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First synthesis of functionalized 5-aryl-3-(trifluoromethyl)phenols by regioselective [3+3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with 3-aryl-3-silyloxy-1-trifluoromethyl-2-en-1-ones

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ABSTRACT

A variety of functionalized 5-aryl-3-(trifluoromethyl)phenols were prepared by the first $TiCl_4$-mediated [3+3] cyclocondensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-aryl-3-trimethylsilyloxy-1-trifluoromethyl-2-en-1-ones.

1. Introduction

The trifluoromethyl group possesses unique stereoelectronic properties and is, therefore, of great importance in organic and medicinal chemistry.[1] The CF_3 and the methyl group are of similar size. However, the high electron-withdrawing effect of the CF_3 group results in a great difference in the physical properties and in the chemical reactivity of CF_3- and CH_3-substituted molecules. This effect plays an important role in drug–receptor interactions. It is worth to be noted that the lipophilicity of CF_3-substituted molecules is often higher than the lipophilicity of their methyl-substituted analogues, which often results in an improvement of their in vivo transport. In addition, undesirable metabolic transformations are often avoided, due to the high chemical and biological stability of the CF_3 group. Therefore, CF_3-substituted arenes and heterocycles play an increasingly important role in drug discovery.[1] Trifluoromethyl- and perfluoroalkyl-substituted molecules show an excellent solubility in fluorophilic solvents. Therefore, CF_3-substituted molecules have been used as ligands[2] in catalytic processes in fluorous biphasic systems and supercritical carbon dioxide.[3] It is worth to be mentioned that CF_3-substituted arenes are present in many organocatalysts (e. g. in CF_3-substituted *N*,*N*′-diarylthioureas).[4,5]

Most of the methods reported so far for the synthesis of trifluoromethyl-substituted arenes rely on the functionalization of arenes by direct introduction of the CF_3 group into a suitable aromatic compound or by transformation of a CX_3 into a CF_3 group.[6,7] An important method relies on the reaction of aryl halides with trifluoromethylcopper. Despite its great utility, this reaction is often restricted to specific substrates as trifluoromethylcopper is relatively unstable and easily decomposes when the reaction with 'difficult' substrates is slow. In addition, the synthesis of more complex starting materials, functionalized and highly substituted aryl halides, can be a tedious and difficult task (due to the formation of regioisomers in electrophilic substitutions, low reactivity, etc.).

An interesting alternative and supplement for direct fluorination methods relies on the application of a 'building block strategy' based on cyclization reactions of suitable CF_3-substituted molecules.[8] This strategy has been applied, for example, to the synthesis of (trifluoromethyl)phenols.[9–11] Kostyuk et al. reported the synthesis of 3,5-bis(trifluoromethyl)anilines by cyclization of 1,1,1,5,5,5-hexafluoroacetylacetone with enamines.[12] Various CF_3-substituted heterocycles have been prepared based on cyclization reactions of α,β-unsaturated trifluoromethylketones.[13,14] The NaH-mediated cyclization of acetylacetone with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one has been reported to give 2-acetyl-5-(trifluoromethyl)phenol.[15] However, this protocol is limited to the synthesis of only one specific example. Recently, we have reported[16] the synthesis of 3-(trifluoromethyl)phenols by cyclocondensation[17,18] of 1,3-bis(silyloxy)-1,3-butadienes[19] with 4-ethoxy-1,1,1-trifluoroalk-3-en-2-ones. Herein, we report what are, to the best of our knowledge, the first formal [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes with 3-aryl-3-trimethylsilyloxy-1-trifluoromethyl-2-en-1-ones. These reactions allow for a convenient

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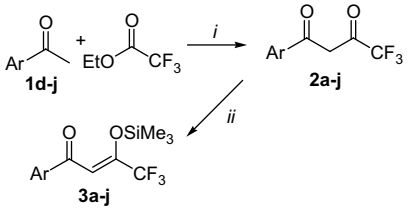
synthesis of a variety of functionalized 5-aryl-3-(trifluoromethyl)phenols, which can be regarded as 3-trifluoromethyl-biaryls.

2. Results and discussion

1,3-Bis(silyloxy)-1,3-butadienes **4a–i** were prepared from the corresponding 1,3-dicarbonyl compounds in one or two steps.[19] 3-Aryl-1,3-diones **2a–c** are commercially available. Derivatives **2d–i** were prepared by LDA-mediated condensation of ketones **1d–i** with ethyl trifluoroacetate (Scheme 1, Table 1). The silylation of **2a–c** was carried out under standard conditions (Me_3SiCl, NEt_3, benzene or toluene) to give 3-aryl-3-trimethylsilyloxy-1-trifluoromethyl-2-en-1-ones **3a–c**. Silyl enol ethers **3d–j** were prepared by reaction of an Et_2O solution of **2d–j** with trimethylsilyl-trifluoromethanesulfonate (Me_3SiOTf) in the presence of NEt_3.



Scheme 1. Synthesis of **3a–j**: conditions: (i) NaOMe, MeOH, 0→20 °C, 20 h; (ii) Me_3SiOTf (0.95 equiv), NEt_3 (1.0 equiv), Et_2O, 0 °C, 30 min, 20 °C, 3 days; the configuration of **3a–j** has not been unambiguously determined.

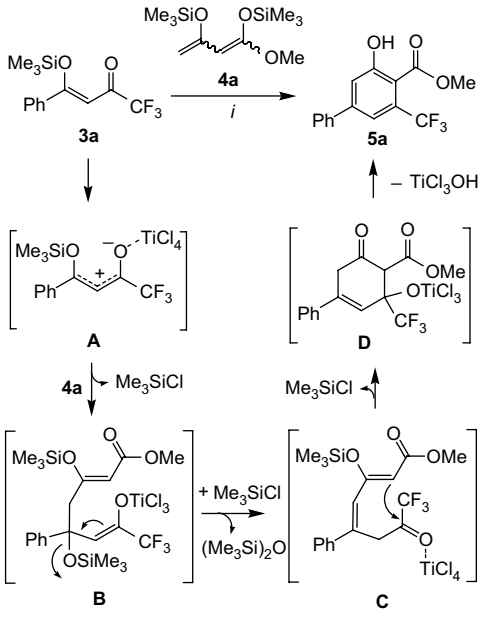
The $TiCl_4$-mediated [3+3] cyclization of **4a** with **3a** afforded 4-phenyl-6-(trifluoromethyl)salicylate **5a** in up to 48% yield (Scheme 2). The product may be regarded also as a functionalized 5-aryl-3-(trifluoromethyl)phenol or as a 3-trifluoromethyl-biaryl (note the different numbering systems). During the optimization of this reaction, the (high) concentration and the temperature played an important role. The moderate yield can be explained by hydrolysis and $TiCl_4$-mediated oxidative dimerization of diene **4a**. The reaction proceeded with excellent regioselectivity. Only the formation of the regioisomer containing the phenyl group located on the opposite site of the ester group was observed. The cyclocondensation and the regioselectivity can be explained by formation of intermediate **A**, attack of the terminal carbon atom of **4a** onto the carbon located next to the phenyl group to give intermediate **B**, cyclization by an S_N' mechanism with displacement of the Cl_3TiO group (intermediates **C** and **D**) and subsequent aromatization.

It has been previously reported that the reaction of **4a** with 3-silyloxy-2-en-1-one **6**, available from benzoylacetone, resulted in formation of 4-methyl-6-phenylsalicylate **7** (Scheme 3).[17,18a] Interestingly, the cyclization of **4a** with 3-silyloxy-2-en-1-ones **6** and **3a** proceeded with opposite regioselectivities. In the case of **7**, the

Table 1
Synthesis of **3a–j**

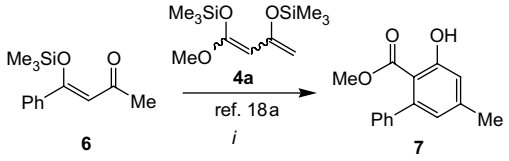
2,3	Ar	%[a] (2)	%[a] (3)
a	Ph	—[b]	
b	2-Naph	—[b]	95
c	4-ClC_6H_4	—[b]	98
d	4-FC_6H_4	41	88
e	4-BrC_6H_4	87	84
f	4-$(O_2N)C_6H_4$	35	82
g	4-$(F_3C)C_6H_4$	63	95
h	4-$(MeO)C_6H_4$	43	90
i	4-MeC_6H_4	72	90
j	4-PhC_6H_4	56	85

[a] Isolated yields.
[b] Commercially available.

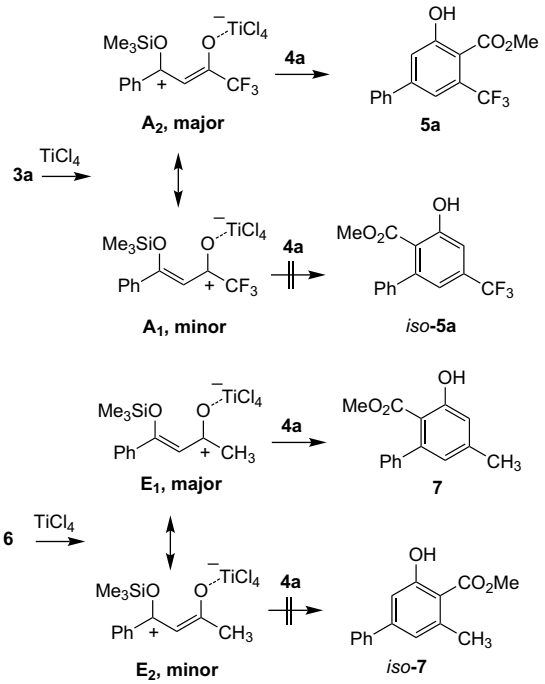


Scheme 2. Possible mechanism of the cyclization of **4a** with **3a**: conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C, 20 h.

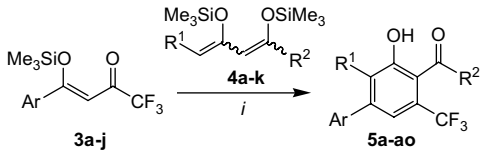
phenyl is located next to the ester group. Obviously, the change of the regioselectivity is a result of the replacement of the CH_3 by a CF_3 group in the 3-silyloxy-2-en-1-one.



Scheme 3. Cyclization of **4a** with **6**: conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C.



Scheme 4. Possible explanation of the different regioselectivity of the cyclization of **4a** with **3a** and **6**.



Scheme 5. Synthesis of **5a–ao**: conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C.

The different regioselectivities might be rationalized by comparison of the resonance structures of the cations formed by reaction of $TiCl_4$ with 3-silyloxy-2-en-1-ones **3a** and **6** (Scheme 4). In the case of the CH_3-substituted substrate **6**, it can be expected that resonance structure $\mathbf{E_1}$ is more stable than $\mathbf{E_2}$, due to the σ-donating effect of the methyl group. The phenyl group is expected to be twisted out of plane. In contrast, $\mathbf{A_2}$ is expected to have a higher impact than $\mathbf{A_1}$, due to the cation-destabilizing effect of the CF_3 group. The reactions presumably proceed, under kinetic reaction control, by attack of the terminal carbon atom of **4a** onto the cationic intermediate, which is predominantly present.

The $TiCl_4$-mediated formal [3+3] cyclization of 3-aryl-3-trimethylsilyloxy-1-trifluoromethyl-2-en-1-ones **3a–j** with 1,3-bis(silyloxy)-1,3-butadienes **4a–k** afforded 5-aryl-3-(trifluoromethyl)-phenols **5a–ao** (Scheme 5, Table 2). Some trends are observed related to the influence of the substitution pattern of the starting materials on the yields. Dienes **4a**,**f**,**h** are derived from simple methyl, isopropyl and ethyl acetoacetate, respectively. Dienes **4b–e**,**i** are prepared from higher β-ketoester homologues. 1,3-Bis(silyl enol ether) **4g** contains a methoxy group located at carbon C-4 of the diene. 1,3-Bis(silyloxy)-1,3-butadienes **4j**,**k** are derived from 1,3-diketones and are generally less reactive than dienes **4a–i** derived from β-ketoesters. The yields of cyclization products derived from diene **4a** are often higher than the yields of products derived from **4b–e**. In addition, the yields of the products prepared from **4a** are often higher than those of products derived from **4j** (however, for **5n** and **5r** the opposite case is true). There is no significant difference between the yields of the products derived from dienes **4b** and **4k**, both containing a methyl group attached to carbon atom C-4 of the diene. The aryl group attached to the enone also has some influence on the yields. The yields of products **5n–r** and **5w–ad**, prepared from enones containing electron-poor aryl groups, are in several cases higher than the yields of those products, which are derived from the other enones. The yields of products **5f**,**g**, derived from naphthyl-substituted enone **3b**, are relatively low.

Table 2
Synthesis of **5a–ao**

3	4	5	Ar	R^1	R^3	%[a] (5)
a	**a**	**a**	Ph	H	OMe	48
a	**b**	**b**	Ph	Me	OMe	51
a	**c**	**c**	Ph	Et	OEt	37
a	**d**	**d**	Ph	^{n}Hex	OMe	56
a	**e**	**e**	Ph	^{n}Oct	OMe	60
b	**a**	**f**	2-Naph	H	OMe	30
b	**f**	**g**	2-Naph	H	O^{i}Pr	30
c	**a**	**h**	4-ClC_6H_4	H	OMe	36
c	**b**	**i**	4-ClC_6H_4	Me	OMe	52
c	**c**	**j**	4-ClC_6H_4	Et	OEt	38
c	**d**	**k**	4-ClC_6H_4	^{n}Hex	OMe	40
c	**e**	**l**	4-ClC_6H_4	^{n}Oct	OMe	45
c	**g**	**m**	4-ClC_6H_4	OMe	OMe	37
d	**b**	**n**	4-FC_6H_4	H	OMe	53
d	**h**	**o**	4-FC_6H_4	H	OEt	32
d	**b**	**p**	4-FC_6H_4	Me	OMe	61
d	**i**	**q**	4-FC_6H_4	Et	OMe	55
d	**j**	**r**	4-FC_6H_4	H	Me	68
e	**b**	**s**	4-BrC_6H_4	Me	OMe	65
e	**g**	**t**	4-BrC_6H_4	OMe	OMe	31
e	**j**	**u**	4-BrC_6H_4	H	Me	68
e	**k**	**v**	4-BrC_6H_4	Me	Et	61
f	**a**	**w**	4-$(O_2N)C_6H_4$	H	OMe	71
f	**b**	**x**	4-$(O_2N)C_6H_4$	Me	OMe	51
f	**j**	**y**	4-$(O_2N)C_6H_4$	H	Me	64
g	**a**	**z**	4-$(F_3C)C_6H_4$	H	OMe	69
g	**b**	**aa**	4-$(F_3C)C_6H_4$	Me	OMe	72
g	**i**	**ab**	4-$(F_3C)C_6H_4$	Et	OMe	63
g	**j**	**ac**	4-$(F_3C)C_6H_4$	H	Me	54
g	**k**	**ad**	4-$(F_3C)C_6H_4$	Me	Et	70
h	**a**	**ae**	4-$(MeO)C_6H_4$	H	OMe	66
h	**b**	**af**	4-$(MeO)C_6H_4$	Me	OMe	51
h	**g**	**ag**	4-$(MeO)C_6H_4$	OMe	OMe	67
i	**a**	**ah**	4-MeC_6H_4	H	OMe	52
i	**b**	**ai**	4-MeC_6H_4	Me	OMe	42
i	**g**	**aj**	4-MeC_6H_4	OMe	OMe	44
i	**j**	**ak**	4-MeC_6H_4	H	Me	49
i	**k**	**al**	4-MeC_6H_4	Me	Et	32
j	**b**	**am**	4-PhC_6H_4	Me	OMe	70
j	**i**	**an**	4-PhC_6H_4	Et	OMe	41
j	**g**	**ao**	4-PhC_6H_4	OMe	OMe	42

[a] Isolated yields.

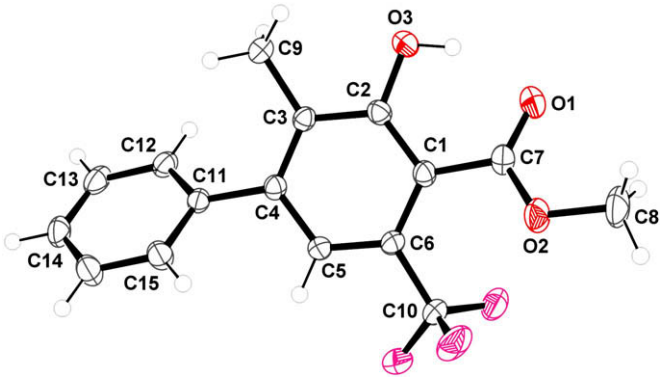


Figure 1. Ortep plot of **5b** (50% probability level).

The ^{1}H NMR spectra of products **5a–ao** show a sharp signal between 9 and 12 ppm, which can be assigned to the proton involved in a hydrogen bond O–H···O. In the ^{19}F NMR spectra, the signals of the CF_3 group of acetophenone and propiophenone derivatives (derived from **4j**,**k**) appear in the range of −53 to −56 ppm and in the range of −58 to −59 ppm for salicylate derivatives (derived from **4a–i**). The CF_3 groups attached to the simple benzene moiety (products **4z–ad**) usually appear at ca. −63 ppm, which is in agreement with the literature.[20] In contrast, CF_3 signals located next to a carbonyl group appear at ca. −70 ppm. The structures of **5b** and **5h** were independently confirmed by X-ray crystal structure analyses (Figs. 1 and 2).[21]

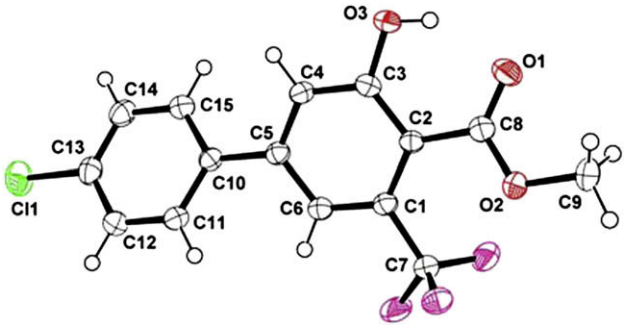


Figure 2. Ortep plot of **5h** (50% probability level).

In conclusion, a variety of sterically encumbered and functionalized 5-aryl-3-(trifluoromethyl)phenols were prepared by the first $TiCl_4$-mediated [3+3] cyclocondensations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-aryl-3-trimethylsilyloxy-1-trifluoromethyl-2-en-1-ones. The products are not readily available by other methods.

3. Experimental section

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected. Compounds **2a–c** are commercially available.

3.2. General procedure for the synthesis of 3-aryl-1-trifluoromethyl-2-en-1-ones 2d–i

Sodium (1.2 equiv) was added to methanol (10.0 equiv) at 0 °C and the mixture was stirred for 30 min. Ethyl trifluoroacetate (1.0 equiv) was added and the solution was stirred for further 30 min. To the solution was added acetophenone **1** (1.0 equiv). The temperature of the reaction mixture was allowed to rise to 20 °C in the period of 3 h and the solution was stirred for 16 h at 20 °C. To the solution was added sulfuric acid (10%, 0.35 mL per 1.0 mmol of **1**) and the mixture was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, heptanes → EtOAc/heptanes=1:10).

3.2.1. 1-(4-Fluorophenyl)-4,4,4-trifluorobutane-1,3-dione (**2d**)

Starting with 1-(4-fluorophenyl)ethanone (3.454 g, 25.0 mmol), **2d** was isolated as a colourless solid (2.423 g, 41%), mp=40–41 °C. ^1H NMR (250 MHz, $CDCl_3$): δ=6.53 (s, 1H, COC*H*COH), 7.20 (dd, $^3J_{H,H}$=9.0 Hz, $^3J_{H,F}$=8.3 Hz, 2H, CFC*H*), 7.99 (dd, $^3J_{H,H}$=9.1 Hz, $^4J_{H,F}$=5.3 Hz, 2H, CFCHC*H*), 15.14 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−76.4 (CF_3), −102.9 (C*F*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=92.2 (q, ^3J=2.1 Hz, COCHCOH), 116.4 (d, ^2J=22.2 Hz, CFCH), 117.2 (q, ^1J=283.2 Hz, *C*F_3), 129.3 (d, ^4J=2.9 Hz, CFCHCH*C*), 130.3 (d, ^3J=9.5 Hz, CFCH*C*H), 166.4 (d, ^1J=256.8 Hz, *C*F), 176.6 (q, ^2J=36.4 Hz, *C*OH), 185.3 (*C*O).

3.2.2. 1-(4-Bromophenyl)-4,4,4-trifluorobutane-1,3-dione (**2e**)

Starting with 1-(4-bromophenyl)ethanone (4.976 g, 25.0 mmol), **2e** was isolated as a pale yellow solid (6.410 g, 87%), mp=60 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=6.54 (s, 1H, COC*H*COH), 7.66 (d, ^3J=8.8 Hz, 2H, Ar*H*), 7.81 (d, ^3J=8.8 Hz, 2H, Ar*H*), 15.02 (s, 1H, O*H*). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−76.5 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=92.3 (COC*H*COH), 117.0 (q, ^1J=283.4 Hz, *C*F_3), 129.0 (*C*H), 129.3 (C_q), 131.7 (C_q), 132.4 (*C*H), 177.5 (q, ^2J=36.5 Hz, *C*OH), 184.9 (*C*O).

3.2.3. 1-(4-Nitrophenyl)-4,4,4-trifluorobutane-1,3-dione (**2f**)

Starting with 1-(4-nitrophenyl)ethanone (4.129 g, 25.0 mmol), **2f** was isolated as a pale yellow solid (2.172 g, 35%), mp=99–100 °C. ^1H NMR (250 MHz, $CDCl_3$): δ=6.62 (s, 1H, COC*H*COH), 8.12 (d, ^3J=9.1 Hz, 2H, Ar*H*), 8.36 (d, ^3J=9.1 Hz, 2H, Ar*H*), 14.70 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−76.7 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=93.4 (COC*H*COH), 116.7 (q, ^1J=283.9 Hz, *C*F_3), 124.1 (*C*H), 128.6 (*C*H), 138.1 (C_q), 150.7 (C_q), 179.2 (q, ^2J=37.0 Hz, *C*OH), 182.2 (*C*O).

3.2.4. 4,4,4-Trifluoro-1-(4-trifluoromethylphenyl)butane-1,3-dione (**2g**)

Starting with 1-(4-trifluoromethylphenyl)ethanone (4.704 g, 25.0 mmol), **2g** was isolated as a colourless liquid (4.507 g, 63%), bp=90–92 °C/2.9 mmHg; ^1H NMR (250 MHz, $CDCl_3$): δ=6.60 (s, 1H, COC*H*COH), 7.78 (d, ^3J=8.2 Hz, 2H, Ar*H*), 8.06 (d, ^3J=8.2 Hz, 2H, Ar*H*), 14.85 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−76.7 (CF_3), −63.3 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=92.9 (q, ^3J=1.8 Hz, COCHCOH), 116.9 (q, ^1J=284 Hz, *C*F_3), 123.4 (q, ^1J=273 Hz, *C*F_3), 126.0 (q, ^3J=3.7 Hz, CF_3CCHCH), 127.9 (CF_3CCH*C*H), 135.2 (q, ^2J=33.0 Hz, CF_3*C*CH), 136.0 (C_q), 178.5 (q, ^2J=36.7 Hz, *C*OH), 183.9 (*C*O).

3.2.5. 1-(4-Methoxyphenyl)-4,4,4-trifluorobutane-1,3-dione (**2h**)

Starting with 1-(4-methoxyphenyl)ethanone (3.755 g, 25.0 mmol), **2h** was isolated as a colourless solid (2.641 g, 41%), mp=59–60 °C; ^1H NMR (250 MHz, $CDCl_3$): δ=3.90 (s, 3H, OCH_3), 6.51 (s, 1H, COC*H*COH), 6.99 (d, ^3J=9.1 Hz, 2H, Ar*H*), 7.94 (d, ^3J=9.1 Hz, 2H, Ar*H*), 15.43 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−76.3 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=55.6 (O*C*H_3), 91.5 (COCHCOH), 114.4 (*C*H), 117.4 (q, ^1J=282.7 Hz, *C*F_3), 125.4 (C_q), 130.0 (*C*H), 164.6 (C_q), 175.8 (q, ^2J=36.0 Hz, *C*OH), 186.2 (*C*O).

3.2.6. 1-(p-Tolyl)-4,4,4-trifluorobutane-1,3-dione (**2i**)

Starting with 1-(4-methylphenyl)ethanone (3.355 g, 25.0 mmol), **2i** was isolated as a colourless solid (4.131 g, 72%), mp=45–46 °C. ^1H NMR (250 MHz, $CDCl_3$): δ=2.45 (s, 3H, CH_3), 6.55 (s, 1H, COC*H*COH), 7.31 (d, ^3J=8.3 Hz, 2H, Ar*H*), 7.85 (d, ^3J=8.3 Hz, 2H, Ar*H*), 15.24 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−76.4 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.8 (*C*H_3), 92.0 (COCHCOH), 117.2 (q, ^1J=283.1 Hz, *C*F_3), 127.7 (*C*H), 129.8 (*C*H), 130.2 (C_q), 145.4 (C_q), 176.8 (q, ^2J=36.1 Hz, *C*OH), 186.4 (*C*O).

3.2.7. 1-(4-Phenylphenyl)-4,4,4-trifluorobutane-1,3-dione (**2j**)

Starting with 1-(4-phenylphenyl)ethanone (3.533 g, 18.0 mmol), **2j** was isolated as a pale red solid (2.947 g, 56%), mp=104 °C. ^1H NMR (250 MHz, $CDCl_3$): δ=6.63 (s, 1H, COC*H*COH), 7.40–7.55 (m, 3H, Ar*H*), 7.65 (d, ^3J=7.9 Hz, 2H, Ar*H*), 7.74 (d, ^3J=8.6 Hz, 2H, Ar*H*), 8.03 (d, ^3J=8.6 Hz, 2H, Ar*H*), 15.24 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−76.4 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=92.2 (COCHCOH), 117.2 (q, ^1J=283.5 Hz, *C*F_3), 127.2 (*C*H), 127.5 (*C*H), 128.2 (*C*H), 128.6 (*C*H), 129.0 (*C*H), 131.5 (C_q), 139.4 (C_q), 146.9 (C_q), 177.3 (q, ^2J=36.2 Hz, *C*OH), 185.6 (*C*O).

3.3. General procedure for the synthesis of 3-aryl-3-silyloxy-1-trifluoromethyl-2-en-1-ones 3a–c

To a stirred benzene solution (2.5 mL per 1.0 mmol of **2a–c**) of **2a–c** (1.0 equiv) was added triethylamine (1.6 equiv). After stirring the solution for 2 h, trimethylchlorosilane (1.8 equiv) was added. The solution was stirred for 72 h and, subsequently, the solvent was removed in vacuo and hexane (1.5 mL per 1.0 mmol of starting material) was added to the residue to give a suspension. The latter was filtered under argon atmosphere. The filtrate was concentrated in vacuo to give silyl enol ethers **3a–c**, which were used without further purification. Due to the unstable nature of the products, MS and analytical data could not be obtained. All products were obtained as mixtures of *E*/*Z*-isomers.

3.3.1. 1,1,1-Trifluoro-4-phenyl-4-[(trimethylsilyl)oxy]-3-buten-2-one (**3a**)

Starting with benzene (60.0 mL), **2a** (5.00 g, 24.6 mmol), triethylamine (3.927 g, 38.8 mmol) and trimethylchlorosilane (2.917 g, 27.0 mmol), **3a** was isolated as a reddish oil (5.729 g, 82%). ^1H NMR (300 MHz, $CDCl_3$): δ=0.20 (m, 9H, Si(CH_3)$_3$), 6.56 (s, 1H, CH), 7.29–7.34 (m, 3H, CH_{Ar}), 7.77–7.80 (m, 2H, CH_{Ar}).

*3.3.2. 4-(Naphth-2-yl)-1,1,1-trifluoro-4-(trimethylsilyloxy)but-3-en-2-one (**3b**)*

Starting with benzene (37.5 mL), **2b** (3.993 g, 15.0 mmol), triethylamine (2.428 g, 24.0 mmol), and trimethylchlorosilane (2.933 g, 27.0 mmol), **3b** was isolated as a yellowish solid (4.82 g, 95%), mp=130–132 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.22 [s, 9H, $Si(CH_3)_3$], 6.75 (s, 1H, CH), 7.46–7.57 (m, 2H, CH), 7.79–7.86 (m, 2H, CH_{Naph}), 7.89–7.94 (m, 2H, CH_{Naph}), 8.35 (m, 1H, CH_{Naph}). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−73.72, −76.39, −78.44. ^{13}C NMR (75 MHz, $CDCl_3$): δ=0.37 [$Si(CH_3)_3$], 106.4 (CH), 122.9, 124.0, 127.0, 128.0, 128.7, 129.7, 130.1 (CH_{Naph}), 130.9 (d, $^1J_{C,F}$=257.5 Hz, CF_3), 171.8 (CO), 188.7 (COSi).

*3.3.3. 4-(4-Chlorophenyl)-1,1,1-trifluoro-4-(trimethylsilyloxy)-but-3-en-2-one (**3c**)*

Starting with benzene (30 mL), **2c** (3.000 g, 12.0 mmol), triethylamine (1.938 g, 19.2 mmol) and trimethylchlorosilane (2.340 g, 21.5 mmol), **3c** was isolated as a yellowish oil (3.80 g, 98%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.13 [s, 9H, $Si(CH_3)_3$], 6.74 (s, 1H, CH), 7.29 (d, ^3J=8.3 Hz, 2H, CH_{Clph}), 7.70 (d, ^3J=8.3 Hz, 2H, CH_{Clph}). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−73.91. ^{13}C NMR (75 MHz, $CDCl_3$): δ=0.2 [$Si(CH_3)_3$], 105.8 (CH), 119.7 (d, $^1J_{C,F}$=276.8 Hz, CF_3), 129.0 ($2CH_{Clph}$), 129.6 ($2CH_{Clph}$), 136.2, 139.8 ($2C_{Clph}$), 185.0 (CO), 187.4 (COSi).

3.4. General procedure for the synthesis of 3-silyloxy-1-(trifluoromethyl)prop-2-en-1-ones 3d–j

To a stirred diethyl ether solution (2 mL per 1.0 mmol of **2**) of **2d**–**j** (1.0 equiv) were added triethylamine (1.0 equiv) and TMSOTf (0.95 equiv) at 0 °C under an argon atmosphere. The solution was stirred for 30 min at 0 °C. The temperature of the reaction mixture was allowed to rise to 20 °C and the stirring was continued for 3 days. A liquid salt layer separated at the bottom of the flask. The upper layer (ether solution containing the product) was transferred to a dry flask by syringe under an argon atmosphere. Diethyl ether (1.5 mL per 1.0 mmol of **2**) was added to the liquid salt layer, the mixture was stirred for 2 min and the layers were allowed to separate in the period of 2 h. The ether solutions were combined and concentrated in vacuo to give silyl enol ethers **3d**–**j**, which were not further purified. Due to their unstable nature, products **3d**–**j** were immediately used for the synthesis of phenols **5** (without detailed spectroscopic characterization).

3.5. General procedure for the synthesis of 5-aryl-3-(trifluoromethyl)phenols 5a–ao

To a stirred dichloromethane solution (2 mL per 1.0 mmol of **3**) of enone **3** (1.0 equiv) and 1,3-bis(silyl enol ether) **4** (1.1 equiv) was added $TiCl_4$ (1.1 equiv) at −78 °C under an argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20 °C in the period of 16 h. To the solution was added hydrochloric acid (10%, 3 mL per 1.0 mmol of **3**) and the mixture was extracted with dichloromethane (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, heptanes→EtOAc/heptanes=1:10).

*3.5.1. Methyl 3-hydroxy-5-(trifluoromethyl)[1,1′-biphenyl]-4-carboxylate (**5a**)*

Starting with **3a** (0.361 g, 1.5 mmol), **4a** (0.426 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **5a** was isolated as a colourless solid (0.213 g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.82 (s, 3H, OCH_3), 7.24 (m, 1H, CH_{Ph}), 7.27 (m, 2H, CH_{Ph}), 7.32 (m, 1H, CH_{Ar}), 7.37 (m, 1H, CH_{Ar}), 7.42–7.44 (m, 2H, CH_{Ph}), 10.55 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.8 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.8 (OCH_3), 109.5 ($CCOOCH_{3Ar}$), 118.0 (q, $^3J_{F,C}$=6.8 Hz, CH_{Ar}), 116.7 (CH_{Ar}), 119.7 (CH_{Ph}), 123.3 (d, ^1J=269.7 Hz, CF_3), 127.1 ($2CH_{Ph}$), 129.0 ($2CH_{Ph}$), 130.7 (q, ^2J=31.6 Hz, $CCF3_{Ar}$), 138.2 (C_{Ph}), 146.7 (C_{Ar}), 162.2 (COH_{Ar}), 169.5 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 1660 (s), 1619 (m), 1452 (s), 1343 (s), 1219 (m), 1136 (s), 966 (m), 882 (m), 694 (m). GC–MS (EI, 70 eV): *m*/*z* (%)=296 ([M^+], 49), 265 (27), 264 (100), 263 (22), 236 (43), 208 (8), 188 (18), 139 (13), 118 (6). HRMS (EI) calcd for $C_{15}H_{11}F_3O_3$: 296.06548, found: 296.06510.

*3.5.2. Methyl 3-hydroxy-2-methyl-5-(trifluoromethyl)[1,1′-biphenyl]-4-carboxylate (**5b**)*

Starting with **3a** (0.361 g, 1.5 mmol), **4b** (0.426 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **5b** was isolated as yellowish solid (0.237 g, 51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.13 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 7.15 (m, 1H, CH_{Ph}), 7.19 (m, 1H, CH_{Ar}), 7.22 (m, 1H, CH_{Ph}), 7.34 (m, 2H, CH_{Ph}), 7.36 (m, 1H, CH_{Ph}), 11.09 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.6 (CH_3), 52.8 (OCH_3), 108.6 ($CCOOCH_{3Ar}$), 120.2 (q, $^3J_{F,C}$=6.8 Hz, CH_{Ar}), 123.5 (d, ^1J=269.0 Hz, CF_3), 127.4 (q, ^2J=31.6 Hz, CCF_{3Ar}), 127.9 (CH_{Ph}), 128.3 ($2CH_{Ph}$), 128.8 ($2CH_{Ph}$), 130.0 (C_{Ph}), 139.7, 146.9 (C_{Ar}), 160.6 (COH_{Ar}), 170.2 (CO). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.0 (CF_3). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2995 (w), 1681 (m), 1609 (w), 1439 (m), 1335 (m), 1274 (s), 1122 (s), 1017 (s), 886 (s), 700 (s). GC–MS (EI, 70 eV): *m*/*z* (%)=310 ([M^+], 68), 279 (27), 278 (80), 277 (100), 257 (9), 250 (36), 231 (7), 201 (24), 181 (57), 152 (24), 152 (24), 115 (5). HRMS (EI) calcd for $C_{16}H_{13}F_3O_3$: 310.08113, found: 310.08062.

*3.5.3. Ethyl 2-ethyl-3-hydroxy-5-(trifluoromethyl)[1,1′-biphenyl]-4-carboxylate (**5c**)*

Starting with **3a** (0.360 g, 1.5 mmol), **4c** (0.495 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **5c** was isolated as a red viscous oil (0.187 g, 37%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.00 (t, ^3J=7.4 Hz, 3H, CH_2CH_3), 1.32 (t, ^3J=7.1 Hz, 3H, OCH_2CH_3), 2.54 (q, ^3J=7.4 Hz, 2H, CH_2CH_3), 4.36 (q, ^3J=7.2 Hz, 2H, OCH_2CH_3), 7.09 (br s, 1H, CH_{Ar}), 7.15 (m, 1H, CH_{Ph}), 7.16–7.19 (m, 2H, CH_{Ph}), 7.30–7.33 (m, 2H, CH_{Ph}), 11.13 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−57.8 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.4 (CH_2CH_3), 12.6 (OCH_2CH_3), 19.8 (CH_2CH_3), 62.2 (OCH_2CH_3), 108.3 ($CCOOCH_2CH_{3Ar}$), 119.5 (q, $^3J_{F,C}$=6.6 Hz, CH_{Ar}), 122.5 (d, $^1J_{F,C}$=269.0 Hz, CF_3), 125.4 (q, ^2J=31.6 Hz, CCF_{3Ar}), 126.7 (CH_{Ph}), 127.2 ($2CH_{Ph}$), 127.5 ($2CH_{Ph}$), 134.2 (C_{Ph}), 139.0, 145.7 (C_{Ar}), 159.1 (COH_{Ar}), 168.7 (CO). GC–MS (EI, 70 eV): *m*/*z* (%)=338 ([M^+], 59), 293 (26), 292 (79), 291 (100), 264 (46), 249 (24), 223 (5), 195 (21), 165 (15). HRMS (EI) calcd for $C_{18}H_{17}F_3O_3$: 338.11243, found: 338.11274.

*3.5.4. Methyl 2-hexyl-3-hydroxy-5-(trifluoromethyl)[1,1′-biphenyl]-4-carboxylate (**5d**)*

Starting with **3a** (0.360 g, 1.5 mmol), **4d** (0.563 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **5d** was isolated as a red viscous oil (0.319 g, 56%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.64 (br t, ^3J=7.0 Hz, 3H, $CH_2(CH_2)_4CH_3$), 0.99–1.34 (m, 8H, $CH_2(CH_2)_4CH_3$), 2.44 (t, ^3J=8.0 Hz, 2H, $CH_2(CH_2)_4CH_3$), 3.81 (s, 3H, OCH_3), 7.01 (m, 1H, CH_{Ar}), 7.08 (m, 1H, CH_{Ph}), 7.11 (m, 1H, CH_{Ph}), 7.23 (m, 2H, CH_{Ph}), 7.25 (m, 1H, CH_{Ph}), 10.91 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−57.8 (CF_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ=13.9 (CH_3), 22.4, 27.3, 29.0, 29.3, 31.3 (CH_2), 52.7 (OCH_3), 109.0 ($CCOOCH_{3Ar}$), 120.5 (q, $^3J_{F,C}$=6.5 Hz, CH_{Ar}), 123.5 (d, $^1J_{F,C}$=269.0 Hz, CF_3), 127.4 (q, $^2J_{F,C}$=31.6 Hz, CCF_{3Ar}), 127.8 (CH_{Ph}), 128.2 ($2CH_{Ph}$), 128.6($2CH_{Ph}$), 134.2 (C_{Ph}), 140.0, 147.0 (C_{Ar}), 160.4 (COH_{Ar}), 170.2 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2927 (w), 2856 (w), 1671 (m), 1610 (w), 1439 (m), 1336 (m), 1280 (s), 1200 (m), 1177 (s), 1030 (w), 947 (m), 885 (m), 770 (m), 701 (s). GC–MS (EI, 70 eV): *m*/*z* (%)=380 ([M^+], 55), 349 (31), 348 (100), 347 (49), 331 (13), 278 (40), 277 (62), 250 (28), 229 (5), 201 (23), 181 (28), 152 (16). HRMS (EI) calcd for $C_{21}H_{23}O_3F_3$: 380.15938, found: 380.15976.

*3.5.5. Methyl 3-hydroxy-2-octyl-5-(trifluoromethyl)[1,1′-biphenyl]-4-carboxylate (**5e**)*

Starting with **3a** (0.360 g, 1.5 mmol), **4e** (0.563 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **5e** was isolated as a red viscous oil

(0.367 g, 60%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.77 (br t, ^3J=6.9 Hz, 3H, $CH_2(CH_2)_6CH_3$), 1.08–1.39 (m, 12H, $CH_2(CH_2)_6CH_3$), 2.25 (t, ^3J=7.8 Hz, 2H, $CH_2(CH_2)_6CH_3$), 3.90 (s, 3H, OCH_3), 7.10 (m, 1H, CH_{Ar}), 7.16 (m, 1H, CH_{Ph}), 7.19 (m, 1H, CH_{Ph}), 7.32 (m, 2H, CH_{Ph}), 7.25 (m, 1H, CH_{Ph}), 10.99 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.6 (CF_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ=13.0 (CH_3), 21.6, 26.3 (CH_2), 28.0 ($3CH_2$), 28.6, 30.8 (CH_2), 51.7 (OCH_3), 108.0 ($CCOOCH_{3Ar}$), 119.5 (q, $^3J_{F,C}$=6.8 Hz, CH_{Ar}), 122.4 (d, $^1J_{F,C}$=269.0 Hz, CF_3), 125.8 (q, $^2J_{F,C}$=31.6 Hz, CCF_{3Ar}), 126.7, 126.9, 127.0, 127.2, 127.5 (CH_{Ph}), 133.2 (C_{Ph}), 139.0 (C_{Ar}), 146.0 (C_{Ar}), 159.4 (COH_{Ar}), 169.2 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2961 (w), 2854 (w), 1672 (w), 1374 (w), 1257 (s), 1087 (m), 1012 (s), 791 (s). GC–MS (EI, 70 eV): *m*/*z* (%)=408 ([M^+], 43), 377 (32), 37 (100), 359 (12), 333 (7), 278 (41), 277 (59), 250 (25), 229 (5), 201 (19), 181 (18), 152 (13). HRMS (EI) calcd for $C_{23}H_{27}O_3F_3$: 408.19068, found: 408.19180.

3.5.6. Methyl 2-hydroxy-4-(naphth-2-yl)-6-(trifluoromethyl)-benzoate (**5f**)

Starting with **3b** (0.338 g, 1.0 mmol), **4a** (0.286 g, 1.1 mmol) and $TiCl_4$ (0.12 mL, 1.1 mmol), **5f** was isolated as a yellow viscous oil (0.098 g, 30%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.93 (s, 3H, OCH_3), 7.41–7.48 (m, 3H, CH), 7.59–7.64 (m, 2H, CH), 7.75–7.87 (m, 3H, CH), 7.98 (m, 1H, CH_{Naph}), 10.80 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.72. ^{13}C NMR (75 MHz, $CDCl_3$): δ=53.0 (OCH_3), 109.6 (*C*COOMe), 118.4 (q, $^3J_{C,F}$=7.5 Hz, CH_{Ar}), 120.1 (CH_{Ar}), 123.4 (d, $^1J_{C,F}$=123.4 Hz, CF_3), 124.7, 126.7, 126.9, 127.0, 127.8, 128.6, 129.1 (CH_{Naph}), 131.0 (q, $^2J_{C,F}$=30 Hz, C_{Ar}), 133.5, 133.7, 135.6 (C_{Naph}), 146.7 (C_{Ar}), 162.4 (COH), 169.7 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3057 (w), 2982 (w), 2923 (w), 2855 (w), 1660 (m), 1615 (w), 1600 (w), 1568 (w), 1511 (w), 1465 (w), 1442 (w), 1406 (w), 1362 (m), 1335 (m), 1323 (m), 1292 (s), 1272 (m), 1240 (m), 1209 (m), 1177 (m), 1148 (m), 1135 (s), 1100 (s), 1053 (m), 1020 (w), 973 (m), 949 (w), 914 (w), 874(w), 855 (m), 815 (m), 786 (w), 747 (m), 705 (m), 658 (w), 607 (w), 591 (w), 555 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=347 ([M^+], 18), 346 (88), 315 (29), 314 (100), 313 (15), 286 (37), 258 (12), 238 (19), 189 (30), 157 (9), 143 (12), 133 (10), 119 (10), 94 (9). HRMS (EI) calcd for $C_{19}H_{13}O_3F_3$ ([M^+]): 346.08113, found: 346.081463.

3.5.7. Isopropyl 2-hydroxy-4-(naphth-2-yl)-6-(trifluoromethyl)-benzoate (**5g**)

Starting with **3b** (0.507 g, 1.5 mmol), **4f** (0.476 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5g** was isolated as a red viscous oil (0.162 g, 30%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.33 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 5.28 (q, ^3J=6.7 Hz, 1H, OCH), 7.42–7.50 (m, 3H, CH), 7.60–7.66 (m, 2H, CH), 7.77–7.88 (m, 3H, CH), 8.05 (m, 1H, CH_{Naph}), 11.05 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−57.52. ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.4 ($2CH_3$), 71.1 [*O*CH(CH_3)$_2$], 110.3 (*C*COO^{i}Pr), 118.3 (q, $^3J_{C,F}$=6.2 Hz, CH_{Ar}), 120.1 (CH_{Ar}), 123.5 (d, $^1J_{C,F}$=271 Hz, CF_3), 124.7, 126.7, 126.9, 127.0, 127.8, 128.6, 129.0 (CH_{Naph}), 130.9 (q, $^2J_{C,F}$=31.4 Hz, C_{Ar}), 133.4, 133.5, 135.7 (C_{Naph}), 146.5 (C_{Ar}), 162.6 (COH), 168.8 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3058 (w), 2983 (w), 2921 (m), 2852 (w), 1660 (m), 1618 (w), 1583 (w), 1511 (w), 1465 (w), 1406 (w), 1363 (s), 1335 (m), 1294 (s), 1274 (m), 1242 (m), 1209 (m), 1178 (m), 1149 (m), 1135 (s), 1100 (s), 1055 (m), 1020 (w), 972 (m), 948 (w), 913 (m), 887(w), 854 (m), 814 (m), 785 (w), 745 (m), 705 (m), 658 (w), 606 (w), 591 (w), 554 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=375 ([M^+], 12), 374 (50), 332 (42), 315 (31), 314 (100), 313 (11), 287 (8), 286 (25), 258 (8), 238 (16), 189 (23), 133 (6), 43 (6). HRMS (EI) calcd for $C_{21}H_{17}O_3F_3$ ([M^+]): 374.11243, found: 374.111760.

3.5.8. Methyl 4′-chloro-3-hydroxy-5-(trifluoromethyl)biphenyl-4-carboxylate (**5h**)

Starting with **3c** (0.483 g, 1.5 mmol), **4a** (0.426 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5h** was isolated as a yellow solid (0.175 g, 36%), mp=87–88 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.89 (s, 3H, OCH_3), 7.26–7.27 (m, 1H, CH_{Ar}), 7.30–7.32 (m, 1H, CH_{Ar}), 7.43 (d, ^3J=8.8 Hz, 2H, CH_{Clph}), 7.37 (d, ^3J=8.4 Hz, 2H, CH_{Clph}), 10.73 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.84. ^{13}C NMR (75 MHz, $CDCl_3$): δ=53.1 (OCH_3), 109.9 (*C*COOMe), 117.9 (q, $^3J_{C,F}$=6.6 Hz, CH_{Ar}), 119.8 (CH_{Ar}), 123.3 (d, $^1J_{C,F}$=228.3 Hz, CF_3), 128.5 ($2CH_{Clph}$), 129.4 ($2C_{Clph}$), 131.1 (d, $^2J_{F,C}$=33.1 Hz, C_{Ar}), 135.5, 136.8 ($2C_{Clph}$), 145.5 (C_{Ar}), 162.4 (COH_{Ar}), 169.5 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3072 (w), 3033 (w), 2954 (w), 2923 (w), 1671 (m), 1619 (w), 1594 (w), 1556 (w), 1503 (w), 1486 (w), 1438 (m), 1337 (m), 1309 (m), 1289 (s), 1246 (m), 1203 (m), 1162 (m), 1130 (s), 1089 (s), 1055 (m), 1012 (m), 967 (m), 931 (m), 883 (m), 861 (w), 826 (s), 802 (m), 726 (m), 711 (m), 696 (m), 637 (w), 622 (w), 569 (w), 543 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=332 ([M^+], ^{37}Cl, 17), 330 ([M^+], ^{35}Cl, 49), 300 (^{37}Cl, 37), 299 (^{37}Cl, 34), 298 (^{35}Cl, 100), 297 (^{35}Cl, 15), 272 (^{37}Cl, 14), 270 (^{35}Cl, 40), 207 (24), 188 (15), 135 (12), 94 (5). HRMS (EI) calcd for $C_{15}H_{10}ClO_3F_3$ ([M^+], ^{35}Cl): 330.02651, found: 330.026277.

3.5.9. Methyl 4′-chloro-3-hydroxy-2-methyl-5-(trifluoromethyl)-biphenyl-4-carboxylate (**5i**)

Starting with **3c** (0.483 g, 1.5 mmol), **4b** (0.452 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5i** was isolated as a slightly yellow viscous oil (0.270 g, 52%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.03 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 7.02 (s, 1H, CH_{Ar}), 7.07 (d, ^3J=8.3 Hz, 2H, CH_{clph}), 7.26 (d, ^3J=8.7 Hz, 2H, CH_{Clph}), 11.03 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.66. ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.8 (CH_3), 52.0 (OCH_3), 108.0 (*C*COOMe), 119.1 (q, $^3J_{C,F}$=7.7 Hz, CH_{Ar}), 122.5 (d, $^1J_{C,F}$=274.2 Hz, CF_3), 126.3 (d, $^2J_{F,C}$=33.2 Hz, C_{Ar}), 127.7 ($2CH_{Clph}$), 128.5 (C_{Ar}), 129.3 ($2CH_{Clph}$), 133.3, 137.2 (C_{Clph}), 144.7 (C_{Ar}), 159.7 (COH), 169.3 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3008 (w), 2956 (w), 2926 (w), 2855 (w), 1671 (w), 1610 (w), 1575 (w), 1559 (w), 1493 (w), 1439 (w), 1405 (w), 1336 (m), 1309 (m), 1281 (s), 1245 (w), 1203 (m), 1133 (s), 1090 (m), 1015 (m), 987 (w), 937 (w), 905 (m), 889 (w), 833 (m), 808 (w), 773 (w), 729 (s), 681 (w), 652 (w), 642 (w), 601 (w), 537 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=346 ([M^+], ^{37}Cl, 20), 344 ([M^+], ^{35}Cl, 61), 314 (^{37}Cl, 23), 313 (^{37}Cl, 56), 312 (^{35}Cl, 65), 311 (^{35}Cl, 100), 278 (15), 277 (94), 257 (24), 249 (29), 219 (9), 201 (35), 170 (6), 152 (21), 138 (11), 114 (11), 100 (8), 75 (7). HRMS (EI) calcd for $C_{16}H_{12}ClO_3F_3$ ([M^+], ^{35}Cl): 344.04216, found: 344.041922.

3.5.10. Ethyl 4′-chloro-2-ethyl-3-hydroxy-5-(trifluoromethyl)-biphenyl-4-carboxylate (**5j**)

Starting with **3c** (0.483 g, 1.5 mmol), **4c** (0.495 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5j** was isolated as a yellowish viscous oil (0.210 g, 38%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.99 (t, ^3J=7.5 Hz, 3H, CH_2CH_3), 1.33 (t, ^3J=7.0 Hz, 3H, OCH_2CH_3), 2.52 (q, ^3J=7.5 Hz, 2H, CH_2CH_3), 4.37 (q, ^3J=7.0 Hz, 2H, OCH_2CH_3), 7.04 (s, 1H, CH_{Ar}), 7.12 (d, ^3J=8.5 Hz, 2H, CH_{Clph}), 7.32 (d, ^3J=8.5 Hz, 2H, CH_{Clph}), 11.14 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−57.94. ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.6, 12.8 ($2CH_3$), 19.9 (CH_2), 61.7 (OCH_2), 109.1 (C_{Ar}-COOMe), 119.5 (q, $^3J_{F,C}$=7.5 Hz, CH_{Ar}), 122.8 (d, $^1J_{F,C}$=240.8 Hz, CF_3), 126.2 (d, $^2J_{F,C}$=34.7 Hz, C_{Ar}), 127.8 ($2CH_{Clph}$), 129.1 ($2CH_{Clph}$), 133.2 (C_{Ar}), 134.4, 137.5 ($2C_{Clph}$), 144.5 (C_{Ar}), 159.6 (COH), 168.8 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2982 (w), 2966 (w), 2932 (w), 2876 (w), 2855 (w), 1668 (w), 1610 (w), 1493 (w), 1464 (w), 1399 (w), 1372 (m), 1331 (w), 1290 (s), 1261 (w), 1230 (w), 1201 (w), 1136 (s), 1091 (w), 1061 (w), 1018 (w), 986 (w), 942 (w), 906 (w), 888 (w), 867 (w), 833 (w), 815 (w), 729 (m), 651 (w), 639 (w), 597 (w), 538 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=374 ([M^+], ^{37}Cl, 12), 372 ([M^+], ^{35}Cl, 36), 328 (^{37}Cl, 10), 327 (^{37}Cl, 28), 326 (^{35}Cl, 26), 325 (^{35}Cl, 46), 298 (15), 292 (19), 291 (100), 263 (7), 243 (7), 201 (7), 165 (10). HRMS (EI) calcd for $C_{18}H_{16}ClO_3F_3$ ([M^+], ^{35}Cl): 372.07346, found: 372.073126.

3.5.11. Methyl 4′-chloro-2-hexyl-3-hydroxy-5-(trifluoromethyl)-biphenyl-4-carboxylate (**5k**)

Starting with **3c** (0.483 g, 1.5 mmol), **4d** (0.568 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **5k** was isolated as a slightly yellow viscous oil (0.251 g, 40%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.73 (t,

^3J=6.3 Hz, 3H, CH_3), 1.03–1.16 (m, 6H, CH_2), 1.30–1.42 (m, 2H, CH_2), 2.49 (t, ^3J=7.6 Hz, 2H, CH_2), 3.90 (s, 3H, OCH_3), 7.04 (s, 1H, CH_{Ar}), 7.11 (d, ^3J=8.4 Hz, 2H, CH_{Clph}), 7.32 (d, ^3J=8.4 Hz, 2H, CH_{Clph}), 11.0 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−57.94. ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 (CH_3), 22.6, 27.5, 29.1, 29.5, 31.5 (5 CH_2), 53.0 (OCH_3), 109.1 (*C*COOMe), 120.4 (q, $^3J_{C,F}$=6.4 Hz, CH_{Ar}), 123.5 (d, $^1J_{C,F}$=269.9 Hz, CF_3), 127.2 (d, $^2J_{C,F}$=33.2 Hz, C_{Ar}), 128.7 ($2CH_{Clph}$), 130.1 ($2CH_{Clph}$), 134.1 (C_{Ar}), 134.4, 138.5 ($2C_{Clph}$), 145.8 (C_{Ar}), 160.5 (COH), 170.3 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2955 (w), 2926 (w), 2856 (w), 1674 (w), 1611 (w), 1493 (w), 1440 (w), 1403 (w), 1339 (w), 1298 (w), 1283 (m), 1237 (w), 1202 (w), 1143 (m), 1092 (w), 1016 (w), 949 (w), 908 (w), 888 (w), 833 (w), 814 (w), 730 (w), 687 (w), 651 (w), 598 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=416 ([M^+], ^{37}Cl, 18), 414 ([M^+], ^{35}Cl, 52), 384 (^{37}Cl, 19), 383 (^{37}Cl, 29), 382 (^{35}Cl, 46), 381 (^{35}Cl, 30), 367 (^{37}Cl, 10), 365 (^{35}Cl, 14), 354 (12), 348 (22), 347 (100), 325 (9), 314 (11), 313 (27), 312 (31), 311 (62), 291 (14), 289 (9), 257 (10), 256 (12), 249 (19), 248 (8), 243 (10), 201 (16). HRMS (EI) calcd for $C_{21}H_{22}ClO_3F_3$ ([M^+], ^{35}Cl): 414.12041, found: 414.119859.

3.5.12. *Methyl 4′-chloro-3-hydroxy-2-octyl-5-(trifluoromethyl)-biphenyl-4-carboxylate (**5l**)*

Starting with **3c** (0.483 g, 1.5 mmol), **4e** (0.614 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5l** was isolated as a yellowish viscous oil (0.300 g, 45%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.74 (t, ^3J=6.2 Hz, 3H, CH_3CH_2), 1.04–1.20 (m, 10H, CH_2), 1.30–1.41 (m, 2H, CH_2), 2.48 (t, ^3J=7.7 Hz, 2H, CH_2), 3.90 (s, 3H, OCH_3), 7.04 (s, 1H, CH_{Ar}), 7.11 (d, ^3J=8.7 Hz, 2H, CH_{Clph}), 7.32 (d, ^3J=8.5 Hz, 2H, CH_{Clph}), 11.0 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.66. ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.2 (CH_3), 22.8, 27.4, 29.2, 29.3,29.4, 29.8, 31.9 ($5CH_2$), 53.0 (OCH_3), 109.6 (*C*COOMe), 120.4 (q, $^3J_{C,F}$=7.0 Hz, CH_{Ar}), 123.5 (d, $^1J_{C,F}$=272.3 Hz, CF_3), 127.2 (d, $^2J_{C,F}$=32.1 Hz, C_{Ar}), 128.7 ($2CH_{Clph}$), 130.1 ($2CH_{Clph}$), 134.1 (C_{Ar}), 134.4, 138.5 (C_{Clph}), 145.8 (C_{Ar}), 160.5 (COH), 170.3 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2954 (w), 2924 (w), 2853 (w), 1672 (m), 1610 (w), 1572 (w), 1492 (w), 1439 (m), 1403 (w), 1336 (m), 1282 (s), 1229 (w), 1200 (s), 1133 (s), 1089 (m), 1015 (m), 994 (w), 955 (w), 907 (w), 887 (w), 832 (s), 813 (w), 758 (w), 728 (m), 685 (w), 655 (w), 643 (w), 598 (w), 537 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=444 ([M^+], ^{37}Cl, 16), 442 ([M^+], ^{35}Cl, 45), 412 (^{37}Cl, 19), 411 (^{37}Cl, 31), 410 (^{35}Cl, 49), 409 (^{35}Cl, 29), 393 (16), 376 (24), 375 (100), 325 (10), 314 (12), 313 (29), 312 (37), 311 (70), 299 (12), 297 (16), 291 (17), 289 (13), 278 (10), 277 (59), 257 (12), 256 (14), 249 (20), 248 (10), 243 (12), 220 (12), 219 (12), 201 (15), 43 (13), 41 (15). HRMS (EI) calcd for $C_{23}H_{26}ClO_3F_3$ ([M^+], ^{35}Cl): 442.15171, found: 442.151120.

3.5.13. *Methyl 4′-chloro-3-hydroxy-2-methoxy-5-(trifluoromethyl)-biphenyl-4-carboxylate (**5m**)*

Starting with **3c** (0.483 g, 1.5 mmol), **4g** (0.360 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5m** was isolated as a colourless viscous oil (0.200 g, 37%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.59 (s, 3H, OMe), 3.93 (s, 3H, COOMe), 7.19 (s, 1H, CH_{Ar}), 7.35 (d, ^3J=9 Hz, 2H, CH_{Clph}), 7.42 (d, ^3J=8.7 Hz, 2H, CH_{Clph}), 10.01 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.72. ^{13}C NMR (75 MHz, $CDCl_3$): δ=53.0, 60.7 (OMe), 112.8 (*C* COOMe), 120.1 (q, $^3J_{C,F}$=12.7 Hz, CH_{Ar}), 123.1 (d, $^1J_{C,F}$=260.9 Hz, CF_3), 124.7 (d, $^2J_{C,F}$=42.9 Hz, C_{Ar}) 128.8 ($2CH_{Clph}$), 130.2 ($2CH_{Clph}$), 134.4 (C_{Ar}), 134.6, 136.7 (C_{Clph}), 148.3 (C_{Ar}OMe), 154.4 (COH), 168.7 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3399 (w), 3006 (w), 2954 (w), 2930 (w), 2852 (w), 1741 (w), 1673 (w), 1609 (w), 1492 (w), 1442 (w), 1415 (w), 1388 (m), 1371 (m), 1321 (m), 1281 (s), 1265 (s), 1247 (s), 1200 (w), 1138 (s), 1090 (m), 1027 (m), 1016 (w), 978 (w), 950 (m), 904 (m), 833 (m), 811 (w), 789 (w), 728 (s), 665 (w), 649 (w), 636 (w), 534 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=362 ([M^+], ^{37}Cl, 18), 360 ([M^+], ^{35}Cl, 51), 330 (^{37}Cl, 29), 329 (^{37}Cl, 57), 328 (^{35}Cl, 80), 327 (^{35}Cl, 100), 309 (^{37}Cl, 11), 307 (^{35}Cl, 16), 300 (11), 299 (10), 293 (39), 282 (14), 273 (15), 265 (14), 250 (10), 229 (13), 175 (9), 146 (21), 121 (10). HRMS (EI) calcd for $C_{16}H_{12}ClO_3F_3$ ([M^+], ^{35}Cl): 360.03707, found: 360.036271.

3.5.14. *4′-Fluoro-3-hydroxy-5-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester (**5n**)*

Starting with **3d** (0.433 g, 1.41 mmol), **4a** (0.430 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5n** was isolated as a pale yellow solid (0.234 g, 53%), mp=69–71 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=4.01 (s, 3H, OCH_3), 7.17 (dd, $^3J_{H,H}$=$^3J_{H,F}$=8.7 Hz, 2H, CFC*H*), 7.37 (d, ^4J=1.7 Hz, 1H, Ar*H*), 7.50 (d, ^4J=1.6 Hz, 1H, Ar*H*), 7.58 (dd, $^3J_{H,H}$=8.9 Hz, $^4J_{H,F}$=5.2 Hz, 2H, CFCHC*H*), 10.86 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−112.5 (C*F*), −58.8 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.9 (OCH_3), 109.6 (C_q), 116.1 (d, ^2J=21.9 Hz, CFCH), 117.9 (q, ^3J=6.8 Hz, *C*HCCF$_3$), 119.6 (*C*H), 123.3 (q, ^1J=273.6 Hz, *C*F$_3$), 128.9 (d, ^3J=8.4 Hz, CFCHCH), 131.0 (q, ^2J=32.0 Hz, *C*CF$_3$), 134.4 (d, ^4J=3.3 Hz, CFCHCH*C*), 145.7 (C_q), 162.3 (*C*OH), 163.4 (d, ^1J=249.4 Hz, *C*F), 169.5 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3016 (w), 2958 (w), 2925 (w), 2854 (w), 1661 (m), 1600 (m), 1516 (m), 1438 (m), 1371 (m), 1347 (m), 1322 (m), 1293 (m), 1240 (m), 1221 (m), 1202 (m), 1174 (m), 1136 (s), 1056 (m). MS (EI, 70 eV): *m*/*z* (%)=314 (M^+, 52), 282 (100), 254 (517), 235 (10), 226 (15), 206 (22), 157 (22). HRMS (EI, 70 eV) calcd for $C_{15}H_{10}F_4O_3$ (M^+): 314.05606, found: 314.05584. Anal. Calcd for $C_{15}H_{10}F_4O_3$ (314.23): C, 57.33; H, 3.21. Found: C, 57.43; H, 3.14.

3.5.15. *4′-Fluoro-3-hydroxy-5-trifluoromethyl-biphenyl-4-carboxylic acid ethyl ester (**5o**)*

Starting with **3d** (2.426 g, 7.92 mmol), **4h** (2.391 g, 8.71 mmol) and $TiCl_4$ (0.96 mL, 8.71 mmol), **5o** was isolated as a yellow solid (0.840 g, 32%), mp=44–45 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.43 (t, ^3J=7.2 Hz, 3H, CH_2CH_3), 4.47 (q, ^3J=7.2 Hz, 2H, CH_2CH_3), 7.12–7.22 (m, 2H, Ar*H*), 7.37 (d, ^4J=1.7 Hz, 1H, Ar*H*), 7.49 (d, ^4J=1.7 Hz, 1H, Ar*H*), 7.54–7.64 (m, 2H, Ar*H*), 10.99 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−112.6 (C*F*), −58.1 (CF_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ=13.5 (CH_2CH_3), 62.4 (CH_2CH_3), 109.8 (d, ^5J=1.4 Hz, CFCHCHC*C*), 116.1 (d, ^2J=21.7 Hz, CFCH), 117.9 (q, ^3J=6.9 Hz, *C*HCCF$_3$), 119.6 (*C*H), 123.3 (q, ^1J=273.6 Hz, *C*F$_3$), 128.9 (d, ^3J=8.4 Hz, CFCHCH), 130.9 (q, ^2J=31.9 Hz, *C*CF$_3$), 134.5 (d, ^4J=3.4 Hz, CFCHCH*C*), 145.5 (C_q), 162.4 (*C*OH), 163.4 (d, ^1J=249.4 Hz, *C*F), 169.1 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3012 (w), 2987 (w), 2943 (w), 2871 (w), 1665 (m), 1599 (m), 1568 (w), 1512 (m), 1468 (w), 1431 (w), 1400 (m), 1366 (m), 1331 (m), 1303 (m), 1288 (m), 1240 (m), 1216 (m), 1137 (s), 1101 (m), 1058 (m). MS (EI, 70 eV): *m*/*z* (%)=328 (M^+, 43), 282 (100), 254 (42), 226 (11), 206 (19), 157 (18). HRMS (EI, 70 eV) calcd for $C_{16}H_{12}F_4O_3$ (M^+): 328.07171, found: 328.07164. Anal. Calcd for $C_{16}H_{12}F_4O_3$ (328.26): C, 58.54; H, 3.68. Found: C, 58.69; H, 3.57.

3.5.16. *1-(4′-Fluoro-3-hydroxy-2-methyl-5-trifluoromethyl-biphenyl-4-yl)-propan-1-one (**5p**)*

Starting with **3d** (0.430 g, 1.40 mmol), **4b** (0.453 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5p** was isolated as a colourless solid (0.279 g, 61%), mp=96–97 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.20 (s, 3H, ArCH_3), 4.01 (s, 3H, OCH_3), 7.10–7.19 (m, 2H, Ar*H*), 7.20 (s, 1H, Ar*H*), 7.24–7.32 (m, 2H, Ar*H*), 11.18 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−113.9 (C*F*), −58.7 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.7 (ArCH_3), 52.9 (OCH_3), 108.8 (C_q), 115.4 (d, ^2J=21.5 Hz, CFCH), 120.2 (q, ^3J=6.7 Hz, *C*HCCF$_3$), 123.4 (q, ^1J=272.8 Hz, *C*F$_3$), 127.1 (q, ^2J=32.1 Hz, *C*CF$_3$), 129.5 (C_q), 130.6 (d, ^3J=8.2 Hz, CFCHCH), 135.7 (d, ^4J=3.5 Hz, CFCHCH*C*), 145.9 (C_q), 160.7 (*C*OH), 162.5 (d, ^1J=247.7 Hz, *C*F), 170.2 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3074 (w), 3052 (w), 3011 (w), 2958 (w), 1661 (m), 1614 (w), 1573 (w), 1506 (w), 1438 (m), 1387 (w), 1366 (w), 1338 (m), 1282 (m), 1248 (m), 1208 (m), 1197 (m), 1161 (m), 1131 (s), 1095 (m), 1024 (m). MS (EI, 70 eV): *m*/*z* (%)=328 (M^+, 37), 295 (100), 268 (9), 219 (15), 199 (18), 170 (14); HRMS (EI, 70 eV) calcd for $C_{16}H_{12}F_4O_3$ (M^+): 328.07171, found: 328.07160. Anal. Calcd for $C_{16}H_{12}F_4O_3$ (328.26): C, 58.54; H, 3.68. Found: C, 58.41; H, 3.83.

*3.5.17. 2-Ethyl-4′-fluoro-3-hydroxy-5-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester (**5q**)*

Starting with **3d** (0.469 g, 1.53 mmol), **4i** (0.476 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5q** was isolated as a colourless solid (0.289 g, 55%), mp=72–74 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.10 (t, ^3J=7.4 Hz, 3H, CH_2CH_3), 2.63 (q, ^3J=7.4 Hz, 2H, CH_2CH_3), 4.01 (s, 3H, OCH_3), 7.09–7.19 (m, 3H, Ar*H*), 7.21–7.31 (m, 2H, Ar*H*), 11.14 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−114.1 (C*F*), −58.7 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.6 (CH_2CH_3), 20.8 (CH_2), 52.9 (OCH_3), 109.3 (C_q), 115.4 (d, ^2J=21.5 Hz, *C*HCF), 120.5 (q, ^3J=6.7 Hz, *C*HCCF$_3$), 123.4 (q, ^1J=273.2 Hz, *C*F$_3$), 127.1 (q, ^3J=32.0 Hz, *C*CF$_3$), 130.3 (d, ^3J=8.1 Hz, *C*HCHCF), 135.5 (C_q), 135.9 (d, ^4J=3.5 Hz, *C*CHCHCF), 145.8 (C_q), 160.4 (*C*OH), 162.5 (d, ^1J=247.2 Hz, *C*F), 170.2 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2988 (w), 2966 (w), 2939 (w), 2876 (w), 1678 (m), 1602 (w), 1512 (m), 1440 (m), 1365 (m), 1336 (m), 1293 (m), 1261 (m), 1225 (m), 1199 (m), 1142 (s), 1124 (s), 1094 (s), 1060 (m). MS (EI, 70 eV): *m*/*z* (%)=342 (M$^+$, 44), 309 (100), 282 (27), 267 (14), 219 (13), 183 (12). HRMS (EI, 70 eV) calcd for $C_{17}H_{14}F_4O_3$ (M$^+$): 342.08736, found: 342.08706.

*3.5.18. 1-(4′-Fluoro-3-hydroxy-5-trifluoromethyl-biphenyl-4-yl)-ethanone (**5r**)*

Starting with **3d** (0.448 g, 1.46 mmol), **4j** (0.403 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5r** was isolated as a pale red solid (0.296 g, 68%), mp=125–128 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.10 (t, ^3J=7.4 Hz, 3H, CH_2CH_3), 2.63 (q, ^3J=7.4 Hz, 2H, CH_2CH_3), 4.01 (s, 3H, OCH_3), 7.09–7.19 (m, 3H, Ar*H*), 7.21–7.31 (m, 2H, Ar*H*), 11.14 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−114.1 (C*F*), −58.7 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.6 (CH_2CH_3), 20.8 (CH_2), 52.9 (OCH_3), 109.3 (C_q), 115.4 (d, ^2J=21.5 Hz, *C*HCF), 120.5 (q, ^3J=6.7 Hz, *C*HCCF$_3$), 123.4 (q, ^1J=273.2 Hz, *C*F$_3$), 127.1 (q, ^3J=32.0 Hz, *C*CF$_3$), 130.3 (d, ^3J=8.1 Hz, *C*HCHCF), 135.5 (C_q), 135.9 (d, ^4J=3.5 Hz, *C*CHCHCF), 145.8 (C_q), 160.4 (*C*OH), 162.5 (d, ^1J=247.2 Hz, *C*F), 170.2 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2988 (w), 2966 (w), 2939 (w), 2876 (w), 1678 (m), 1602 (w), 1512 (m), 1440 (m), 1365 (m), 1336 (m), 1293 (m), 1261 (m), 1225 (m), 1199 (m), 1142 (s), 1124 (s), 1094 (s), 1060 (m). MS (EI, 70 eV): *m*/*z* (%)=342 (M$^+$, 44), 309 (100), 282 (27), 267 (14), 219 (13), 183 (12). HRMS (EI, 70 eV) calcd for $C_{17}H_{14}F_4O_3$ (M$^+$): 342.08736, found: 342.08706.

*3.5.19. 1-4′-Bromo-3-hydroxy-2-methyl-5-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester (**5s**)*

Starting with **3e** (0.817 g, 2.22 mmol), **4b** (0.686 g, 2.50 mmol) and $TiCl_4$ (0.28 mL, 2.50 mmol), **5s** was isolated as a colourless solid (0.559 g, 65%), mp=85–86 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.20 (s, 3H, ArCH_3), 4.01 (s, 3H, OCH_3), 7.16 (s, 1H, Ar*H*), 7.19 (d, ^3J=8.5 Hz, 2H, Ar*H*), 7.59 (d, ^3J=8.5 Hz, 2H, Ar*H*), 11.18 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.7 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.7 (ArCH_3), 52.9 (OCH_3), 109.0 (C_q), 119.9 (q, ^3J=6.8 Hz, *C*HCCF$_3$), 122.3 (C_q), 123.4 (q, ^1J=273.1 Hz, *C*F$_3$), 127.2 (q, ^2J=32.1 Hz, *C*CF$_3$), 129.3 (C_q), 130.5 (*C*H), 131.6 (*C*H), 138.6 (C_q), 145.6 (C_q), 160.7 (*C*OH), 170.1 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3400 (w), 3011 (w), 2972 (w), 2958 (w), 1694 (m), 1607 (w), 1589 (m), 1502 (w), 1483 (w), 1439 (m), 1410 (w), 1357 (m), 1318 (m), 1279 (m), 1260 (m), 1200 (m), 1131 (s), 1106 (s), 1072 (m), 1018 (m), 1009 (m). MS (EI, 70 eV): *m*/*z* (%)=390 (M$^+$, ^{81}Br, 50), 388 (M$^+$, ^{79}Br, 51), 358 (61), 357 (76), 356 (62), 355 (59), 277 (100), 257 (36), 201 (57), 152 (30). HRMS (EI, 70 eV) calcd for $C_{16}H_{12}^{79}BrF_3O_3$ (M$^+$): 387.99164, found: 387.99125; calcd for $C_{16}H_{12}^{81}BrF_3O_3$ (M$^+$): 389.98960, found: 389.98956. Anal. Calcd for $C_{16}H_{12}BrF_3O_3$ (389.16): C, 49.38; H, 3.11; Br, 20.53. Found: C, 49.53; H, 3.05; Br, 20.35.

*3.5.20. 4′-Bromo-3-hydroxy-2-methoxy-5-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester (**5t**)*

Starting with **3e** (0.734 g, 1.97 mmol), **4g** (0.639 g, 2.20 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol), **5t** was isolated as a pale red solid (0.248 g, 31%), mp=80–83 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.68 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.27 (s, 1H, Ar*H*), 7.44 (d, ^3J=8.6 Hz, 2H, Ar*H*), 7.60 (d, ^3J=8.6 Hz, 2H, Ar*H*), 8.78 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.7 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=53.0 (OCH_3), 60.7 (OCH_3), 112.9 (C_q), 120.1 (q, ^3J=6.5 Hz, *C*HCCF$_3$), 122.9 (C_q), 123.2 (q, ^1J=273.1 Hz, *C*F$_3$), 124.7 (q, ^2J=32.3 Hz, *C*CF$_3$), 128.6 (*C*H), 130.6 (*C*H), 134.9 (C_q), 136.7 (C_q), 148.3 (C_q), 154.4 (*C*OH), 168.7 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922 (w), 2850 (w), 1665 (m), 1634 (w), 1491 (w), 1446 (m), 1415 (m), 1386 (m), 1341 (m), 1288 (s), 1269 (s), 1255 (s), 1200 (m), 1160 (m), 1120 (s), 1071 (m), 1029 (m), 1008 (m). MS (EI, 70 eV): *m*/*z* (%)=406 (^{81}Br, M$^+$, 51), 404 (^{79}Br, M$^+$, 52), 373 (100), 371 (78), 293 (42), 273 (30), 250 (39), 146 (18). HRMS (EI, 70 eV) calcd for $C_{16}H_{12}^{79}BrF_3O_4$ (M$^+$): 403.98656, found: 403.98622; calcd for $C_{16}H_{12}^{81}BrF_3O_4$ (M$^+$): 405.98451, found: 405.98440.

*3.5.21. 1-(4′-Bromo-3-hydroxy-5-trifluoromethyl-biphenyl-4-yl)-ethanone (**5u**)*

Starting with **3e** (0.867 g, 2.36 mmol), **4j** (0.660 g, 2.70 mmol) and $TiCl_4$ (0.30 mL, 2.70 mmol), **5u** was isolated as a pale yellow solid (0.575 g, 68%), mp=130–133 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.67 (q, ^6J=1.8 Hz, 3H, CH_3), 7.34 (d, ^4J=1.8 Hz, 1H, Ar*H*), 7.42–7.49 (m, 3H, Ar*H*), 7.58–7.64 (m, 2H, Ar*H*), 9.92 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−55.7 (CF_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ=31.5 (q, ^5J=5.3 Hz, *C*H$_3$), 117.3 (q, ^3J=5.8 Hz, *C*HCCF$_3$), 119.8 (*C*H), 120.8 (C_q), 123.5 (C_q), 123.7 (q, ^1J=273.3 Hz, *C*F$_3$), 128.6 (*C*H), 129.5 (q, ^2J=31.7 Hz, *C*CF$_3$), 132.3 (*C*H), 137.1 (C_q), 144.6 (C_q), 158.6 (*C*OH), 204.6 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3171 (w), 3072 (w), 2926 (w), 2851 (w), 1683 (m), 1612 (m), 1588 (m), 1563 (w), 1488 (m), 1431 (m), 1391 (m), 1338 (m), 1290 (m), 1246 (m), 1153 (m), 1129 (s), 1108 (m), 1075 (m), 1011 (m). MS (EI, 70 eV): *m*/*z* (%)=360 (M$^+$, ^{81}Br, 38), 358 (M$^+$, ^{79}Br, 38), 345 (98), 343 (100), 297 (20), 295 (23), 188 (30), 139 (10). HRMS (EI, 70 eV) calcd for $C_{15}H_{10}^{79}BrF_3O_2$ (M$^+$): 357.98108, found: 357.98198; calcd for $C_{15}H_{10}^{81}BrF_3O_2$ (M$^+$): 359.97903, found: 359.97903. Anal. Calcd for $C_{15}H_{10}BrF_3O_2$ (359.14): C, 50.16; H, 2.81; Br, 22.25. Found: C, 50.04; H, 2.75; Br, 22.21.

*3.5.22. 1-(4′-Bromo-3-hydroxy-2-methyl-5-trifluoromethyl-biphenyl-4-yl)-propan-1-one (**5v**)*

Starting with **3e** (0.769 g, 2.09 mmol), 1,3-bis-silyl enol ether **4k** (0.600 g, 2.20 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol), **5v** was isolated as a pale yellow solid (0.497 g, 61%), mp=110–114 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.22 (t, ^3J=7.2 Hz, 3H, CH_2CH_3), 2.19 (s, 3H, ArCH_3), 2.94 (q, ^3J=7.3 Hz, 2H, CH_2CH_3), 7.13 (s, 1H, Ar*H*), 7.17 (d, ^3J=8.5 Hz, 2H, Ar*H*), 7.59 (d, ^3J=8.5 Hz, 2H, Ar*H*), 8.98 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−55.7 (CF_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ=8.8 (CH_3), 13.6 (CH_3), 37.2 (q, ^5J=4.4 Hz, CH_2), 119.7 (q, ^3J=5.4 Hz, *C*HCCF$_3$), 121.1 (C_q), 122.3 (C_q), 123.9 (q, ^1J=273.9 Hz, *C*F$_3$), 126.8 (q, ^2J=31.8 Hz, *C*CF$_3$), 128.9 (C_q), 130.5 (*C*H), 131.7 (*C*H), 138.5 (C_q), 144.4 (C_q), 155.2 (*C*OH), 208.6 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3435 (w), 2997 (w), 2979 (w), 2943 (w), 2919 (w), 1678 (m), 1610 (w), 1591 (w), 1556 (w), 1480 (m), 1415 (w), 1352 (m), 1313 (m), 1257 (s), 1198 (m), 1173 (m), 1144 (m), 1110 (s), 1099 (s), 1072 (m), 1045 (m). MS (EI, 70 eV): *m*/*z* (%)=388 (M$^+$, ^{81}Br, 15), 386 (M$^+$, ^{79}Br, 14), 359 (95), 357 (100), 311 (15), 309 (15), 201 (19); HRMS (EI, 70 eV) calcd for $C_{17}H_{14}^{79}BrF_3O_2$ (M$^+$): 386.01238, found: 386.01156, calcd for $C_{17}H_{14}^{81}BrF_3O_2$ (M$^+$): 388.01033, found: 388.01127. Anal. Calcd for $C_{17}H_{14}BrF_3O_2$ (388.19): C, 52.73; H, 3.64; Br, 20.64. Found: C, 52.78; H, 3.52; Br, 20.66.

*3.5.23. 5-Hydroxy-4′-nitro-3-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester (**5w**)*

Starting with **3f** (0.516 g, 1.55 mmol), **4a** (0.430 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5w** was isolated as a pale yellow solid (0.377 g, 71%), mp=135–137 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=4.03 (s, 3H, OCH_3), 7.45 (d, ^4J=1.6 Hz, 1H, Ar*H*), 7.54 (d, ^4J=1.6 Hz, 1H, Ar*H*), 7.77 (d, ^3J=8.9 Hz, 2H, Ar*H*), 8.34 (d, ^3J=8.9 Hz, 2H, Ar*H*), 10.83 (s, 1H,

O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.9 (C*F*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=53.2 (O*C*H$_3$), 111.0 (*C*$_q$), 118.0 (q, ^3J=6.8 Hz, *C*HCCF$_3$), 120.5 (*C*HCOH), 123.0 (q, ^1J=274.1 Hz, *C*F$_3$), 124.3 (*C*H), 128.1 (*C*H), 131.4 (q, ^2J=32.3 Hz, *C*CF$_3$), 144.1 (*C*$_q$), 144.5 (*C*$_q$), 148.1 (*C*$_q$), 162.2 (*C*OH), 169.2 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3113 (w), 3083 (w), 2958 (w), 2862 (w), 1668 (m), 1596 (w), 1520 (m), 1443 (m), 1344 (m), 1293 (m), 1210 (m), 1138 (s), 1105 (m), 1060 (m). MS (EI, 70 eV): *m*/*z* (%)=341 (M$^+$, 35), 309 (100), 281 (17), 251 (14), 206 (13). HRMS (EI, 70 eV) calcd for $C_{15}H_{10}F_3NO_5$ (M$^+$): 341.05056, found: 341.05088.

3.5.24. 3-Hydroxy-2-methyl-4′-nitro-5-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester (**5x**)

Starting with **3f** (0.500 g, 1.50 mmol), **4b** (0.453 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5x** was isolated as a pale yellow solid (0.274 g, 51%), mp=199–201 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.20 (s, 3H, ArC*H*$_3$), 4.02 (s, 3H, OC*H*$_3$), 7.19 (s, 1H, Ar*H*), 7.49 (d, ^3J=8.8 Hz, 2H, Ar*H*), 8.33 (d, ^3J=8.8 Hz, 2H, Ar*H*), 11.21 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.7 (C*F*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.7 (ArCH$_3$), 53.1 (OCH$_3$), 109.7 (*C*$_q$), 119.5 (q, ^3J=6.8 Hz, *C*HCCF$_3$), 123.2 (q, ^1J=273.0 Hz, *C*F$_3$), 123.7 (*C*H), 127.6 (q, ^2J=32.3 Hz, *C*CF$_3$), 129.5 (*C*$_q$), 129.9 (*C*H), 144.4 (*C*$_q$), 146.3 (*C*$_q$), 147.6 (*C*$_q$), 160.7 (*C*OH), 169.9 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3111 (w), 3083 (w), 3013 (w), 2960 (w), 2929 (w), 2855 (w), 1665 (m), 1596 (w), 1567 (w), 1516 (m), 1441 (w), 1410 (w), 1334 (m), 1285 (m), 1247 (m), 1205 (m), 1132 (s), 1013 (m). MS (EI, 70 eV): *m*/*z* (%)=355 (M$^+$, 61), 323 (93), 306 (84), 276 (100), 257 (13), 201 (38), 152 (20). HRMS (EI, 70 eV) calcd for $C_{16}H_{12}F_3NO_5$ (M$^+$): 355.06621, found: 355.06610. Anal. Calcd for $C_{16}H_{12}F_3NO_5$ (355.27): C, 54.09; H, 3.40; N, 3.94. Found: C, 54.34; H, 3.37; N, 3.56.

3.5.25. 1-(5-Hydroxy-4′-nitro-3-trifluoromethyl-biphenyl-4-yl)-ethanone (**5y**)

Starting with **3f** (0.482 g, 1.45 mmol), **4j** (0.403 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5y** was isolated as a pale red solid (0.303 g, 64%), mp=167–169 °C. ^{1}H NMR (250 MHz, $(CD_3)_2CO$): δ=2.61 (s, 3H, C*H*$_3$), 7.61 (s, 1H, Ar*H*), 7.63 (s, 1H, Ar*H*), 8.03 (d, ^3J=8.9 Hz, 2H, Ar*H*), 8.40 (d, ^3J=8.9 Hz, 2H, Ar*H*), 9.87 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $(CD_3)_2CO$): δ=−53.8 (C*F*$_3$). ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ=31.8 (*C*H$_3$), 117.1 (q, ^3J=5.0 Hz, *C*HCCF$_3$), 119.3 (*C*HCOH), 124.6 (q, ^1J=273.5 Hz, *C*F$_3$), 125.0 (*C*H), 128.8 (q, ^2J=31.9 Hz, *C*CF$_3$), 129.2 (*C*H), 129.7 (*C*$_q$), 141.9 (*C*$_q$), 146.0 (*C*$_q$), 148.8 (*C*$_q$), 155.7 (*C*OH), 201.4 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3457 (w), 3084 (w), 3012 (w), 2923 (w), 2852 (w), 1696 (m), 1615 (w), 1597 (w), 1582 (w), 1519 (m), 1438 (m), 1348 (s), 1323 (m), 1247 (m), 1144 (m), 1126 (s), 1115 (s). MS (EI, 70 eV): *m*/*z* (%)=325 (M$^+$, 22), 310 (100), 264 (21), 188 (7). HRMS (EI, 70 eV) calcd for $C_{15}H_{10}F_3NO_4$ (M$^+$): 325.05564, found: 325.05522.

3.5.26. 3-Hydroxy-5,4′-bis(trifluoromethyl)-biphenyl-4-carboxylic acid methyl ester (**5z**)

Starting with **3g** (0.718 g, 2.01 mmol), **4a** (0.573 g, 2.20 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol), **5z** was isolated as a pale yellow solid (0.510 g, 69%), mp=70–72 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=4.02 (s, 3H, OC*H*$_3$), 7.43 (d, ^4J=1.8 Hz, 1H, Ar*H*), 7.54 (d, ^4J=1.7 Hz, 1H, Ar*H*), 7.67–7.78 (m, 4H, Ar*H*), 10.83 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−62.7 (C*F*$_3$), −58.9 (C*F*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=53.1 (OCH$_3$), 110.5 (*C*$_q$), 118.0 (q, ^3J=6.8 Hz, *C*HCCF$_3$), 120.2 (*C*HCOH), 123.2 (q, ^1J=273.5 Hz, *C*F$_3$), 123.9 (q, ^1J=272.0 Hz, *C*F$_3$), 126.1 (q, ^3J=3.8 Hz, CF$_3$C*C*HCH), 127.6 (*C*H), 131.1 (q, ^2J=32.7 Hz, *C*CF$_3$), 131.2 (q, ^2J=32.2 Hz, *C*CF$_3$), 141.8 (*C*$_q$), 145.1 (*C*$_q$), 162.2 (*C*OH), 169.4 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3233 (w), 3071 (w), 2961 (w), 2901 (w), 1682 (m), 1617 (m), 1563 (w), 1485 (w), 1360 (m), 1348 (m), 1322 (s), 1294 (s), 1274 (s), 1205 (m), 1172 (m), 1139 (s), 1108 (s), 1070 (s), 1054 (s), 1014 (m). MS (EI, 70 eV): *m*/*z* (%)=364 (M$^+$, 38), 332 (100), 304 (56), 285 (10), 207 (20), 188 (11). HRMS (EI, 70 eV) calcd for $C_{16}H_{10}F_3O_3$ (M$^+$): 364.05286, found: 364.05252. Anal. Calcd for $C_{16}H_{10}F_6O_3$ (364.24): C, 52.76; H, 2.77. Found: C, 52.35; H, 2.91.

3.5.27. 3-Hydroxy-2-methyl-5,4′-bis(trifluoromethyl)-biphenyl-4-carboxylic acid methyl ester (**5aa**)

Starting with silyl enol ether **3g** (0.659 g, 1.85 mmol), 1,3-bis-silyl enol ether **4b** (0.604 g, 2.20 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol), **5aa** was isolated as a colourless solid (0.501 g, 72%), mp=90–91 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.20 (s, 3H, ArC*H*$_3$), 4.02 (s, 3H, OC*H*$_3$), 7.20 (s, 1H, Ar*H*), 7.43 (d, ^3J=8.1 Hz, 2H, Ar*H*), 7.73 (d, ^3J=8.1 Hz, 2H, Ar*H*), 11.20 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−62.7 (C*F*$_3$), −58.7 (C*F*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.7 (ArCH$_3$), 53.0 (OCH$_3$), 109.3 (*C*$_q$), 119.8 (q, ^3J=6.8 Hz, *C*HCCF$_3$), 123.3 (q, ^1J=273.2 Hz, *C*F$_3$), 124.0 (q, ^1J=272.6 Hz, *C*F$_3$), 125.5 (q, ^3J=3.8 Hz, CF$_3$CCHCH), 127.4 (q, ^2J=32.2 Hz, *C*CF$_3$), 129.3 (CF$_3$CCHCH), 129.5 (*C*$_q$), 130.2 (q, ^2J=32.7 Hz, *C*CF$_3$), 143.4 (*C*$_q$), 145.3 (*C*$_q$), 160.7 (*C*OH), 170.1 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3392 (w), 3083 (w), 2961 (w), 2856 (w), 1695 (m), 1610 (w), 1440 (m), 1359 (m), 1323 (s), 1200 (m), 1136 (s), 1108 (s), 1066 (s), 1014 (s). MS (EI, 70 eV): *m*/*z* (%)=378 (M$^+$, 52), 347 (29), 346 (65), 345 (100), 277 (86), 249 (22), 201 (24). Anal. Calcd for $C_{17}H_{12}F_6O_3$ (378.27): C, 53.98; H, 3.20. Found: C, 53.81; H, 3.32.

3.5.28. 2-Ethyl-3-hydroxy-5,4′-bis(trifluoromethyl)-biphenyl-4-carboxylic acid methyl ester (**5ab**)

Starting with **3g** (0.734 g, 2.06 mmol), **4i** (0.635 g, 2.20 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol), **5ab** was isolated as a pale red solid (0.508 g, 63%), mp=78–80 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.10 (t, ^3J=7.4 Hz, 3H, CH$_2$C*H*$_3$), 2.61 (q, ^3J=7.4 Hz, 2H, C*H*$_2$CH$_3$), 4.02 (s, 3H, OC*H*$_3$), 7.15 (s, 1H, Ar*H*), 7.42 (d, ^3J=8.0 Hz, 2H, Ar*H*), 7.72 (d, ^3J=8.1 Hz, 2H, Ar*H*), 11.14 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−62.6 (C*F*$_3$), −58.7 (C*F*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.7 (CH$_2$CH$_3$), 20.9 (*C*H$_2$), 53.0 (OCH$_3$), 109.8 (*C*$_q$), 120.1 (q, ^3J=6.7 Hz, *C*HCCF$_3$), 125.4 (q, ^3J=3.7 Hz, CF$_3$CCH), 127.3 (q, ^2J=32.3 Hz, *C*CF$_3$), 129.0 (*C*H), 130.2 (q, ^2J=32.8 Hz, *C*CF$_3$), 135.4 (*C*$_q$), 143.5 (*C*$_q$), 145.2 (*C*$_q$), 160.4 (*C*OH), 170.1 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2980 (w), 2959 (w), 2946 (w), 2883 (w), 1681 (m), 1607 (w), 1563 (w), 1485 (w), 1443 (m), 1411 (w), 1365 (m), 1321 (s), 1292 (s), 1264 (s), 1227 (m), 1198 (m), 1164 (s), 1126 (s), 1117 (s), 1101 (s), 1070 (s), 1058 (s), 1018 (m). MS (EI, 70 eV): *m*/*z* (%)=392 (M$^+$, 44), 359 (66), 317 (11), 291 (100), 263 (12). HRMS (EI, 70 eV) calcd for $C_{18}H_{14}F_6O_3$ (M$^+$): 392.08417, found: 392.08409.

3.5.29. 1-(3-Hydroxy-5,4′-bis(trifluoromethyl)-biphenyl-4-yl)-ethanone (**5ac**)

Starting with **3g** (0.696 g, 1.95 mmol), **4j** (0.538 g, 2.20 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol), **5ac** was isolated as a colourless solid (0.365 g, 54%), mp=141–143 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.68 (q, ^6J=1.7 Hz, 3H, C*H*$_3$), 7.39 (d, ^4J=1.5 Hz, 1H, Ar*H*), 7.48 (d, ^4J=1.2 Hz, 1H, Ar*H*), 7.66–7.78 (m, 4H, Ar*H*), 9.78 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−62.7 (C*F*$_3$), −55.8 (C*F*$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=31.6 (q, ^5J=5.1 Hz, *C*H$_3$), 117.6 (q, ^3J=5.6 Hz, *C*HCCF$_3$), 120.3 (*C*HCOH), 121.4 (*C*$_q$), 126.1 (q, ^3J=3.8 Hz, CF$_3$C*C*HCH), 129.6 (q, ^2J=31.7 Hz, *C*CF$_3$), 131.0 (q, ^2J=32.8 Hz, *C*CF$_3$), 141.7 (*C*$_q$), 144.3 (*C*$_q$), 158.4 (*C*OH), 204.5 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3176 (w), 1688 (m), 1651 (w), 1615 (w), 1594 (w), 1574 (w), 1440 (w), 1399 (m), 1364 (m), 1321 (s), 1292 (m), 1271 (m), 1246 (m), 1155 (m), 1113 (s), 1070 (s), 1047 (m), 1016 (m). MS (EI, 70 eV): *m*/*z* (%)=348 (M$^+$, 28), 333 (100), 285 (26), 237 (6), 188 (10). HRMS (EI, 70 eV) calcd for $C_{16}H_{10}F_6O_2$ (M$^+$): 348.05795, found: 348.05739. Anal. Calcd for $C_{16}H_{10}F_6O_2$ (348.24): C, 55.18; H, 2.89. Found: C, 54.89; H, 3.18.

3.5.30. 1-(3-Hydroxy-2-methyl-5,4′-bis(trifluoromethyl)-biphenyl-4-yl)-propan-1-one (**5ad**)

Starting with **3g** (0.698 g, 1.96 mmol), **4k** (0.600 g, 2.20 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol), **5ad** was isolated as a pale yellow solid (0.516 g, 70%), mp 111–112 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.23 (t, ^3J=7.2 Hz, 3H, CH$_2$C*H*$_3$), 2.19 (s, 3H, ArC*H*$_3$), 2.95 (q, ^3J=7.2 Hz, 2H, C*H*$_2$CH$_3$), 7.15 (s, 1H, Ar*H*), 7.43 (d, ^3J=8.0 Hz, 2H,

ArH), 7.72 (d, ^3J=8.0 Hz, 2H, ArH), 8.95 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−62.7 (CF_3), −55.7 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.7 (CH_3), 13.6 (CH_3), 37.3 (CH_2), 119.7 (q, ^3J=5.4 Hz, $CHCCF_3$), 121.5 (C_q), 123.8 (q, ^1J=273.3 Hz, CF_3), 124.0 (q, ^1J=272.1 Hz, CF_3), 125.5 (q, ^3J=3.8 Hz, $CHCCF_3$), 125.6 (q, ^2J=31.9 Hz, CCF_3), 129.0 (C_q), 129.3 (CH), 130.2 (q, ^2J=32.6 Hz, CCF_3), 143.3 (C_q), 144.2 (C_q), 155.1 (COH), 208.6 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3252 (w), 2981 (w), 2945 (w), 2885 (w), 1691 (m), 1618 (w), 1605 (w), 1581 (w), 1405 (w), 1363 (m), 1324 (s), 1302 (m), 1259 (m), 1232 (m), 1170 (m), 1160 (m), 1140 (m), 1101 (s), 1065 (s), 1045 (m). MS (EI, 70 eV): *m*/*z* (%)=376 (M^+, 22), 357 (12), 347 (100), 299 (46), 201 (14). HRMS (EI, 70 eV) calcd for $C_{18}H_{14}F_6O_2$ (M^+): 376.08925, found: 376.08879. Anal. Calcd for $C_{18}H_{14}F_6O_2$ (376.29): C, 57.45; H, 3.75. Found: C, 57.46; H, 3.79.

3.5.31. 3-Hydroxy-4′-methoxy-5-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester (**5ae**)

Starting with **3h** (0.439 g, 1.38 mmol), **4a** (0.430 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5ae** was isolated as a pale red solid (0.295 g, 66%), mp=91–93 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.87 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.00 (d, ^3J=8.8 Hz, 2H, ArH), 7.37 (d, ^4J=1.7 Hz, 1H, ArH), 7.52 (d, ^4J=1.8 Hz, 1H, ArH), 7.57 (d, ^3J=8.8 Hz, 2H, ArH), 10.88 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.8 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.8 (OCH_3), 55.4 (OCH_3), 108.8 (C_q), 114.5 (CH), 117.6 (q, ^3J=6.9 Hz, $CHCCF_3$), 118.9 (CHCOH), 123.4 (q, ^1J=273.7 Hz, CF_3), 128.3 (CH), 130.5 (C_q), 130.7 (q, ^2J=31.8 Hz, CCF_3), 146.3 (C_q), 160.5 ($COCH_3$), 162.3 (COH), 169.6 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3063 (w), 3019 (w), 2954 (w), 2932 (w), 2840 (w), 1667 (m), 1606 (m), 1584 (m), 1514 (m), 1440 (m), 1372 (m), 1342 (m), 1311 (m), 1285 (s), 1246 (s), 1215 (m), 1200 (m), 1170 (s), 1133 (s), 1113 (s), 1057 (m), 1031 (s). MS (EI, 70 eV): *m*/*z* (%)=326 (M^+, 87), 294 (100), 266 (40), 251 (25), 223 (14). HRMS (EI, 70 eV) calcd for $C_{16}H_{13}F_3O_4$ (M^+): 326.07604, found: 326.07580.

3.5.32. 1-(3-Hydroxy-4′-methoxy-2-methyl-5-trifluoromethyl-biphenyl-4-yl)-propan-1-one (**5af**)

Starting with **3h** (0.478 g, 1.43 mmol), **4b** (0.453 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5af** was isolated as a pale yellow solid (0.248 g, 51%), mp=49–51 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.23 (s, 3H, $ArCH_3$), 3.87 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 6.98 (d, ^3J=8.8 Hz, 2H, ArH), 7.21–7.28 (m, 3H, ArH), 11.20 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.6 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.7 ($ArCH_3$), 52.8 (OCH_3), 55.3 (OCH_3), 108.3 (C_q), 113.8 (CH), 120.4 (q, ^3J=6.8 Hz, $CHCCF_3$), 123.5 (q, ^1J=272.8 Hz, CF_3), 126.9 (q, ^2J=31.9 Hz, CCF_3), 129.3 (C_q), 130.1 (CH), 132.1 (C_q), 146.7 (C_q), 159.4 ($COCH_3$), 160.7 (COH), 170.3 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3036 (w), 3018 (w), 2961 (w), 2936 (w), 2841 (w), 1678 (m), 1612 (m), 1559 (w), 1515 (m), 1456 (w), 1439 (m), 1415 (m), 1392 (m), 1361 (m), 1305 (m), 1275 (s), 1246 (s), 1195 (m), 1179 (s), 1165 (m), 1133 (s), 1115 (s), 1019 (s). MS (EI, 70 eV): *m*/*z* (%)=340 (M^+, 100), 307 (53), 280 (77), 277 (67), 265 (24), 237 (12), 211 (13). HRMS (EI, 70 eV) calcd for $C_{17}H_{15}F_3O_4$ (M^+): 340.09170, found: 340.09182. Anal. Calcd for $C_{17}H_{15}F_3O_4$ (340.29): C, 60.00; H, 4.44. Found: C, 60.10; H, 4.71.

3.5.33. 3-Hydroxy-2,4′-dimethoxy-5-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester (**5ag**)

Starting with **3h** (0.509 g, 1.60 mmol), **4g** (0.479 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5ag** was isolated as a pale red solid (0.383 g, 67%), mp=59–60 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.66 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 6.99 (d, ^3J=8.9 Hz, 2H, ArH), 7.29 (s, 1H, ArH), 7.53 (d, ^3J=8.9 Hz, 2H, ArH), 9.98 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.7 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.9 (OCH_3), 55.3 (OCH_3), 60.4 (OCH_3), 112.1 (C_q), 114.0 (CH), 120.3 (q, ^3J=6.4 Hz, $CHCCF_3$), 123.3 (q, ^1J=272.9 Hz, CF_3), 124.4 (q, ^2J=32.3 Hz, CCF_3), 128.3 (C_q), 130.2 (CH), 137.5 (C_q), 148.2 (C_q), 154.2 ($COCH_3$), 159.8 (COH), 168.8 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 2932 (w), 2839 (w), 1738 (w), 1689 (m), 1668 (m), 1608 (m), 1556 (w), 1515 (m), 1448 (m), 1440 (m), 1424 (m), 1397 (m), 1325 (m), 1306 (m), 1276 (s), 1249 (s), 1202 (m), 1177 (m), 1159 (s), 1109 (s), 1037 (m), 1024 (m). MS (EI, 70 eV): *m*/*z* (%)=356 (M^+, 100), 323 (66), 293 (54), 281 (32), 253 (15), 225 (15). HRMS (EI, 70 eV) calcd for $C_{17}H_{15}F_3O_5$ (M^+): 356.08661, found: 356.08573. Anal. Calcd for $C_{17}H_{15}F_3O_5$ (356.29): C, 57.31; H, 4.24. Found: C, 57.46; H, 4.41.

3.5.34. 3-Hydroxy-4′-methyl-5-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester (**5ah**)

Starting with **3i** (0.612 g, 2.02 mmol), **4a** (0.573 g, 2.20 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol), **5ah** was isolated as a pale red solid (0.328 g, 52%), mp=83–85 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.41 (s, 3H, $ArCH_3$), 4.00 (s, 3H, OCH_3), 7.28 (d, ^3J=7.9 Hz, 2H, ArH), 7.41 (d, ^4J=1.7 Hz, 1H, ArH), 7.48–7.56 (m, 3H, ArH), 9.76 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.8 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.2 ($ArCH_3$), 52.8 (OCH_3), 109.4 (C_q), 117.8 (q, ^3J=6.7 Hz, $CHCCF_3$), 119.4 (CHCOH), 123.4 (q, ^1J=273.6 Hz, CF_3), 127.0 (CH), 129.8 (CH), 130.7 (q, ^2J=31.9 Hz, CCF_3), 135.4 (C_q), 139.2 (C_q), 146.6 (C_q), 162.1 (COH), 169.6 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3338 (w), 3021 (w), 2986 (w), 2959 (w), 2860 (w), 1692 (m), 1668 (m), 1613 (m), 1519 (w), 1480 (w), 1440 (m), 1345 (m), 1286 (s), 1247 (m), 1208 (m), 1189 (m), 1158 (s), 1131 (s), 1153 (m), 1017 (m). MS (EI, 70 eV): *m*/*z* (%)=310 (M^+, 62), 278 (100), 263 (28), 250 (38), 153 (12). HRMS (EI, 70 eV) calcd for $C_{16}H_{10}F_3O_3$ (M^+): 310.08113, found: 310.08057.

3.5.35. 3-Hydroxy-2,4′-dimethyl-5-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester (**5ai**)

Starting with **3i** (0.615 g, 2.03 mmol), **4b** (0.604 g, 2.20 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol), **5ai** was isolated as a yellow oil (0.274 g, 42%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.23 (s, 3H, $ArCH_3$), 2.42 (s, 3H, $ArCH_3$), 4.01 (s, 3H, OCH_3), 7.17–7.32 (m, 5H, ArH), 11.19 (s, 1H, OH). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−58.6 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.7 ($ArCH_3$), 21.3 ($ArCH_3$), 52.8 (OCH_3), 108.4 (C_q), 120.4 (q, ^3J=6.8 Hz, $CHCCF_3$), 123.5 (q, ^1J=273.0 Hz, CF_3), 126.9 (q, ^2J=31.9 Hz, CCF_3), 128.8 (CH), 129.1 (CH), 129.3 (C_q), 136.9 (C_q), 137.8 (C_q), 147.0 (C_q), 160.7 (COH), 170.3 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3027 (w), 2955 (w), 2924 (w), 2862 (w), 1669 (m), 1609 (w), 1563 (w), 1516 (w), 1439 (m), 1387 (m), 1360 (m), 1334 (s), 1280 (s), 1243 (m), 1201 (s), 1128 (s), 1018 (m). MS (EI, 70 eV): *m*/*z* (%)=324 (M^+, 44), 292 (25), 277 (100), 201 (10), 165 (8). HRMS (EI, 70 eV) calcd for $C_{17}H_{15}F_3O_3$ (M^+): 324.09678, found: 324.09653.

3.5.36. 3-Hydroxy-2-methoxy-4′-methyl-5-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester (**5aj**)

Starting with **3i** (0.641 g, 2.12 mmol), **4g** (0.639 g, 2.20 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol), **5aj** was isolated as a pale red solid (0.321 g, 44%), mp=60–61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.42 (s, 3H, $ArCH_3$), 3.66 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.24–7.31 (m, 3H, ArH), 7.46 (d, ^3J=8.2 Hz, 2H, ArH), 9.84 (s, 1H, OH). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−58.7 (CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.2 ($ArCH_3$), 52.9 (OCH_3), 60.6 (OCH_3), 112.5 (C_q), 120.5 (q, ^3J=6.4 Hz, $CHCCF_3$), 123.3 (q, ^1J=273.2 Hz, CF_3), 124.3 (q, ^2J=32.3 Hz, CCF_3), 128.7 (CH), 129.3 (CH), 133.2 (C_q), 137.8 (C_q), 138.5 (C_q), 148.3 (C_q), 154.0 (COH), 168.7 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3030 (w), 2925 (w), 2852 (w), 1740 (w), 1681 (m), 1604 (w), 1518 (w), 1446 (w), 1418 (w), 1394 (w), 1368 (m), 1326 (m), 1285 (m), 1268 (m), 1249 (m), 1199 (m), 1187 (m), 1149 (m), 1140 (m), 1121 (s), 1027 (m), 1018 (m). Anal. Calcd for $C_{17}H_{15}F_3O_4$ (340.29): C, 60.00; H, 4.44. Found: C, 60.37; H, 4.51.

3.5.37. 1-(3-Hydroxy-4′-methyl-5-trifluoromethyl-biphenyl-4-yl)-ethanone (**5ak**)

Starting with **3i** (0.608 g, 2.01 mmol), **4j** (0.538 g, 2.20 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol), **5ak** was isolated as a slightly

brownish solid (0.287 g, 49%), mp=148–151 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.42 (s, 3H, ArC*H*$_3$), 2.67 (q, ^6J=1.8 Hz, 3H, C*H*$_3$), 7.29 (d, ^3J=8.0 Hz, 2H, Ar*H*), 7.37 (s, 1H, Ar*H*), 7.47–7.54 (m, 3H, Ar*H*), 10.09 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−55.5 (C*F*$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=21.2 (Ar*C*H$_3$), 31.5 (q, ^5J=5.5 Hz, *C*H$_3$), 117.5 (q, ^3J=5.9 Hz, *C*HCCF$_3$), 119.6 (*C*H), 119.9 (*C*$_q$), 123.8 (q, ^1J=273.9 Hz, *C*F$_3$), 126.9 (*C*H), 129.3 (q, ^2J=31.5 Hz, *C*CF$_3$), 129.8 (*C*H), 135.2 (*C*$_q$), 139.4 (*C*$_q$), 146.0 (*C*$_q$), 158.9 (*C*OH), 204.6 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3192 (w), 2925 (w), 1666 (m), 1611 (m), 1590 (m), 1567 (m), 1525 (w), 1505 (w), 1430 (m), 1400 (w), 1338 (m), 1279 (m), 1252 (m), 1191 (m), 1130 (s), 1049 (m). MS (EI, 70 eV): *m*/*z* (%)=294 (M$^+$, 43), 279 (100), 231 (21), 188 (8). HRMS (EI, 70 eV) calcd for $C_{16}H_{13}F_3O_2$ (M$^+$): 294.08622, found: 294.08637.

3.5.38. 1-(3-Hydroxy-2,4′-dimethyl-5-trifluoromethyl-biphenyl-4-yl)-propan-1-one (**5al**)

Starting with **3i** (0.602 g, 1.99 mmol), **4k** (0.600 g, 2.20 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol), **5al** was isolated as a pale red solid (0.205 g, 32%), mp=110–113 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.22 (t, ^3J=7.2 Hz, 3H, CH$_2$C*H*$_3$), 2.21 (s, 3H, ArC*H*$_3$), 2.42 (s, 3H, ArC*H*$_3$), 2.94 (q, ^3J=7.2 Hz, 2H, C*H*$_2$CH$_3$), 7.15–7.30 (m, 5H, Ar*H*), 8.23 (s, 1H, O*H*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−55.8 (C*F*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.7 (*C*H$_3$), 13.7 (*C*H$_3$), 21.2 (*C*H$_3$), 37.3 (*C*H$_2$), 119.9 (q, ^3J=5.4 Hz, *C*HCCF$_3$), 121.2 (*C*$_q$), 124.0 (q, ^1J=273.3 Hz, *C*F$_3$), 125.1 (q, ^2J=31.2 Hz, *C*CF$_3$), 128.8 (*C*H), 129.0 (*C*$_q$), 129.1 (*C*H), 136.8 (*C*$_q$), 137.7 (*C*$_q$), 145.7 (*C*$_q$), 155.0 (*C*OH), 208.8 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3316 (w), 2979 (w), 2943 (w), 2882 (w), 1690 (m), 1607 (m), 1564 (w), 1518 (m), 1456 (w), 1408 (w), 1361 (m), 1300 (m), 1262 (m), 1218 (m), 1184 (m), 1125 (s), 1098 (s), 1046 (m). MS (EI, 70 eV): *m*/*z* (%)=322 (M$^+$, 18), 293 (100), 245 (20), 201 (8). HRMS (EI, 70 eV) calcd for $C_{18}H_{17}F_3O_2$ (M$^+$): 322.11752, found: 322.11690.

3.5.39. 3″-Hydroxy-2″-methyl-5″-trifluoromethyl-[1,1′;4′,1″]terphenyl-4″-carboxylic acid methyl ester (**5am**)

Starting with **3j** (0.523 g, 1.44 mmol), **4b** (0.453 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5am** was isolated as a colourless solid (0.386 g, 70%), mp=156–157 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.29 (s, 3H, ArC*H*$_3$), 4.02 (s, 3H, OC*H*$_3$), 7.30 (s, 1H, Ar*H*), 7.36–7.43 (m, 3H, Ar*H*), 7.45–7.52 (m, 2H, Ar*H*), 7.63–7.72 (m, 4H, Ar*H*), 11.22 (s, 1H, O*H*). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−58.6 (C*F*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.8 (Ar*C*H$_3$), 52.9 (OCH$_3$), 108.6 (*C*$_q$), 120.3 (q, ^3J=6.8 Hz, *C*HCCF$_3$), 123.5 (q, ^1J=272.6 Hz, *C*F$_3$), 127.1 (q, ^2J=32.1 Hz, *C*CF$_3$), 127.1 (*C*H), 127.6 (*C*H), 128.9 (*C*H), 129.3 (*C*H), 129.4 (*C*$_q$), 138.7 (*C*$_q$), 140.4 (*C*$_q$), 140.9 (*C*$_q$), 146.6 (*C*$_q$), 160.7 (*C*OH), 170.2 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3034 (w), 2960 (w), 2923 (w), 2859 (w), 1668 (m), 1603 (w), 1569 (w), 1548 (w), 1525 (w), 1487 (w), 1442 (m), 1408 (w), 1385 (w), 1336 (m), 1286 (m), 1242 (m), 1201 (m), 1155 (m), 1127 (s). MS (EI, 70 eV): *m*/*z* (%)=386 (M$^+$, 100), 353 (66), 326 (50), 277 (46), 257 (39), 228 (14), 177 (10). HRMS (EI, 70 eV) calcd for $C_{22}H_{17}F_3O_3$ (M$^+$): 386.11243, found: 386.11185.

3.5.40. 2″-Ethyl-3″-hydroxy-5″-trifluoromethyl-[1,1′;4′,1″]terphenyl-4″-carboxylic acid methyl ester (**5an**)

Starting with **3j** (0.524 g, 1.44 mmol), **4i** (0.476 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5an** was isolated as a pale red solid (0.234 g, 41%), mp=173–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.16 (t, ^3J=7.4 Hz, 3H, CH$_2$C*H*$_3$), 2.71 (q, ^3J=7.4 Hz, 2H, C*H*$_2$CH$_3$), 4.02 (s, 3H, OC*H*$_3$), 7.25 (s, 1H, Ar*H*), 7.35–7.42 (m, 3H, Ar*H*), 7.45–7.52 (m, 2H, Ar*H*), 7.63–7.71 (m, 4H, Ar*H*), 11.13 (s, 1H, O*H*). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−58.6 (C*F*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.8 (CH$_2$*C*H$_3$), 20.9 (*C*H$_2$), 52.8 (OCH$_3$), 109.1 (*C*$_q$), 120.6 (q, ^3J=6.7 Hz, *C*HCCF$_3$), 123.5 (q, ^1J=272.7 Hz, *C*F$_3$), 127.0 (q, ^2J=32.1 Hz, *C*CF$_3$), 127.0 (*C*H), 127.1 (*C*H), 127.6 (*C*H), 128.9 (*C*H), 129.0 (*C*H), 135.4 (*C*$_q$), 138.9 (*C*$_q$), 140.4 (*C*$_q$), 140.8 (*C*$_q$), 146.5 (*C*$_q$), 160.5 (*C*OH), 170.2 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3032 (w), 2957 (w), 2941 (w), 2879 (w), 1668 (m), 1603 (w), 1568 (w), 1521 (w), 1486 (w), 1440 (m), 1407 (w), 1366 (m), 1284 (m), 1258 (m), 1199 (m), 1130 (s), 1059 (m). MS (EI, 70 eV): *m*/*z* (%)=400 (M$^+$, 100), 367 (35), 340 (69), 325 (15), 291 (26). HRMS (EI, 70 eV) calcd for $C_{23}H_{19}F_3O_3$ (M$^+$): 400.12808, found: 400.12753.

3.5.41. 3″-Hydroxy-2″-methoxy-5″-trifluoromethyl-[1,1′;4′,1″]terphenyl-4″-carboxylic acid methyl ester (**5ao**)

Starting with **3j** (0.530 g, 1.45 mmol), **4g** (0.479 g, 1.65 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol), **5ao** was isolated as a pale red solid (0.246 g, 42%), mp=142–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.64 (s, 3H, OC*H*$_3$), 3.94 (s, 3H, OC*H*$_3$), 7.29 (s, 1H, Ar*H*), 7.35–7.44 (m, 3H, Ar*H*), 7.55–7.65 (m, 6H, Ar*H*). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−58.7 (C*F*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=53.0 (OCH$_3$), 60.7 (OCH$_3$), 112.7 (*C*$_q$), 120.4 (q, ^3J=6.4 Hz, *C*HCCF$_3$), 123.3 (q, ^1J=272.9 Hz, *C*F$_3$), 124.5 (q, ^2J=32.0 Hz, *C*CF$_3$), 127.1 (*C*H), 127.2 (*C*H), 127.6 (*C*H), 128.9 (*C*H), 129.3 (*C*H), 135.0 (*C*$_q$), 137.4 (*C*$_q$), 140.3 (*C*$_q$), 141.3 (*C*$_q$), 148.4 (*C*$_q$), 154.2 (*C*OH), 168.7 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3033 (w), 2956 (w), 2853 (w), 1668 (m), 1602 (m), 1557 (w), 1486 (w), 1446 (m), 1415 (w), 1393 (w), 1336 (m), 1286 (m), 1251 (m), 1199 (m), 1184 (m), 1157 (m), 1120 (s), 1036 (m). MS (EI, 70 eV): *m*/*z* (%)=402 (M$^+$, 100), 369 (71), 346 (27), 341 (29), 207 (65), 175 (33). HRMS (EI, 70 eV) calcd for $C_{22}H_{17}F_3O_7$ (M$^+$): 402.10735, found: 402.10692.

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References and notes

1. While the size of the methyl and trifluoromethyl group is comparable, the latter possesses a strong electron-withdrawing effect. Therefore, the replacement of a CH_3 group by a CF_3 group in a molecule results in a great change of its electronic properties and reactivity. The trifluoromethyl group of drugs plays an important role in drug–receptor interactions and in the in vivo transport. In addition, the high chemical and biological stability of the CF_3 group allows to avoid unwanted metabolic transformations. For reviews, see: (a) *Fluorine in Bioorganic Chemistry*; Filler, R., Kobayasi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993; (b) Filler, R. *Fluorine Containing Drugs in Organofluorine Chemicals and their Industrial Application*; Pergamon: New York, NY, 1979; Chapter 6; (c) Hudlicky, M. *Chemistry of Organic Compounds*; Ellis Horwood: Chichester, UK, 1992; See also: (d) Ryckmanns, T.; Balancon, L.; Berton, O.; Genicot, C.; Lamberty, Y.; Lallemand, B.; Passau, P.; Pirlot, N.; Quéré, L.; Talaga, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 261; (e) Malamas, M. S.; Sredy, J.; Moxham, C.; Katz, A.; Xu, W.; McDevitt, R.; Adebayo, F. O.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Taylor, J. R. *J. Med. Chem.* **2000**, *43*, 1293; (f) Ciha, A. J.; Ruminski, P. G. *J. Agric. Food Chem.* **1991**, *39*, 2072.
2. (a) Schmidbaur, H.; Kumberger, O. *Chem. Ber.* **1993**, *126*, 3; (b) Dinger, M. B.; Henderson, W. *J. Organomet. Chem.* **1998**, *560*, 233; (c) Liedtke, J.; Loss, S.; Widauer, C.; Grützmacher, H. *Tetrahedron* **2000**, *56*, 143.
3. See for example: (a) Schneider, S.; Tzschucke, C. C.; Bannwarth, W. In *Multiphase Homogeneous Catalysis*; Cornils, B., Herrmann, W. A., Horvath, I. T., Leitner, W., Mecking, S., Olivier-Booubigou, H., Vogt, D., Eds.; Wiley VCH: 2005; Chapter 4, p 346; (b) Clarke, D.; Ali, M. A.; Clifford, A. A.; Parratt, A.; Rose, P.; Schwinn, D.; Bannwarth, W.; Rayner, C. M. *Curr. Top. Med. Chem.* **2004**, *7*, 729.
4. (a) Wittkopp, A.; Schreiner, P. R. *The chemistry of dienes and polyenes*; John Wiley & Sons: New York, NY, 2000; Vol. 2; (b) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289; (c) Wittkopp, A.; Schreiner, P. R. *Chem.—Eur. J.* **2003**, *9*, 407; (d) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315; (e) Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779; (f) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.
5. Review: Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.
6. Review: McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555.
7. (a) Paratian, J. M.; Sibille, S.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1992**, 53; (b) Tordeux, M.; Langlois, B.; Wakselman, C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2293.
8. Ding, W.; Pu, J.; Zhang, C. *Synthesis* **1992**, 635.
9. For cyclocondensations, see: (a) Guan, H.-P.; Hu, C.-M. *Synthesis* **1996**, 1363; (b) Guan, H.-P.; Hu, C.-M. *J. Fluorine Chem.* **1996**, *78*, 101; (c) Guan, H.-P.; Hu, Q.-S.; Hu, C.-M. *Chin. J. Chem.* **1996**, *14*, 87.
10. For the metalation of (trifluoromethyl)arenes and subsequent coupling with electrophiles, see: (a) Marzi, E.; Mongin, F.; Spitaleri, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 2911; (b) Dmowski, W.; Piasecka-Maciejewska, K. *J. Fluorine Chem.* **1996**, *78*, 59.

11. For Diels–Alder reactions, see: (a) Abubakar, A. B.; Booth, B. L.; Suliman, N. N. E.; Tipping, A. E. *J. Fluorine Chem.* **1992**, *56*, 359; (b) Barlow, M. G.; Suliman, N. N. E.; Tipping, A. E. *J. Fluorine Chem.* **1995**, *70*, 59.
12. (a) Volochnyuk, D. M.; Kostyuk, A. N.; Sibgatulin, D. A.; Chernega, A. N.; Pinchuk, A. M.; Tolmachev, A. A. *Tetrahedron* **2004**, *60*, 2361; (b) Volochnyuk, D. M.; Kostyuk, A. N.; Sibgatulin, D. A.; Chernega, A. N. *Tetrahedron* **2005**, *61*, 2839.
13. (a) Gambaryan, N. P.; Simonyan, L. A.; Petrovskii, P. V. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1967**, 918; (b) Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, 499; (c) Hojo, M.; Masuda, R.; Sakaguchi, S.; Takagawa, M. *Synthesis* **1986**, 1016; (d) Colla, A.; Martins, M. A. P.; Clar, G.; Krimmer, S.; Fischer, P. *Synthesis* **1991**, 483; (e) Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1989**, 215.
14. Reviews: (a) Nenaidenko, V. G.; Sanin, A. V.; Balenkova, E. S. *Russ. Chem. Rev.* **1999**, *68*, 437; (b) Billard, T. *Chem.—Eur. J.* **2006**, *12*, 974; (c) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. *Tetrahedron* **2007**, *63*, 7753.
15. Zanatta, N.; Barichello, R.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **1999**, 765.
16. (a) Mamat, C.; Pundt, T.; Dang, T. H. T.; Klassen, R.; Reinke, H.; Köckerling, M.; Langer, P. *Eur. J. Org. Chem.* **2008**, 492 for the synthesis of 5-thienyl-substituted phenols, see: (b) Hussain, I.; Riahi, A.; Yawer, M. A.; Görls, H.; Langer, P. *Org. Biomol. Chem.* **2008**, *6*, 3542 for perfluoro-substituted phenols, see: (c) Büttner, S.; Lubbe, M.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2008**, *64*, 7968; (d) Lubbe, M.; Mamat, C.; Fischer, C.; Langer, P. *Tetrahedron* **2007**, *63*, 413.
17. For a review on [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes, see: Feist, H.; Langer, P. *Synthesis* **2007**, 327.
18. (a) Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534; (b) Chan, T. H.; Brook, M. A. *Tetrahedron Lett.* **1985**, *26*, 2943.
19. For a review on 1,3-bis(silyloxy)-1,3-butadienes in general, see: Langer, P. *Synthesis* **2002**, 441.
20. Berger, S.; Braun, S.; Kalinowski, H.-O. *NMR-Spektroskopie von Nichtmetallen, Bd. 4—^{19}F-NMR-Spektroskopie*; Thieme: Stuttgart, 1994; p 36.
21. CCDC-715404 and 700728 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.