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DABCO-Catalyzed Synthesis of Trifluoromethylated Furans from Propargyl Alcohols and Methyl 2-Perfluoroalkynoate

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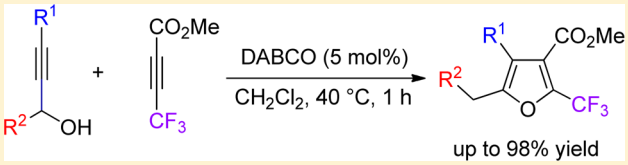
Supporting Information

ABSTRACT: The DABCO-catalyzed reaction of propargyl alcohols with methyl 2-perfluoroalkynoate to give trifluoromethylated furans in up to 98% yield under mild conditions has been developed. The established allene−enol and control experiments indicate that the reaction should proceed through a Michael addition and Claisen rearrangement/cyclization process.



INTRODUCTION

Furan is one of the most fundamental heterocyclic compounds. More than ten kinds of furan derivatives have been adopted as drugs and materials, such as nitrofurantoin, furazolidone, nitrofural, etc.[1] Specifically, the introduction of a trifluoromethyl group (CF_3) to these compounds may improve the activity of bioactive substances since the C−F bond is hard for enzymes to metabolize.[2] A large number of biologically active compounds have been shown to contain the trifluoromethylated furan subunit (Figure 1),[3] and these compounds have

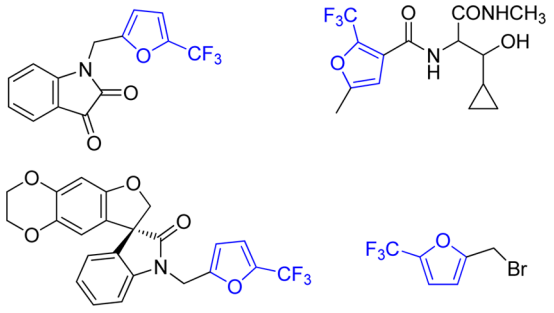
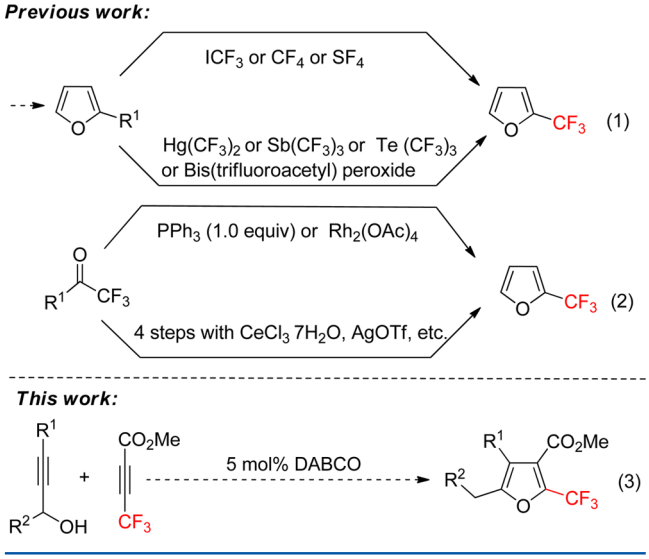


Figure 1. Examples of biologically active trifluoromethylated furans.

found extensive applications[4] in medicinal (treatment of cancers,[4a] HIV,[3c] and inflammations,[4b]), agrochemical (insecticides/acaricides,[4c] furancarboxamides[4d]), and material sciences (liquid crystals,[4e] photoresist polymers,[4f] self-assembling monolayers[4g]). Therefore, the development of versatile and mild synthetic methods for the synthesis of trifluoromethylated furan compounds is of great significance.

In the past decades, various methods have been employed to construct these compounds (Scheme 1, eq 1).[5] However, transition-metal catalysts[5a,c] or harsh reaction conditions (e.g., strong acid or base,[5a] gas phase,[5d] elevated temperature[5f]) are generally required. Furthermore, disadvantages such as the use

Scheme 1. Synthesis of Trifluoromethylated Furans



of prohibitive trifluoromethylating regents [e.g., $Hg(CF_3)_2$,[5c] bis(trifluoroacetyl) peroxide[5e]], narrow substrate scope,[5a−f] and low product yields have limited the application of these methods. To the best of our knowledge, only a few methods to construct these molecules with more than five different substrates have been reported (Scheme 1, eq 2).[6] The sequence of adding a propargyl alcohol to an electron-deficient alkyne followed by Claisen rearrangement and heterocyclization to generate heterocycles is a powerful strategy for the construction of versatile products.[7] The groups of Kirsch,[8] Jiang,[9] and Tellado[10] have reported syntheses of furans and other heterocycles from oxaenynes or directed from propargyl

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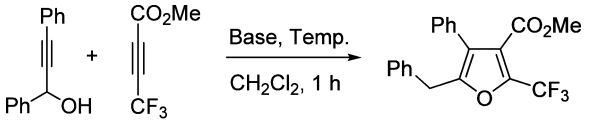
alcohol and alkynes. We recently reported the synthesis of polyfluoroalkyl-substituted cyclobutenes from 3-aza-1,5-enynes using methyl 2-perfluoroalkynoate as the terminal material.[11] Considering the straightforward synthesis of methyl 2-perfluoroalkynoate from commercially available starting materials and our continued interest in 3-aza-1,5-enyne chemistry,[12] we speculated that methyl 2-perfluoroalkynoate could be applied for the synthesis of trifluoromethylated furans with the assistance of some catalyst. Herein we report the DABCO-catalyzed synthesis of trifluoromethylated furans from propargyl alcohols and methyl 2-perfluoroalkynoate (Scheme 1, eq 3).

RESULTS AND DISCUSSION

Initially, 1,3-diphenylprop-2-yn-1-ol (**1a**) and methyl 4,4,4-trifluorobut-2-ynoate (**2**) were selected as the reaction substrates to optimize the reaction conditions (Table 1). The

Table 1. Screening of the Reaction Conditions[a]



1a **2** **3a**

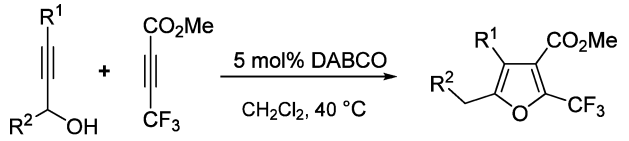
entry	T (°C)	base	**1a** (equiv)	yield (%)[b]
1	25	DABCO	1	67
2	25	DBU	1	trace
3	25	NEt_3	1	trace
4	25	K_2CO_3	1	N.R.[c]
5	25	NaOAc	1	N.R.[c]
6	25	–	1	N.R.[c]
7	25	DABCO	2	79
8	40	DABCO	2	98

[a]0.2 mmol of **2**, x equiv of **1a**, and 5 mmol % DABCO. **2** in 5 mL of CH_2Cl_2 was added slowly to the solution of **1a** and DABCO in 1 mL of CH_2Cl_2 and reacted for 1 h. [b]Isolated yields based on **2**. [c]N.R. = no reaction.

corresponding furan **3a** was obtained in 67% yield when the reaction was conducted at a 1:1 molar ratio in the presence of 5 mol % 1,4-diazabicyclo[2.2.2]octane (DABCO) at room temperature under an argon atmosphere (entry 1). Among the bases tested (DABCO, DBU, Et_3N, K_2CO_3, NaOAc), only DABCO could selectively afford the furan compound after 1 h (entries 1–5). The structure of product **3** was unambiguously confirmed by single-crystal X-ray diffraction analysis of its derivative **3c**.[13] The reaction did not proceed in the absence of DABCO (entry 6). We were delighted to find that the product was obtained in a more satisfactory yield (98%) when the reaction was conducted at a 2:1 molar ratio (**1a**/**2**) at 40 °C (entry 8).

With this result in hand, the reactions of propargyl alcohols **1** with **2** were examined, as shown in Table 2. Both aryl R^1 and R^2 groups bearing substituents with electron-donating (entries 2–5) or electron-withdrawing groups (entries 6–14) were well-tolerated, and the desired products were obtained in good to excellent yields. A fused ring such as naphthalene was suitable for this process (entries 15 and 16). The reaction also appeared to be quite tolerant with respect to the position of the substituents on the benzene ring (entries 4–9, 17, and 18). It is noteworthy that when R^2 was an alkyl group or H, this cyclization could not proceed even with a longer reaction time

Table 2. Scope of the Synthesis of Trifluoromethylated Furans[a]



1 **2** **3**

entry	**1**	R^1	R^2	yield (%)[b]
1	**1a**	Ph	Ph	98 (**3a**)
2	**1b**	Ph	3-MeC_6H_4	82 (**3b**)
3	**1c**	Ph	4-$^tBuC_6H_4$	86 (**3c**)
4	**1d**	Ph	2-$MeOC_6H_4$	85 (**3d**)
5	**1e**	Ph	4-$MeOC_6H_4$	72 (**3e**)
6	**1f**	Ph	2-FC_6H_4	98 (**3f**)
7	**1g**	Ph	3-FC_6H_4	76 (**3g**)
8	**1h**	Ph	4-FC_6H_4	98 (**3h**)
9	**1i**	Ph	4-$CF_3C_6H_4$	95 (**3i**)
10	**1j**	Ph	4-CNC_6H_4	82 (**3j**)
11	**1k**	Ph	4-ClC_6H_4	97 (**3k**)
12	**1l**	Ph	2,3-$Cl_2C_6H_3$	95 (**3l**)
13	**1m**	Ph	4-BrC_6H_4	87 (**3m**)
14	**1n**	Ph	4-IC_6H_4	94 (**3n**)
15	**1o**	Ph	1-naphthyl	91 (**3o**)
16	**1p**	Ph	2-naphthyl	77 (**3p**)
17	**1q**	2-MeC_6H_4	Ph	76 (**3q**)
18	**1r**	4-MeC_6H_4	Ph	98 (**3r**)
19	**1s**	4-ClC_6H_4	Ph	89 (**3s**)
20	**1t**	4-$CF_3C_6H_4$	Ph	90 (**3t**)
21	**1u**	4-FC_6H_4	2,3-$Cl_2C_6H_3$	96 (**3u**)

[a]Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), and DABCO (0.01 mmol) in CH_2Cl_2 (6.0 mL) at 40 °C under argon for 1 h. [b]Isolated yields.

(48 h) or higher reaction temperature (140 °C), indicating that an aryl R^2 substitution is crucial to this catalytic transformation.

To elucidate the mechanism of the present protocol, the experiments shown in Scheme 2 were carried out. On the basis of these experimental results, a plausible mechanism is proposed (Scheme 3). Initially, zwitterion **4**[14] is formed from DABCO and alkynoate **2** and is attacked by propargyl alcohol **1** to form the corresponding propargyl vinyl ether *E*-**5** or *Z*-**5**.[15] Fortunately, the addition products *E*-**5a** and *Z*-**5a** were obtained when propargyl alcohol **1v** was reacted with dimethyl acetylenedicarboxylate (DMAD) instead of **2** catalyzed by 5 mol % DABCO in CH_2Cl_2 at 25 °C (Scheme 2, eq 5). When either *Z*-**5a** or *E*-**5a** was reacted at 110 °C, furan **9b** was obtained (Scheme 2, eq 6). Notably, **9b** was also successfully isolated from the corresponding alkynol and DMAD in 71% yield (Scheme 2, eq 7). Either *E*-**5** or *Z*-**5** undergoes Claisen rearrangement[16] to furnish allene–ketone **6**. Keto–enol tautomerism between **6** and **7** may happen in the presence of DABCO as the base. Allene–enol **7a**[11] was isolated via aza-Claisen rearrangement/hydrolysis/tautomerism of the corresponding 3-aza-1,5-enyne. When **7a** was allowed to react under the standard reaction conditions, the corresponding product **3a** and 1-oxatriene **8a** were generated in a 23:77 ratio as determined by ^1H NMR analysis (Scheme 2, eq 3). In contrast, in the absence of DABCO, no furan product was detected by ^1H NMR spectroscopy (Scheme 2, eq 4), indicating that DABCO also plays an important role in the transformation of the allene–enol intermediate to the furan product. Allene–

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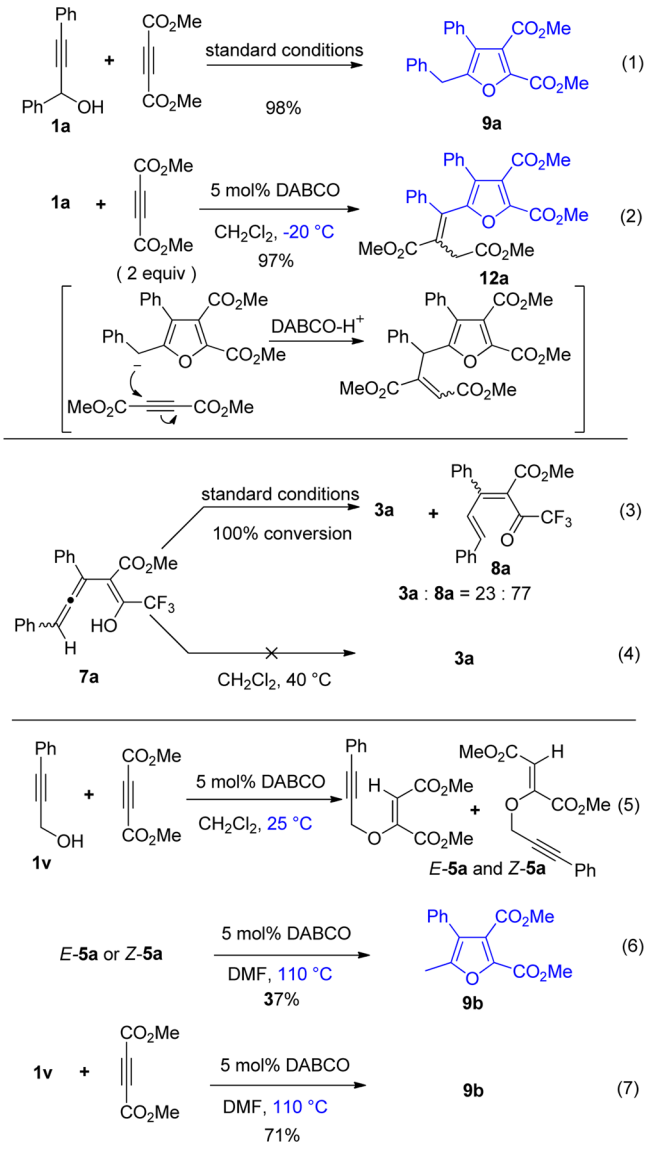
Scheme 2. Mechanistic Studies



ketone **6** could also be transformed into 1-oxatriene **8** by a 1,3-H shift (Scheme 2, eq 3). The N atom of DABCO accepts the proton of allene−enol **7** to form heterocyclic anion **10** and DABCO−H cation **11**. The above-mentioned process was supported by the following two experiments. Trifluoromethylated furan **3a** was still the only product even at −20 °C. Thus, we used DMAD instead of **2**, and a new furan **9a** was obtained in 98% yield under the standard reaction conditions (Scheme 2, eq 1). An unexpected furan **12a** was obtained in 97% yield when the reaction was conducted at a 1:2 molar ratio at −20 °C for 24 h (Scheme 2, eq 2). Furan **12a** might be a result of the reaction of anion intermediate **10a** with another molecule of DMAD, and a benzyl anion might be involved in this process. This supports well the existence of anion **10**. Finally, a proton is abstracted from **11** to **10** to generate furan **3** and release the DABCO catalyst.

CONCLUSION

We have developed an efficient route for the DABCO-catalyzed synthesis of trifluoromethylated furans from propargyl alcohols and methyl 2-perfluoroalkynoate in up to 98% yield. Both the established allene−enol and control experiments suggest that the reaction proceeds through a Michael addition and Claisen rearrangement/cyclization process. The mild and effective reaction conditions and the broad substrate scope make this reaction practical.

EXPERIMENTAL SECTION

General Considerations. Reactions were carried out under an atmosphere of argon using standard Schlenk techniques, unless otherwise noted. Column chromatography was carried out on silica gel (300−400 mesh) using a forced flow of eluent at 0.3−0.5 bar pressure. For TLC, silica gel GF254 was used with visualization by fluorescence quenching under UV light. Solvents were dried according to standard procedures and were distilled prior to use.

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded at 400, 100, and 377 MHz, respectively. The ^{1}H NMR chemical shifts were recorded in parts per million downfield from tetramethylsilane (TMS) using the solvent resonance as the internal standard (2.05 ppm for CD_3COCD_3 or 7.26 ppm for $CDCl_3$). The ^{13}C NMR chemical shifts were recorded in parts per million downfield using the central peak of $CDCl_3$ (77.16 ppm) or CD_3COCD_3 (29.84 ppm) as the internal standard. Coupling constants (J) are reported in hertz and refer to apparent peak multiplicities. The abbreviations s, d, t, q, and m stand for singlet, doublet, triplet, quartet, and multiplet, respectively. All of the ^{13}C NMR spectra were proton-decoupled.

General Procedures. Propargyl alcohols was prepared from aldehydes and terminal alkynes following the procedures described in ref 17.

Methyl 2-perfluoroalkynoate **2** was prepared from methyl bromoacetate, triphenylphosphine, and trifluoroacetic anhydride as described in the literature:[18] (1) To 262.3 g (1.0 mol) of triphenylphosphine in 1000 mL of ethyl acetate was added 160.7 g (1.05 mol) of methyl bromoacetate in 500 mL of ethyl acetate at 0 °C. After the mixture was stirred overnight at room temperature, the white precipitate was filtered off, washed with petroleum ether, and dried under vacuum at room temperature for 4 h, affording [(methoxycarbonyl)methyl]triphenylphosphonium bromide (382.8 g, 92% yield).[18a] (2) NEt_3 (206.7 g, 2.02 mol) was slowly added to a suspension of [(methoxycarbonyl)methyl]triphenylphosphonium bromide (382.8 g, 0.92 mol) in dry THF (2 L) at 0 °C under a nitrogen atmosphere. The mixture was stirred for 1 h at 0 °C. Trifluoroacetic anhydride (210.0 g, 1.0 mol) was added dropwise at 0 °C over about 3 h. Stirring was maintained for 2 h, after which the suspension was filtered. The white precipitate was washed with cold THF (1 L), and the mother liquors were concentrated. The oily residue was triturated in water (2 L), filtered, and washed with water (1 L) to give a pale-yellow solid. After recrystallization in a methanol/water mixture, the product, methyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)-acetoacetate, was obtained as very pale yellow crystals (384.3 g, 97%).[18b] (3) Methyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)-acetoacetate (384.2 g, 0.886 mol) was pyrolyzed by slow warming to 200−220 °C under reduced pressure. The distillate was condensed in a Dewar condenser cooled with liquid N_2 gas. Product **2** (97.4 g, 71% yield) was obtained as pale-yellow liquid.[18b]

Allene−enol was prepared from 3-aza-1,5-enyne following the procedures described in ref 11.

Propargyl alcohol **1** (0.4 mmol) and DABCO (0.01 mmol) were placed in a dried flask, and **2** (0.2 mmol) in 5 mL of CH_2Cl_2 was added slowly. The resulting mixture was stirred at 40 °C under an argon atmosphere until the complete consumption of **2** as detected by TLC. The solvent was evaporated under vacuum, and the crude product was directly purified by silica gel flash column chromatography using 20:1 petroleum ether/ethyl acetate as the eluent to give the desired compound **3**.

*Methyl 5-Benzyl-4-phenyl-2-(trifluoromethyl)furan-3-carboxylate (**3a**).* Oil (71.3 mg, 98% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, J = 6.9 Hz, 3H), 7.19 (s, 3H), 7.13 (d, J = 7.2 Hz, 2H), 7.03 (d, J = 7.2 Hz, 2H), 3.87 (s, 2H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 152.9, 141.2 (q, J = 42.0 Hz), 136.7, 130.5, 130.1, 129.7,

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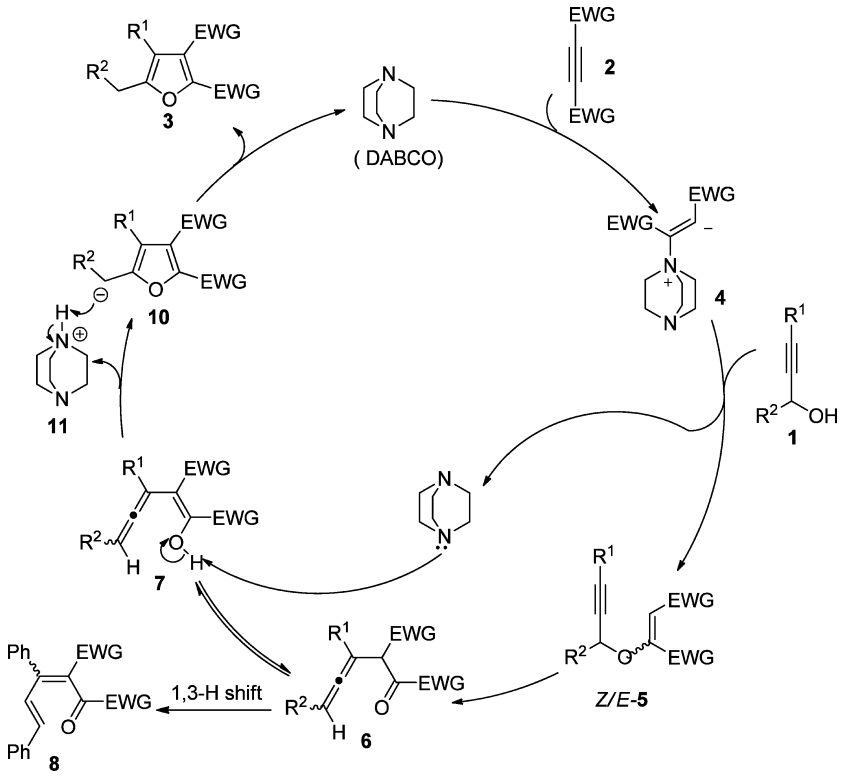
Scheme 3. Proposed Mechanism



129.5, 129.2, 128.9, 128.3, 127.6, 127.0, 124.0 (q, J = 299.0 Hz), 52.3, 32.3; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.10; HRMS (Q-TOF, ESI) calcd for $C_{20}H_{16}F_3O_3$ $[M + H]^+$ 361.1046, found 361.1051.

*Methyl 5-(3-Methylbenzyl)-4-phenyl-2-(trifluoromethyl)furan-3-carboxylate (**3b**).* Oil (61 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 4.4, 7.0 Hz, 5H), 7.07 (t, J = 7.4 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 3.83 (s, 2H), 3.63 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 153.0, 141.2 (q, J = 42.0 Hz), 138.5, 136.6, 130.5, 129.8, 129.2, 128.7, 128.4, 128.2, 127.7, 125.4, 123.9 (q, J = 270.0 Hz), 120.2, 117.6, 52.3, 32.2, 21.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.10; HRMS (Q-TOF, ESI) calcd for $C_{21}H_{18}F_3O_3$ $[M + H]^+$ 375.1203, found 375.1212.

*Methyl 5-(4-(tert-Butyl)benzyl)-4-phenyl-2-(trifluoromethyl)-furan-3-carboxylate (**3c**).* White solid (71 mg, 86% yield), mp 90−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J = 7.0 Hz, 3H), 7.27−7.16 (m, 4H), 6.99 (d, J = 8.0 Hz, 2H), 3.86 (s, 2H), 3.65 (s, 3H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 153.2, 149.9, 141.0 (q, J = 35.0 Hz), 133.7, 130.6, 129.8, 129.2, 128.7, 128.4, 128.2, 127.7, 125.8, 123.8 (q, J = 289.0 Hz), 52.3, 34.5, 31.8, 31.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.10; HRMS (Q-TOF, ESI) calcd for $C_{24}H_{24}F_3O_3$ $[M + H]^+$ 417.1672, found 417.1668.

*Methyl 5-(2-Methoxybenzyl)-4-phenyl-2-(trifluoromethyl)furan-3-carboxylate (**3d**).* Oil (66.3 mg, 85% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, J = 6.3 Hz, 3H), 7.28 (dd, J = 7.7, 1.8 Hz, 2H), 7.20 (t, J = 7.8 Hz, 1H), 7.00 (dd, J = 7.5, 1.5 Hz, 1H), 6.87 (t, J = 7.9 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 3.97 (s, 2H), 3.73 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 157.1, 153.0, 140.5 (q, J = 36.0 Hz), 130.8, 129.7, 129.5, 128.9, 128.3, 128.2, 128.0, 127.7, 125.1, 123.8 (q, J = 259.0 Hz), 120.2, 110.4, 55.2, 52.3, 26.7; ^{19}F NMR (377 MHz, $CDCl_3$) δ −61.89. HRMS (Q-TOF, ESI) calcd for $C_{21}H_{18}F_3O_4$ $[M + H]^+$ 391.1152, found 391.1151.

*Methyl 5-(4-Methoxybenzyl)-4-phenyl-2-(trifluoromethyl)furan-3-carboxylate (**3e**).* Oil (56 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 6.9 Hz, 3H), 7.21−7.15 (m, 2H), 6.96 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.6 Hz, 2H), 3.82 (s, 2H), 3.69 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 158.6, 153.3, 150.0, 141 (q, J = 42.0 Hz), 137.4, 130.5, 129.8, 129.5, 128.8, 128.4, 128.2, 123.5 (q, J = 268.0 Hz), 114.2, 55.3, 52.3, 31.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.10; HRMS (Q-TOF, ESI) calcd for $C_{21}H_{18}F_3O_4$ $[M + H]^+$ 391.115, found 391.115.

*Methyl 5-(2-Fluorobenzyl)-4-phenyl-2-(trifluoromethyl)furan-3-carboxylate (**3f**).* Oil (74 mg, 98% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (q, J = 5.6 Hz, 3H), 7.22−7.10 (m, 3H), 6.89−6.78 (m, 2H), 6.73 (d, J = 11.5 Hz, 1H), 3.86 (s, 2H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J = 232.0 Hz), 151.0, 141.6 (q, J = 42.0 Hz), 139.1 (q, J = 7.0 Hz), 133.2, 131.1, 130.4, 130.3, 129.7, 128.8, 128.5, 128.3, 124.2, 124.1 (q, J = 284.0 Hz), 115.6 (d, J = 21.0 Hz), 114.1 (d, J = 21.0 Hz), 52.3, 32.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ −61.99, −112.69; HRMS (Q-TOF, ESI) calcd for $C_{20}H_{14}F_4O_3$ $[M + H]^+$ 379.0952, found 379.0959.

*Methyl 5-(3-Fluorobenzyl)-4-phenyl-2-(trifluoromethyl)furan-3-carboxylate (**3g**).* Oil (57 mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (q, J = 6.0 Hz, 4H), 7.19 (dd, J = 7.3, 1.5 Hz, 2H), 7.01−6.88 (m, 3H), 3.92 (s, 2H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, J = 245.0 Hz), 159.5, 151.6, 141.6 (q, J = 42.0 Hz), 133.3, 132.3, 131.9, 130.4, 129.9, 129.7, 129.0, 128.8, 128.6, 124.5 (q, J = 280.0 Hz), 115.7 (d, J = 21.0 Hz), 114.1 (d, J = 21.0 Hz), 52.3, 32.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.38, −117.6; HRMS (Q-TOF, ESI) calcd for $C_{20}H_{14}F_4O_3$ $[M + H]^+$ 379.0952, found 379.0958.

*Methyl 5-(4-Fluorobenzyl)-4-phenyl-2-(trifluoromethyl)furan-3-carboxylate (**3h**).* Oil (74 mg, 98% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.27 (m, 3H), 7.16 (dd, J = 7.5, 1.8 Hz, 2H), 6.98 (dd, J = 8.5, 5.4 Hz, 2H), 6.86 (t, J = 8.6 Hz, 2H), 3.83 (s, 2H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (d, J = 244.0 Hz), 162.0, 152.7, 141.1 (q, J = 43.0 Hz), 132.4, 130.9, 130.8, 130.4, 129.9, 129.2, 128.3, 123.9 (q, J = 320.0 Hz), 115.8 (d, J = 21.0 Hz), 115.6 (d, J = 21.0 Hz), 52.3, 31.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ −55.05, −61.98; HRMS (Q-TOF, ESI) calcd for $C_{20}H_{14}F_4O_3$ $[M + H]^+$ 379.0952, found 379.0958.

*Methyl 4-Phenyl-2-(trifluoromethyl)-5-(4-(trifluoromethyl)-benzyl)furan-3-carboxylate (**3i**).* Oil (81 mg, 95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.6 Hz, 2H), 7.31 (s, 3H), 7.16 (t, J = 7.9 Hz, 4H), 3.94 (s, 2H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 151.7, 140.7 (q, J = 69.8 Hz), 133.3, 131.3, 130.2, 129.9, 129.7, 129.3, 128.9, 128.5, 125.8 (q, J = 3.8 Hz), 124.5 (q, J = 216 Hz), 120.1 (q, J = 269.6 Hz), 52.4, 32.2; ^{19}F NMR (377 MHz,

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$CDCl_3$) δ −62.06, −62.60; HRMS (Q-TOF, ESI) calcd for $C_{21}H_{15}F_6O_3$ $[M + H]^+$ 429.0920, found 429.0928.

*Methyl 5-(4-Cyanobenzyl)-4-phenyl-2-(trifluoromethyl)furan-3-carboxylate (**3j**).* Oil (63 mg, 82% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.3 Hz, 2H), 7.38 (dd, J = 5.3, 1.7 Hz, 3H), 7.20 (t, J = 7.6 Hz, 4H), 4.01 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 151.1, 142.0 (q, J = 52.5 Hz), 132.7, 130.0, 129.6, 129.3, 129.0, 128.7, 128.6, 128.5, 127.5, 125.6, 124.7, 121.3 (q, J = 267.4 Hz), 52.4, 32.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.05; HRMS (Q-TOF, ESI) calcd for $C_{21}H_{15}F_3NO_3$ $[M + H]^+$ 386.0999, found 386.1007.

*Methyl 5-(4-Chlorobenzyl)-4-phenyl-2-(trifluoromethyl)furan-3-carboxylate (**3k**).* Oil (76 mg, 97% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 7.2 Hz, 3H), 7.20−7.11 (m, 4H), 6.94 (d, J = 8.5 Hz, 2H), 3.82 (s, 2H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 152.3, 141.2 (q, J = 42.2 Hz), 135.1, 133.2, 132.9, 130.9, 130.3, 129.8, 129.1, 128.8, 128.3, 124.1 (q, J = 264.6 Hz), 117.4, 52.3, 32.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.03; HRMS (Q-TOF, ESI) calcd for $C_{20}H_{15}ClF_3O_3$ $[M + H]^+$ 395.0656, found 395.0658.

*Methyl 5-(2,3-Dichlorobenzyl)-4-phenyl-2-(trifluoromethyl)furan-3-carboxylate (**3l**).* Oil (81.5 mg, 95% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.24 (m, 4H), 7.17−7.13 (m, 2H), 7.02 (t, J = 7.9 Hz, 1H), 6.86 (dd, J = 7.7, 1.4 Hz, 1H), 4.06 (s, 2H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 150.8, 141.3 (q, J = 42.0 Hz), 136.7, 133.5, 132.2, 130.1, 129.5, 129.3, 128.5, 128.4, 128.2, 127.8, 127.4, 125.0 (q, J = 269.2 Hz), 119.8, 52.4, 31.0. ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.10; HRMS (Q-TOF, ESI) calcd for $C_{20}H_{14}Cl_2F_3O_3$ $[M + H]^+$ 429.0267, found 429.0274.

*Methyl 5-(4-Bromobenzyl)-4-phenyl-2-(trifluoromethyl)furan-3-carboxylate (**3m**).* Oil (76 mg, 87% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 6.9 Hz, 5H), 7.25 (d, J = 6.7 Hz, 2H), 6.99 (d, J = 7.8 Hz, 2H), 3.91 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 152.2, 141.3 (q, J = 46.0 Hz), 135.6, 131.9, 131.0, 130.2, 129.7, 129.3, 128.4, 127.8, 124.1 (q, J = 286.0 Hz), 121.0, 117.4, 52.3, 31.7; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.10; HRMS (Q-TOF, ESI) calcd for $C_{20}H_{15}BrF_3O_3$ $[M + H]^+$ 439.0151, found 439.0153.

*Methyl 5-(4-Iodobenzyl)-4-phenyl-2-(trifluoromethyl)furan-3-carboxylate (**3n**).* Oil (91 mg, 94% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 6.5 Hz, 3H), 7.16 (dd, J = 5.1, 2.6 Hz, 2H), 6.79 (t, J = 8.9 Hz, 2H), 3.82 (s, 2H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 152.1, 141.4 (q, J = 41.0 Hz), 137.9, 136.3, 130.3, 129.7, 128.4, 128.5, 127.8, 124.1, 120.0 (q, J = 280.0 Hz), 117.4, 92.4, 52.4, 31.9; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.10. HRMS (Q-TOF, ESI) calcd for $C_{20}H_{15}F_3IO_3$ $[M + H]^+$ 487.0012, found 487.0016.

*Methyl 5-(Naphthalen-1-ylmethyl)-4-phenyl-2-(trifluoromethyl)-furan-3-carboxylate (**3o**).* Oil (75 mg, 91% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.47−7.34 (m, 6H), 7.27 (dd, J = 6.5, 3.1 Hz, 2H), 7.14 (d, J = 7.0 Hz, 1H), 4.40 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 152.8, 141.2 (q, J = 42.0 Hz), 134.2, 133.6, 132.4, 130.5, 129.8, 128.5, 128.3, 127.8, 127.7, 127.0, 126.6, 126.4, 125.9, 124.1, 120.0 (q, J = 267.0 Hz), 52.4, 32.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ −61.90; HRMS (Q-TOF, ESI) calcd for $C_{24}H_{18}F_3O_3$ $[M + H]^+$ 411.1203, found 411.1209.

*Methyl 5-(Naphthalen-2-ylmethyl)-4-phenyl-2-(trifluoromethyl)-furan-3-carboxylate (**3p**).* Oil (63 mg, 77% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75−7.62 (m, 3H), 7.45 (s, 1H), 7.34 (m, J = 20.3, 7.6, 2.4 Hz, 5H), 7.18 (m, J = 21.8, 8.2, 2.0 Hz, 3H), 4.03 (s, 2H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 152.8, 141.2 (q, J = 44.0 Hz), 134.2, 133.6, 132.4, 130.5, 129.8, 128.5, 128.3, 127.8, 127.7, 127.0, 126.6, 126.4, 125.9, 124.1, 120.0 (q, J = 280.9 Hz), 52.4, 32.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.10; HRMS (Q-TOF, ESI) calcd for $C_{24}H_{18}F_3O_3$ $[M + H]^+$ 411.1203, found 411.1207.

*Methyl 5-Benzyl-4-(o-tolyl)-2-(trifluoromethyl)furan-3-carboxylate (**3q**).* Oil (57 mg, 76% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.18 (m, 6H), 7.11 (d, J = 7.5 Hz, 1H), 7.06 (d, J = 7.4 Hz, 2H), 3.81 (q, J = 5.7 Hz, 2H), 3.67 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 152.9, 141.2 (q, J = 48.0 Hz) 137.8, 136.5, 130.4, 130.1, 130.0, 129.1, 128.7, 128.6, 127.8, 127.8, 126.9, 123.1, 119.9 (q, J = 276.3 Hz), 52.2, 32.4, 20.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ −61.75; HRMS (Q-TOF, ESI) calcd for $C_{21}H_{18}F_3O_3$ $[M + H]^+$ 375.1203, found 375.1212.

*Methyl 5-Benzyl-4-(p-tolyl)-2-(trifluoromethyl)furan-3-carboxylate (**3r**).* Oil (73 mg, 98% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, J = 7.2 Hz, 2H), 7.16−7.10 (m, 3H), 7.06 (dd, J = 11.7, 7.6 Hz, 4H), 3.87 (s, 2H), 3.65 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 152.8, 141.8 (q, J = 49.0 Hz), 138.0, 136.9, 129.6, 128.8, 128.5, 127.8, 127.4, 126.9, 123.8, 120.2 (q, J = 276.5 Hz), 117.5, 52.3, 32.3, 21.39; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.10; HRMS (Q-TOF, ESI) calcd for $C_{21}H_{18}F_3O_3$ $[M + H]^+$ 375.1203, found 375.1209.

*Methyl 5-Benzyl-4-(4-chlorophenyl)-2-(trifluoromethyl)furan-3-carboxylate (**3s**).* Oil (70 mg, 89% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.3 Hz, 2H), 7.23−7.13 (m, 3H), 7.11 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 7.5 Hz, 2H), 3.85 (s, 2H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 153.1, 141.8 (q, J = 39.0 Hz), 136.5, 134.4, 131.2, 130.7, 129.2, 129.1, 128.5, 128.4, 127.1, 122.0, 120.8 (q, J = 268.5 Hz), 52.4, 32.3; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.10; HRMS (Q-TOF, ESI) calcd for $C_{20}H_{15}ClF_3O_3$ $[M + H]^+$ 395.0656, found 395.0662.

*Methyl 5-Benzyl-2-(trifluoromethyl)-4-(4-(trifluoromethyl)-phenyl)furan-3-carboxylate (**3t**).* Oil (77 mg, 90% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.19 (t, J = 7.2 Hz, 2H), 7.14 (d, J = 7.0 Hz, 1H), 7.01 (d, J = 7.4 Hz, 2H), 3.85 (s, 2H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 152.3, 141.0 (q, J = 42.0 Hz), 135.1, 133.2, 132.1, 129.4, 128.6, 128.4, 127.3, 127.2, 124.2 (q, J = 297.2 Hz), 121.6 (q, J = 245.9 Hz), 112.6, 51.2, 31.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.95, −62.70; HRMS (Q-TOF, ESI) calcd for $C_{21}H_{15}F_6O_3$ $[M + H]^+$ 429.0920, found 429.0926.

*Methyl 5-(2,3-Dichlorobenzyl)-4-(4-fluorophenyl)-2-(trifluoromethyl)furan-3-carboxylate (**3u**).* Oil (85 mg, 96% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.0 Hz, 1H), 7.23−7.16 (m, 2H), 7.07 (dt, J = 17.0, 8.1 Hz, 3H), 6.94 (d, J = 7.7 Hz, 1H), 4.11 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 161.6 (q, J = 220.8 Hz), 151.0, 141.0 (q, J = 42.9 Hz), 136.5, 133.6, 132.2, 131.4, 129.4, 128.3, 127.8, 127.4, 126.0, 124.0 (q, J = 201.4 Hz), 120.0, 115.6 (q, J = 21.7 Hz), 52.4, 31.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ −61.89, −113.28; HRMS (Q-TOF, ESI) calcd for $C_{20}H_{13}Cl_2F_4O_3$ $[M + H]^+$ 447.0000, found 447.0179.

*(E)-Methyl 3,5-Diphenyl-2-(2,2,2-trifluoro-1-hydroxyethylidene)-penta-3,4-dienoate (**7a**).* Known compound.[11] ^1H NMR (400 MHz, $CDCl_3$) δ 13.09 (s, 1H), 7.37−7.29 (m, 8H), 7.26−7.21 (m, 2H), 6.62 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 172.9, 135.1, 133.2, 131.0, 128.9, 128.8, 128.3, 127.9, 127.6, 127.5, 126.0, 119.4 (q, J = 277.7 Hz), 102.3, 98.2, 53.3.

*Methyl 3,5-Diphenyl-2-(2,2,2-trifluoroacetyl)penta-2,4-dienoate (**8a**).* Oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 15.9 Hz, 1H), 7.39−7.36 (m, 2H), 7.31 (dd, J = 5.0, 1.8 Hz, 3H), 7.25 (dd, J = 5.0, 1.8 Hz, 3H), 7.11 (dd, J = 7.4, 1.8 Hz, 2H), 6.49 (d, J = 15.9 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1 (q, J = 37 Hz), 163.2, 159.7, 145.8, 135.7, 135.3, 130.2, 129.5, 129.2, 128.9, 128.8, 128.3, 126.1, 124.1, 116.7 (q, J = 290 Hz), 52.4; HRMS (Q-TOF, ESI) calcd for $C_{20}H_{15}F_3O_3$ $[M + H]^+$ 361.0973, found 361.0972.

*Mixture of **3a** and **8a**.* ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 15.9 Hz, 1.1H), 7.39−7.36 (m, 5.16H), 7.30 (m, 5.46H), 7.27−7.21 (m, 5.41H), 7.16 (s, 2.41H), 7.10 (dd, J = 7.5, 1.8 Hz, 2.19H), 7.03 (d, J = 7.0 Hz, 0.68H), 6.49 (dd, J = 15.7, 13.3 Hz, 1.79H), 3.87 (s, 0.61H), 3.77 (s, 3H), 3.63 (s, 0.93H), 3.45 (s, 1.13H).

*(E)-Dimethyl 2-(3-Phenylprop-2-ynyloxy)maleate (E-**5a**).* Known compound.[9b] White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 9.4 Hz, 2H), 7.24 (d, J = 6.9 Hz, 3H), 6.31 (s, 1H), 5.07 (s, 2H), 3.77 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 163.0, 151.8, 131.5, 128.6, 128.1, 121.8, 110.9, 88.7, 82.6, 60.8, 52.7, 51.5.

*(Z)-Dimethyl 2-(3-Phenylprop-2-ynyloxy)maleate (Z-**5a**).* Known compound.[9b] White solid; ^1H NMR (400 MHz, acetone-d_6) δ 7.44 (d, J = 7.2 Hz, 2H), 7.34 (d, J = 6.5 Hz, 3H), 5.48 (s, 1H), 4.88 (s, 2H), 3.85 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 165.3, 162.8, 159.8, 131.2, 128.6, 127.9, 121.1, 94.1, 88.2, 80.6, 57.8, 52.1, 50.8.

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*Dimethyl 5-Benzyl-4-phenylfuran-2,3-dicarboxylate (**9a**).*[15a] White solid (68 mg, 98% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, J = 42.4, 22.3, 7.0 Hz, 10H), 4.04 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 158.1, 154.2, 140.2, 136.7, 130.3, 128.9, 128.7, 128.3, 128.1, 126.8, 126.5, 123.7, 52.6, 52.2, 32.5.

*Dimethyl 5-Methyl-4-phenylfuran-2,3-dicarboxylate (**9b**).*[15a] White solid (39 mg, 98% yield); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.41−7.23 (m, 5H), 3.87 (s, 3H), 3.76 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 164.7, 158.4, 153.8, 140.1, 131.6, 129.5, 129.5, 128.6, 127.5, 123.0, 52.8, 12.6.

*(E)-Dimethyl 5-(4-Methoxy-2-(methoxycarbonyl)-4-oxo-1-phenylbut-1-enyl)-4-phenylfuran-2,3-dicarboxylate (**12a**, Z/E mixture).* Oil (95 mg, 97% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 5H), 7.17−7.12 (m, 11H), 7.09 (dd, J = 6.5, 3.0 Hz, 2H), 7.03 (dd, J = 6.5, 2.9 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.69 (s, 3H), 3.65 (s, 3H), 3.54 (s, 3H), 3.48 (s, 2H), 3.45 (s, 2H), 3.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 169.6, 168.8, 167.5, 163.7, 163.6, 157.9, 157.7, 151.7, 150.4, 141.4, 140.5, 138.7, 137.2, 137.1, 135.8, 130.9, 130.7, 129.4, 129.09, 129.06, 128.9, 128.84, 128.75, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.82, 127.77, 127.3, 126.7, 126.5, 125.6, 52.7, 52.6, 52.4, 52.34, 52.28, 52.1, 51.9, 51.8, 37.9, 37.3; HRMS (Q-TOF, ESI) calcd for $C_{27}H_{25}O_9$ $[M + H]^+$ 493.1493, found 493.1483.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C, and ^{19}F NMR spectra, HRMS spectra, and crystallographic data (CIF) for compound **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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