 4946.

17 R. L. Greenaway, C. D. Campbell, O. T. Holton, C. A. Russell, E. A. Anderson, *Chem. Eur. J.* 2011, **17**, 14366.

18 J. Deng, W. Chen, C. Zhu, S. Chuang, *Adv. Synth. Catal*. 2015, **357**, 1453.

19 X. Li, H. Yu, Y. Huang, *Adv. Synth. Catal*. 2017, **359**, 1379.

20 (*a*) J. Agarwal, O. Bayounes, S. Thorimbert, L. Dechoux, *RSC Advances*, 2014, **4**, 2772. (*b*) K. Plevovà, L. Chang, E. Martin, Q. Llopis, L. Dechoux, S. Thorimbert, *Adv. Synth. Catal.* 2016, **358**, 3293. (*c*) L. Chang, K. Plevovà, S. Thorimbert, L. Dechoux, *J. Org. Chem,* 2017, **82**, 5499.

21 S. Büttner, A. Riahi, I. Hussain, M. A. Yawer, M. Lubbe, A. Villinger, H. Reinke, C. Fischer, P. Langer, *Tetrahedron*, *2009*, **65**, 2124.

22 M. Mamat, H. P. Reinke, P. Langer, *Naturforsch*. 2009, **64b**, 423.

23 T. Q. Yu, Y. Fu, L. Liu, Q. X. Guo *J. Org. Chem.*, 2006, **71** , 6157.

24 (*a*) H. Li, R. Zhu, W. Shi, K. He, Z. Shi, *Org. Lett.*, 2012, **14** , 4850. (*b*) P. Gandeepan, C.H. Hung, C. H. Cheng, *Chem. Commun*., 2012, **48**, 9379.

25 L. M. Bishop, J. E. Barbarow, R. E. Bergman, D. Trauner *Angew. Chem. Int. Ed*. 2008, **47**, 8100.

26 L. M. Bishop, R. E. Roberson, R. G. Bergman, D. Trauner, *Synthesis*, 2010, 2233.

27 N. A. Magomedov, P. L. Ruggiero, Y. Tang, *J. Am. Chem. Soc*. 2004, **126**, 1624.

28 (a) O. Doebner, *Ber. Dtsch. Chem. Ges.* 1902, **25**, 1136. (b) A. Galat, *J. Am. Chem. Soc.* 1946, **68**, 376. (c) S. Thorimbert, C. Taillier, S. Bareyt, D. Humilière, M. Malacria, *Tetrahedron Lett.* 2004, **45**, 9123. (d) A. Ear, V. Toum, S. Thorimbert, L. Dechoux *Synlett* 2014, **25**, 1713.

29 For a review concerning the bioactivities of natural benzophenones see: S-B. Wu, C. Long, E. J. Kennelly, *Nat. Prod. Rep*. 2014, **31**, 1158.

30 For some publications concerning biological effects of fluorinated benzophenone derivatives see: (a) J. H. Chan, G. A. Freeman, J. H. Tidwell, K. R. Romines, L. T. Schaller, J. R Cowan, S. S. Gonzales, G. S. Lowell, C. W. Andrews III, D. J. Reynolds, M. St Clair, R. J. Hazen, R. G. Ferris, K. L. Creech, G. B. Roberts, S. A. Short, K. Weaver, G. W. Koszalka, L. R. Boone, *J. Med. Chem*. 2004, **47**, 1175. (b) J. Ren, P. P. Chamberlain, A. Stamp, S. A. Short, K. L. Weaver, K. R. Romines, R. Hazen, A. Freeman, R. G. Ferris, C. Webster Andrews, L. Boone, J. H. Chan, D. K. Stammers, *J. Med. Chem*. 2008, **51**, 5000. (c) F. Belluti, A. De Simone, A. Tarozzi, M.

Bartolini, A. Djemil, A. Bisi, S. Gobbi, S. Montanari, A. Cavalli, V. Andrisano, G. Bottegoni, A. Rampa, *Eur. J. Med. Chem*. 2014, **78**, 157.