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3-Trifluoromethylated Coumarins and Carbostyrils *via* Radical Trifluoromethylation of *ortho*-Functionalized Cinnamic Esters

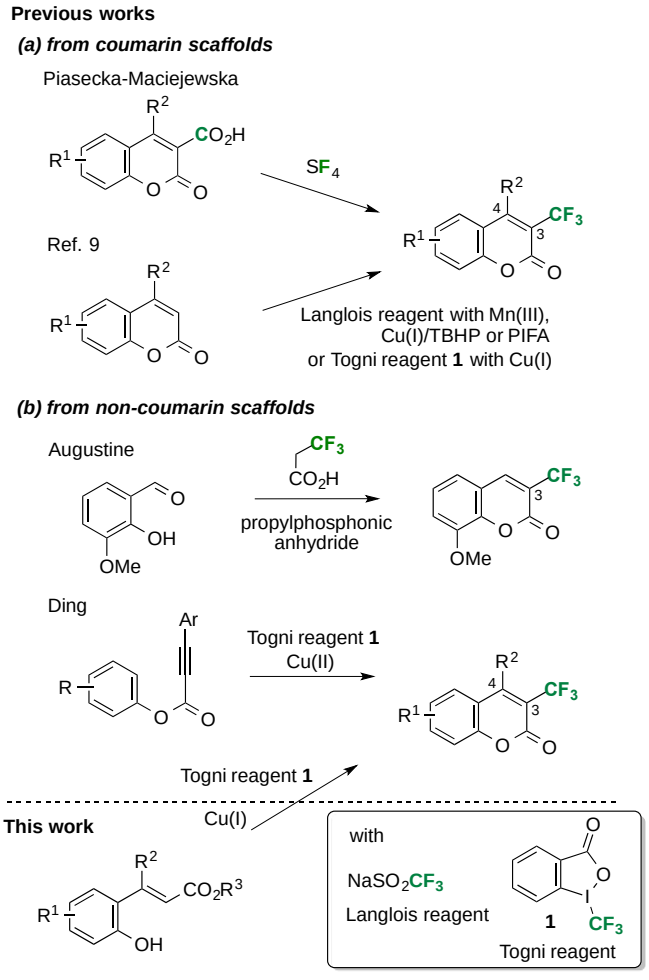
Slim Chaabouni,[a,b,c] Florent Simonet,[a] Alison François,[a] Souhir Abid,[b] Chantal Galaup,[c] and Stefan Chassaing*[a]

Abstract: A method for the trifluoromethylation of *ortho*-hydroxycinnamic esters was developed to achieve the regioselective synthesis of 3-trifluoromethylated coumarins. The reaction proceeds with Togni reagent as the CF_3 source under mild conditions and with good functional group tolerance. The scope of this copper-mediated method was further expanded to the synthesis of 3-trifluoromethylated carbostyrils starting from *ortho*-aminocinnamic derivatives. Interestingly, a sequential one-pot synthesis of 3-trifluoromethylated coumarins starting from salicylaldehydes was further developed. The mechanism of this cascade reaction was explored and a radical pathway was found consistent with the obtained results.

Introduction

Methods to incorporate fluorine into organic molecules have emerged as valuable and highly demanded synthetic tools in the last decade, with relevance from agricultural and pharmaceutical chemistries to materials science.[1,2] Indeed, it is commonly accepted that the anchoring of a fluorine-containing group onto useful organic scaffolds often leads to an improvement of its chemical, physical and biological profiles.[3] To date, the trifluoromethyl (CF_3) group has appeared as the archetypal and most sought-after fluorine-containing group, as revealed by the huge and ever-increasing number of trifluoromethylated compounds as well as trifluoromethylating methods/reagents reported in the literature.[2a,4]

In particular, some efforts have been made to incorporate the CF_3 group into the coumarin scaffold, a heterocyclic scaffold encountered in numerous natural and synthetic products of relevance in life[5] and materials[6] sciences. However, regioisomeric 3- and 4-trifluoromethylated coumarins have so far not received the same level of attention, especially regarding their synthesis. While synthetic methods towards 4-trifluoromethylated coumarins are highly documented in the literature,[7] less examples focused on the regiocontrolled synthesis of their 3-trifluoromethylated isomers, most of those examples employing coumarin scaffolds as substrates (**Scheme 1a**). First, the group of Piasecka-Maciejewska succeeded in the synthesis of 3-trifluoromethylcoumarins *via* the fluorination of 3-carboxylated coumarins using sulfur tetrafluoride as fluorine source.[8] Much more recently, several groups elaborated efficient methods for the direct trifluoromethylation of already existing coumarin scaffolds, using Langlois or Togni (**1**) reagents as CF_3 sources and under transition metal-mediated or metal-free conditions.[9] To date, only two examples utilizing non-coumarin scaffolds as starting materials have been reported (**Scheme 1b**).[10] The group of Augustine[10a] achieved the one-pot synthesis of a methoxylated 3-trifluoromethylcoumarin *via* a propylphosphonic anhydride-mediated Perkin condensation, while Ding[10b] described a copper-catalyzed cascade construction method starting from acyclic arylpropiolates as substrates and using Togni reagent **1** as CF_3 source.



Scheme 1. Synthesis of 3-trifluoromethylated coumarins.

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Similarly, some attention has also been given to the incorporation of a CF_3 group into the lactam-based equivalent of the coumarin scaffold, namely the carbostyril scaffold[11]. As in the case of coumarins, 4-trifluoromethylated carbostyrils have received huge attention regarding their synthesis as well as their biological and imaging properties,[12] while examples of their 3-trifluoromethylated regioisomers are very scarce in the literature.[13] Of note the so-reported methods towards 3-trifluoromethylated carbostyrils utilize a cyclic scaffold (ie the carbostyril scaffold) as substrates, again as with coumarins.

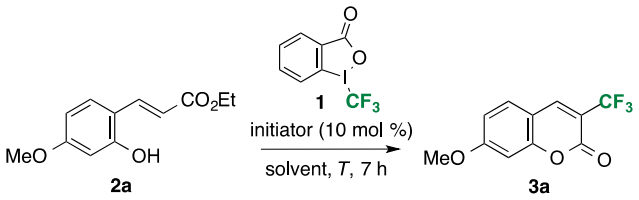
Herein we set out an alternative and complementary cascade approach for the construction of 3-trifluoromethylated coumarins and carbostyrils *via* the direct trifluoromethylation of easy-to-prepare acyclic scaffolds, namely *ortho*-hydroxy- and *ortho*-amino-cinnamic esters, and using Togni reagent **1** as CF_3 source.

Results and Discussion

To evaluate the potential of our trifluoromethylation approach depicted in the bottom of **Scheme 1**, initial investigations were conducted on *ortho*-hydroxylated ethyl cinnamate **2a** as model substrate and Togni reagent **1** as CF_3 source[14] (**Table 1**). Readily available **2a**[15] was first submitted to standard trifluoromethylation conditions, *i.e.* reaction at 80 °C in the presence of 10 mol % CuI as initiator and with DMF as solvent. Gratifyingly, the desired 3-trifluoromethylated coumarin **3a** was formed in good yield under these conditions, using 1.5 equiv. of **1** either in a pure synthetic form or in its commercial stabilized form (**Table 1**, entry 1).[16] Various solvents were then examined but without any improvement in efficiency (**Table 1**, entries 1-4). DMF proved to be the best solvent, being more effective than dichloromethane and acetonitrile (**Table 1**, entries 2 and 3 *vs* 1). In a protic solvent such as ethanol, the reaction was also effective but at a much slower rate than in DMF (**Table 1**, entry 4 *vs* 1). In this reaction, the temperature was shown to be crucial as a significant decrease in conversion and yield was observed when lowering the temperature to 60 °C (**Table 1**, entry 5 *vs* 1). Similarly, increasing the temperature to 100 °C had a deleterious effect on the reaction progress, probably due to the unstable feature of **1** upon heating (**Table 1**, entry 6). Regarding the **1**/**2a** ratio, the initial 1.5:1 ratio appeared optimal, as lowering the ratio to 1.3:1 led to a reduced yield while increasing to 2:1 provided similar results (**Table 1**, entries 7 and 8 *vs* 1).

Following these results, we screened various Cu^I salts as initiators/catalysts. We were pleased to find that the trifluoromethylated scaffold **3a** was formed in moderate to good yields in the presence of all investigated salts (**Table 1**, entries 1 and 9-11). Cu^I halides, *i.e.* CuI, CuBr and CuCl, provided quite similar and good results (68-75 % yield), when the use of cuprous oxide only led to a moderate yield of 48 %. Due to our interest in metalated zeolites and their applications as heterogeneous catalysts in organic synthesis,[17] we further evaluated the potential of Cu^I-USY in this trifluoromethylation process (**Table 1**, entry 12). Interestingly enough, the zeolite-based Cu^I-USY material proved functional, furnishing the desired product **3a** with a promising yield of 56 %.[18] Of note, a control experiment revealed that the reaction could be promoted without any Cu^I salts, but with a considerably lower efficiency in terms of conversion and yield (**Table 1**, entry 13 *vs* 1).

Table 1. Screening of reaction conditions for the trifluoromethylation of *E*-ethyl 3-(2-hydroxy-4-methoxyphenyl)acrylate **2a** with Togni reagent **1**.[a]



Entry	Solvent	Initiator	*T* (°C)	Yield of **3a** [%][b]
1	DMF	CuI	80	75 (70[c])
2	CH_3CN	CuI	80	55
3	CH_2Cl_2	CuI	80	67
4	EtOH	CuI	80	29[d]
5	DMF	CuI	60	39[d]
6	DMF	CuI	100	-[d,e]
7[f]	DMF	CuI	80	55
8[g]	DMF	CuI	80	72
9	DMF	CuBr	80	70
10	DMF	CuCl	80	68
11	DMF	Cu_2O	80	48
12	DMF	Cu^I-USY	80	56[d]
13	DMF	None	80	29[d]

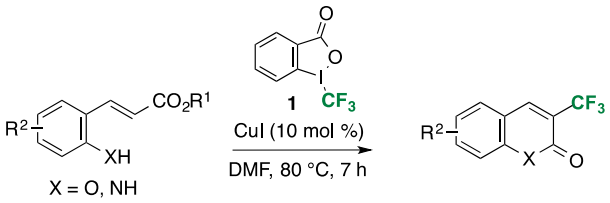
[a] Reactions run in the dark on a 0.25 mmol scale with **2a** (1.0 equiv with a 0.25 M concentration) and freshly prepared **1** (1.5 equiv), unless otherwise stated. [b] Yields of isolated pure product. [c] Reaction run with commercial form of Togni reagent **1**. [d] Incomplete conversion. [e] Complex mixture of products. [f] Reactions run with 1.3 equiv of **1**. [g] Reactions run with 2.0 equiv of **1**.

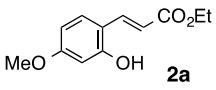
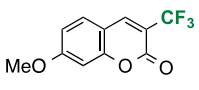
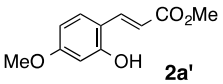
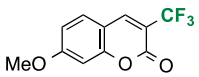
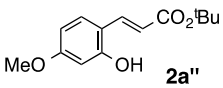
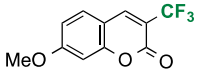
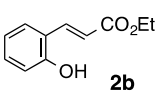
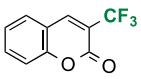
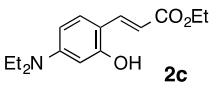
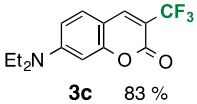
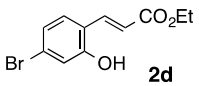
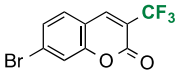
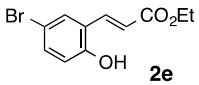
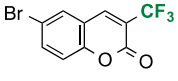
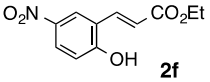
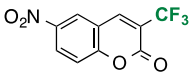
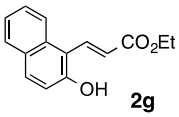
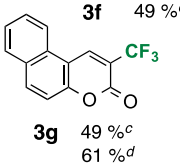
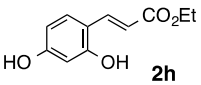
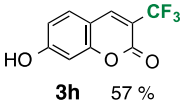
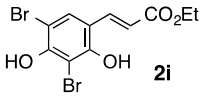
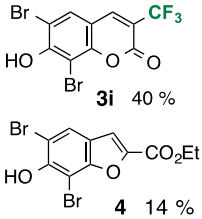
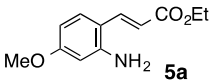
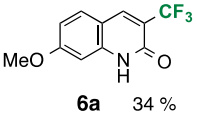
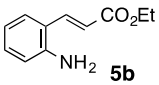
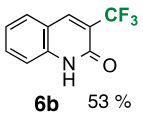
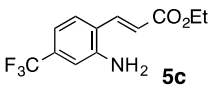
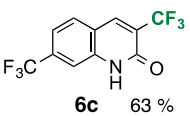
With these reaction conditions in hands, we next explored the scope and limitations of this trifluoromethylation process (**Table 2**). For this purpose, diverse *ortho*-substituted cinnamic derivatives were thus prepared and submitted to the optimal conditions described in entry 1 of **Table 1**.

The nature of the alkyl substituent R^1 of the ester moiety was first examined. Shifting R^1 from ethyl to methyl or *t*-butyl enabled the trifluoromethylation reaction but with lower efficiency, especially in the case of the sterically demanding *t*-butyl group (**Table 2**, entries 2 and 3 *vs* 1). Hence the ethyl group was fixed as R^1 substituent for the ensuing studies. Several ethyl *ortho*-hydroxycinnamates **2b-i** bearing various aryl substitution

patterns were then evaluated as possible substrates (**Table 2**, entries 4-11). While exposure of **2b-i** to the trifluoromethylation conditions provided all desired products **3b-i**, the obtained results revealed several manifest effects of the substitution pattern on the reaction. Regarding electronic effects, it is clear that the more electron-donating the R^2 group, the more effective was the reaction, as shown by the increasing reaction efficiency seen from simple cinnamate **2b** through the model **2a** to the *N,N*-diethylamino analogue **2c** (**Table 2**, entry 4 *vs* 1 *vs* 5). This trend was further confirmed when the aryl moiety was equipped with electron-withdrawing groups, such as bromine or nitro groups (**Table 2**, entries 6-8). Regioisomeric bromine-substituted cinnamates **2d** and **2e** proved suitable substrates for the transformation, but only modest yields were obtained under standard conditions due to incomplete conversion. To circumvent this issue, a slight modification - *i.e.* extension of reaction time to 24 h with addition of CuI (10 mol %) and **1** (0.5 equiv) after 7 h - has been applied to the procedure, thus furnishing the expected coumarins **3d,e** with increased yields. Applying these modified reaction conditions to nitro-substituted and naphtyl derivatives (respectively **2f** and **2g**) also gave the expected products **3f** and **3g** in appropriate yields (Table 2, entries 8 and 9). Moreover, hydroxy-substituted cinnamates **2h** and **2i** were subjected to standard conditions to afford phenolic compounds **3h** and **3i** (**Table 2**, entries 10 and 11). Interestingly, the highly substituted cinnamate **2i** was converted to the novel benzofurane **4** as byproduct, in addition to the expected product **3i**.

Table 2. Scope of the trifluoromethylation reaction.[a]



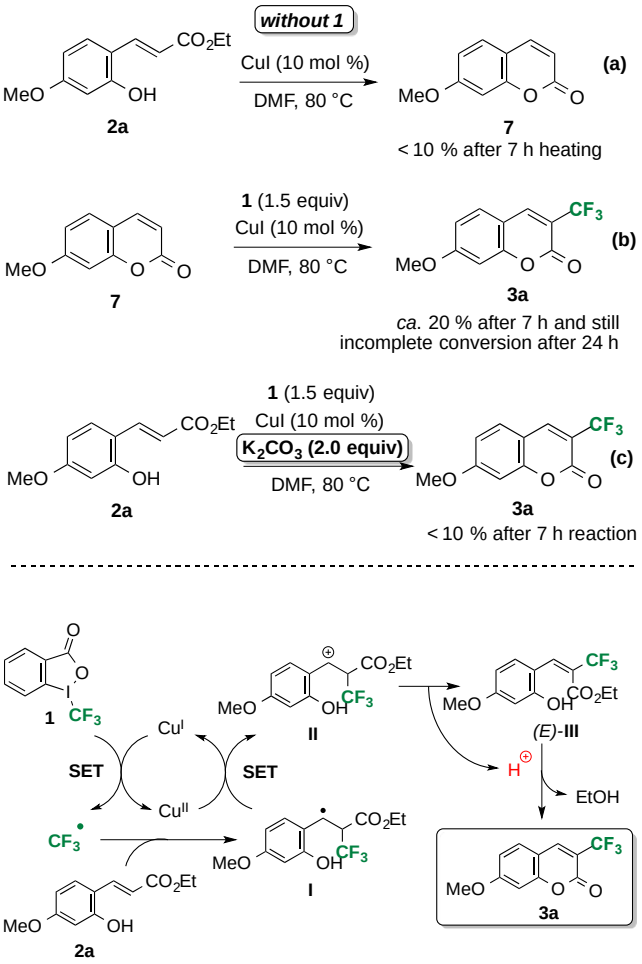
Entry	Precursor	Product(s) and yield [%][b]
1	 **2a**	 **3a** 75 %
2	 **2a'**	 **3a** 56 %
3	 **2a''**	 **3a** 49 %
4	 **2b**	 **3b** 69 %
5	 **2c**	 **3c** 83 %
6	 **2d**	 **3d** 59 %[c] 77 %[d]
7	 **2e**	 **3e** 49 %[c] 69 %[d]
8	 **2f**	 **3f** 49 %[d]
9	 **2g**	 **3g** 49 %[c] 61 %[d]
10	 **2h**	 **3h** 57 %
11	 **2i**	 **3i** 40 % **4** 14 %
12	 **5a**	 **6a** 34 %
13	 **5b**	 **6b** 53 %
14	 **5c**	 **6c** 63 %

[a] Reactions run in the dark on a 0.25 mmol scale with **2a-i/5a-c** (1.0 equiv with a 0.25 M concentration) and freshly prepared **1** (1.5 equiv), unless otherwise stated. [b] Yields of isolated pure product. [c] Incomplete conversion. [d] Reaction time extended to 24 h, with addition of CuI (10 mol %) and **1** (0.5 equiv) after 7 h to complete the reaction.

To further expand the scope, *ortho*-aminocinnamic derivatives **5a-c** were prepared[19] and were successfully engaged in the trifluoromethylation process, as shown by the effective formation of 3-trifluromethylated carbostyrils **6a-c** (**Table 2**, entries 12-14). In sharp contrast with the previous hydroxylated series, the more electron-donating the R^2 group, the less effective was here the trifluoromethylation.

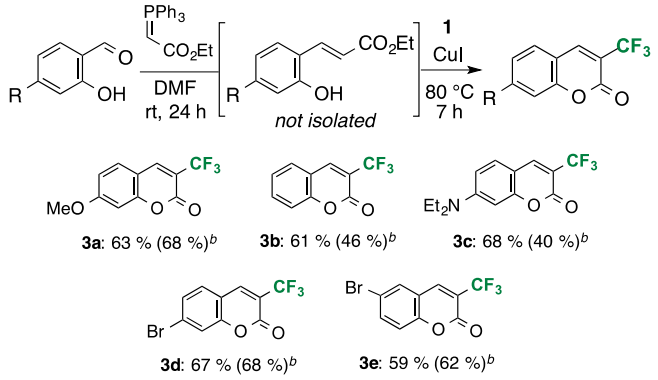
Considering mechanistic aspects, the reaction clearly involves a cascade of successive events, mainly including an intermolecular trifluoromethylation event together with the formation of the heterocyclic pyrone ring *via* a lactonization event. In order to determine in what order these key events would occur, two first control experiments were carried out (**Scheme 2**, equations (a) and (b)). While the thermal conversion of cinnamate **2a** to coumarin **7** proved unsubstantial in the absence of Togni reagent **1** (**Scheme 2**, equation (a)), coumarin **7** appeared as a poor substrate under the optimized trifluoromethylation conditions (**Scheme 2**, equation (b)). Taken together, these results revealed that the lactonization event does not take place prior to the trifluoromethylation event. To further gain insight into the reaction mechanism, inhibition experiments were conducted on the model reaction between **1** and **2a**, using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-*p*-cresol (BHT) as radical scavengers. In both cases, the formation of **3a** was seriously inhibited[20] and the TEMPO-CF_3 adduct was detected in the crude mixture of the TEMPO-based control experiment, thus supporting the involvement of radical species (including the CF_3 radical) in this cascade reaction.

According to these experimental results and literature precedents,[14] a plausible mechanism is proposed in the bottom of **Scheme 2**. The reaction pathway starts with the generation of the CF_3 free radical *via* the well-established single-electron transfer (SET) process involving **1** and Cu^I.[14] The so-formed CF_3 radical regioselectively adds to cinnamate **2a** to give the benzylic radical intermediate **I**, which subsequently undergoes a second SET process to furnish carbocation intermediate **II** and concomitantly recycle the active Cu^I species. Then, deprotonation of intermediate **II** generates trifluoromethylated cinnamate **III** as key intermediate, with the stable *E*-configuration.[21] *E*-intermediate **III** ultimately leads to the desired coumarin **3a** *via* the previously suggested lactonization event. Importantly, a control experiment performed in the presence of potassium carbonate supported the facts that the final lactonization step is under proton catalysis (**Scheme 2**, equation (c)).



Scheme 2. Control experiments and resulting proposed mechanism.

Lastly, we examined the feasibility of a sequential one-pot version starting with salicylaldehydes, as commercially available and cheap materials. As shown in **Scheme 3**, the one-pot two-step sequence, made up of a Wittig reaction prior to the trifluoromethylation of the cinnamate intermediate, proved to be suitable and useful for the synthesis of 3-trifluoromethylated coumarins **3a-e**, giving rise to the desired products in moderate to good yields without the need for isolation/purification of the cinnamate intermediate. Noteworthy is that the one-pot version is at least equally efficient as the standard two-step synthesis, even more efficient in the cases of **3b,c** (**Scheme 3**).



Scheme 3. Sequential one-pot synthesis[a] of 3-trifluoromethylated coumarins from salicylaldehydes. [a]One-pot version run with : *i)* salicylaldehyde (1.0 equiv) and ylide (1.05 equiv) for the Wittig step, and *ii)* **1** (2.0 equiv) and CuI (20 mol %) for the trifluoromethylation step. [b]Overall yields of isolated pure product *via* the standard two-step synthesis.

Conclusions

In summary, we presented here a novel approach for the synthesis of 3-trifluoromethylcoumarins starting with readily prepared *ortho*-hydroxycinnamic esters as substrates and Togni reagent as CF_3 source. The method offers a wide scope and tolerates a variety of functional groups, including alkoxy, hydroxy, amino, nitro, naphtyl and halide substituents. Under the so-elaborated trifluoromethylation conditions, *ortho*-aminocinnamic esters were also shown to be suitable substrates for the synthesis of 3-trifluoromethylcarbosstyrils, another class of relevant trifluoromethylated heteroarenes.
Work is currently underway to expand the potential of *ortho*-substituted cinnamic derivatives as valuable building blocks for heterocyclic synthesis.

Experimental Section

General: All starting materials were commercial and were used as received, unless otherwise stated. In particular, the Togni reagent **1** was synthesized according to a recently reported two-step procedure[22] whereas *ortho*-hydroxy- and *ortho*-amino-cinnamic esters, **2a-i** and **5a-c** respectively, were easily prepared from commercially available starting materials.[15,19] – The reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F_{254}, Merck) using UV-light for visualization. Column chromatographies were performed on silica gel 60 (0.040-0.063 mm, Merck) using mixtures of ethyl acetate (or diethyl ether) and cyclohexane as eluents. – Evaporation of solvents were conducted under reduced pressure at temperatures less than 30°C unless otherwise noted. – Melting points (M.p.) were measured with a Stuart SMP30 apparatus in open capillary tubes and are uncorrected. – IR spectra were obtained from the 'Service Commun de Spectroscopie Infrarouge et Raman' of the Plateforme Technique, Institut de Chimie de Toulouse. Values are reported in cm^{-1}. – ^1H, ^{19}F & ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300 and 75 MHz, respectively. Chemical shifts δ and coupling constants J are given in ppm and Hz, respectively. Chemical shifts δ are reported relative to residual solvent as an internal standard ($CDCl_3$: 7.26 ppm for ^1H and 77.0 ppm for ^{13}C – [D_6]acetone: 2.05 ppm for ^1H and 29.8 ppm for ^{13}C). Carbon multiplicities were determined by DEPT135 experiments. – ElectroSpray Ionization (ESI), Desorption Chemical Ionization (DCI) and Atmospheric-Pressure Chemical Ionization (APCI) low/high-resolution mass spectra were obtained from the 'Service Commun de Spectroscopie de Masse' of the Plateforme Technique, Institut de Chimie de Toulouse.

General procedure for the synthesis of 3-trifluoromethylated coumarins 3a-i and quinolin-2-ones 6a-c: In a 5 mL microwave reactor under argon were successively added *ortho*-substituted cinnamic ester **2a-i**[15]/**5a-c**[16] (0.25 mmol, 1 equiv.), copper(I) iodide (5 mg, 0.025 mmol, 10 mol%), dry DMF as solvent (1 mL) and TOGNI reagent **1** (121 mg, 0.38 mmol, 1.5 equiv.). After stirring in the dark at 80°C for 7 h, the resulting mixture was diluted with 20 mL of diethyl ether and the resulting organic phase was washed with aqueous 1M $NaHCO_3$ (3 x 10 mL), brine (2 x 10 mL), dried over $MgSO_4$ and evaporated. Purification of the crude by column chromatography, eluting with an appropriate cyclohexane/EtOAc or cyclohexane/Et_2O mixture, afforded the desired trifluoromethylated product **3a-i/6a-c** in pure form.

7-Methoxy-3-trifluoromethyl-*2H*-chromen-2-one 3a: Using the general procedure and starting from *ortho*-hydroxylated cinnamic ester **2a**,[15] the expected coumarin **3a** was isolated as a yellowish solid. – Yield: 75 %. – R_f = 0.55 (7:3 PE/EtOAc). – M.p. 111-113°C. – FTIR-ATR (neat): 2990, 2860, 1740, 1610, 1125 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.07 (s, 1H), 7.49 (d, ^3J = 8.8 Hz, 1H), 6.85 (dd, ^3J = 8.8 Hz & ^4J = 2.5 Hz, 1H), 6.85 (d, ^4J = 2.5 Hz, 1H), 3.91 (s, 3H) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.0, 156.8, 156.4, 143.2 (q, $^3J_{C\text{-}F}$ = 4.5 Hz), 130.5, 121.7 (q, $^1J_{C\text{-}F}$ = 271 Hz), 113.9, 113.8 (q, $^2J_{C\text{-}F}$ = 33 Hz), 110.4, 100.7, 56.0 ppm. – ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = -65.65 ppm. – MS (DCI, positive mode) *m/z* (rel intensity) 245 ($[M+H]^+$, 15), 262 ($[M+NH_4]^+$, 100).

3-Trifluoromethyl-*2H*-chromen-2-one 3b: Using the general procedure and starting from *ortho*-hydroxylated cinnamic ester **2b**,[15] the expected coumarin **3b** was isolated as a yellowish solid. – Yield: 69 %. – R_f = 0.35 (8:2 PE/EtOAc). – M.p. 116-118°C. – FTIR-ATR (neat): 3065, 2913, 1730, 1125 cm^{-1}. – ^1H NMR (300 MHz, [D_6]acetone, 25 °C): δ = 8.61 (s, 1H), 7.92 (dd, ^3J = 7.7 Hz & ^4J = 1.5 Hz, 1H), 7.80 (td, ^3J = 7.7 Hz & ^4J = 1.6 Hz, 1H), 7.47 (td, ^3J = 7.6 Hz & ^4J = 1.1 Hz, 1H), 7.45 (bd, ^3J = 7.6 Hz, 1H) ppm. – ^{13}C NMR (75 MHz, [D_6]acetone, 25 °C): δ = 156.3, 155.6, 145.3 (q, $^3J_{C\text{-}F}$ = 4.8 Hz), 135.4, 131.1, 126.0, 122.8 (q, $^1J_{C\text{-}F}$ = 270 Hz), 118.1, 117.6 (q, $^2J_{C\text{-}F}$ = 29 Hz), 117.3 ppm. – ^{19}F NMR (282 MHz, [D_6]acetone, 25 °C): δ = -66.63 ppm. – MS (DCI, positive mode) *m/z* (rel intensity) 214 ($[M+H]^+$, 10), 232 ($[M+NH_4]^+$, 100).

7-(*N,N*-Diethylamino)-3-trifluoromethyl-*2H*-chromen-2-one 3c: Using the general procedure and starting from *ortho*-hydroxylated cinnamic ester **2c**,[15] the expected coumarin **3c** was isolated as a yellowish solid. – Yield: 83 %. – R_f = 0.55 (CH_2Cl_2). – M.p. 52-55°C. – FTIR-ATR (neat): 2980, 1735, 1605, 1520, 1230, 1130 cm^{-1}. – ^1H NMR (300 MHz, [D_6]acetone, 25 °C): δ = 8.24 (s, 1H), 7.58 (d, ^3J = 9.1 Hz, 1H), 6.81 (dd, ^3J = 9.1 Hz & ^4J = 2.5 Hz, 1H), 6.55 (d, ^4J = 2.4 Hz, 1H) ppm. – ^{13}C NMR (75 MHz, [D_6]acetone, 25 °C): δ = 158.7, 157.5, 153.8, 144.6 (q, $^3J_{C\text{-}F}$ = 4.5 Hz), 132.1, 123.9 (q, $^1J_{C\text{-}F}$ = 271 Hz), 110.6, 108.7 (q, $^2J_{C\text{-}F}$ = 32 Hz), 106.9, 97.3, 45.4, 12.6 ppm. – ^{19}F NMR (282 MHz, [D_6]acetone, 25 °C): δ = -65.00 ppm. – MS (DCI, positive mode) *m/z* (rel intensity) 286 ($[MH]^+$, 100). – HRMS (DCI, positive mode): *m/z*: calcd for $C_{14}F_3H_{15}NO_2$ 286.1055, found 286.1057 $[M+H]^+$.

7-Bromo-3-trifluoromethyl-*2H*-chromen-2-one 3d: Using the general procedure[23] and starting from *ortho*-hydroxylated cinnamic ester **2d**,[15] the expected coumarin **3d** was isolated as a white solid. – Yield: 77 %. – R_f = 0.45 (8:2 PE/EtOAc). – M.p. 90-93°C. – FTIR-ATR (neat): 3440,

3065, 1750, 1600, 1140 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.12 (s, 1H), 7.57 (d, ^4J = 1.6 Hz, 1H), 7.54-7.47 (m, 2H) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 155.1, 154.7, 142.6 (q, $^3J_{C-F}$ = 4.8 Hz), 130.3, 128.8, 121.2 (q, $^1J_{C-F}$ = 272 Hz), 120.3, 117.8 (q, $^2J_{C-F}$ = 33 Hz), 115.7 ppm. – ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = -66.20 ppm. – MS (DCI, positive mode) *m/z* (rel intensity) 267 (55), 292 ($[M(^{79}Br)+H]^+$, 100), 294 ($[M(^{81}Br)+H]^+$, 100). – HRMS (DCI, positive mode): *m/z*: calcd for $C_{10}BrF_3H_5O_2$ 292.9423, found 292.9425 $[M+H]^+$.

6-Bromo-3-trifluoromethyl-*2H*-chromen-2-one 3e: Using the general procedure[23] and starting from *ortho*-hydroxylated cinnamic ester **2e**,[15] the expected coumarin **3e** was isolated as a yellowish solid. – Yield: 69 %. – R_f = 0.75 (7:3 PE/EtOAc). – M.p. 116-119°C. – FTIR-ATR (neat): 3065, 1740, 1715, 1635 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.09 (s, 1H), 7.77-7.73 (m, 2H), 7.30-7.27 (m, 1H) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 155.1, 153.4, 142.0 (q, $^3J_{C-F}$ = 4.3 Hz), 137.1, 131.6, 124.6 (q, $^1J_{C-F}$ = 271 Hz), 119.2, 118.7, 118.0 (q, $^2J_{C-F}$ = 30 Hz) ppm. – ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = -66.90 ppm. – MS (DCI, positive mode) *m/z* (rel intensity) 292 ($[M(^{79}Br)+H]^+$, 100), 294 ($[M(^{81}Br)+H]^+$, 100).

6-Nitro-3-trifluoromethyl-*2H*-chromen-2-one 3f: Using the general procedure[23] and starting from *ortho*-hydroxylated cinnamic ester **2f**,[15] the expected coumarin **3f** was isolated as a yellowish solid. – Yield: 49 %. – R_f = 0.65 (8:2 PE/EtOAc). – M.p. 156-159°C. – FTIR-ATR (neat): 3080, 1745, 1620 cm^{-1}. – ^1H NMR (300 MHz, [D_6]acetone, 25 °C): δ = 8.88 (d, ^4J = 2.8 Hz, 1H), 8.83 (s, 1H), 8.60 (dd, ^3J = 9.1 Hz & ^4J = 2.8 Hz, 1H), 7.70 (d, ^3J = 9.1 Hz, 1H) ppm. – ^{13}C NMR (75 MHz, [D_6]acetone, 25 °C): δ = 159.1, 155.4, 145.3, 142.0 (q, $^3J_{C-F}$ = 3.6 Hz), 129.6, 126.8, 122.4 (q, $^1J_{C-F}$ = 271 Hz), 119.4 (q, $^2J_{C-F}$ = 33 Hz), 118.9, 118.5 ppm. – ^{19}F NMR (282 MHz, [D_6]acetone, 25 °C): δ = -67.15 ppm. – MS (DCI, positive mode) *m/z* (rel intensity) 256 ($[M-H]^-$, 100).

3-Trifluoromethyl-*3H*-benzo*[f]*chromen-3-one (3g): Using the general procedure[23] and starting from *ortho*-hydroxylated cinnamic ester **2g**,[15] the expected coumarin **3g** was isolated as a yellowish solid. – Yield: 61 %. – R_f = 0.35 (9:1 PE/EtOAc). – M.p. 156-160°C. – FTIR-ATR (neat): 3070, 1730, 1575 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.88 (s, 1H), 8.24 (d, ^3J = 8.3 Hz, 1H), 8.12 (d, ^3J = 9.0 Hz, 1H), 7.95 (d, ^3J = 8.1 Hz, 1H), 7.77 (td, ^3J = 8.3 Hz & ^4J = 1.2 Hz, 1H), 7.64 (td, ^3J = 8.1 Hz & ^4J = 1.0 Hz, 1H), 7.49 (d, ^3J = 9.0 Hz, 1H) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 156.0, 155.2, 138.8 (q, $^3J_{C-F}$ = 5.1 Hz), 136.0, 130.3, 129.4, 129.3, 129.2, 126.8, 121.6 (q, $^1J_{C-F}$ = 274 Hz), 121.1, 116.6, 116.2 (q, $^2J_{C-F}$ = 35 Hz), 111.2 ppm. – ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = -66.20 ppm. – MS (DCI, positive mode) *m/z* (rel intensity) 265 ($[M+H]^+$, 55).

7-Hydroxy-3-trifluoromethyl-*2H*-chromen-2-one 3h: Using the general procedure and starting from *ortho*-hydroxylated cinnamic ester **2h**,[15] the expected coumarin **3h** was isolated as a yellowish solid. – Yield: 57 %. – R_f = 0.25 (7:3 PE/EtOAc). – M.p. 166-170°C. – FTIR-ATR (neat): 3275, 3095, 1720, 1620 cm^{-1}. – ^1H NMR (300 MHz, [D_6]acetone, 25 °C): δ = 10.09 (s, 1H, OH), 8.47 (s, 1H), 7.77 (d, ^3J = 8.6 Hz, 1H), 6.98 (dd, ^3J = 8.5 Hz & ^4J = 2.4 Hz, 1H), 6.85 (d, ^4J = 2.4 Hz, 1H) ppm. – ^{13}C NMR (75 MHz, [D_6]acetone, 25 °C): δ = 165.5, 158.9, 157.8, 146.2 (q, $^3J_{C-F}$ = 5.0 Hz), 133.7, 124.3 (q, $^1J_{C-F}$ = 270 Hz), 115.9, 114.0 (q, $^2J_{C-F}$ = 33 Hz), 111.9, 104.2 ppm. – ^{19}F NMR (282 MHz, [D_6]acetone, 25 °C): δ = -66.00 ppm. – MS (APCI, positive mode) *m/z* (rel intensity) 211 (100), 231 ($[M+H]^+$, 80).

6,8-Dibromo-7-hydroxy-3-trifluoromethyl-*2H*-chromen-2-one 3i: Using the general procedure and starting from *ortho*-hydroxylated cinnamic ester **2i**,[15] the expected coumarin **3i** was isolated as a yellowish solid, as well as the benzofurane **4** as by-product. – Yield: 40 %. – R_f = 0.15 (3:7 PE/EtOAc). – M.p. 152-155°C. – FTIR-ATR (neat): 3340, 2925, 1735, 1635, 1230 cm^{-1}. – ^1H NMR (300 MHz, [D_6]acetone, 25 °C): δ = 8.51 (s, 1H), 8.16 (s, 1H) ppm. – ^{13}C NMR (75 MHz, [D_6]acetone, 25 °C): δ = 157.4, 155.8, 153.6, 144.3 (q, $^3J_{C-F}$ = 4.8 Hz), 133.3, 122.8 (q, $^1J_{C-F}$ = 271 Hz), 114.7 (q, $^2J_{C-F}$ = 34 Hz), 112.9, 107.9, 99.2 ppm. – ^{19}F NMR (282 MHz, [D_6]acetone, 25 °C): δ = -66.20 ppm. – MS (ESI, positive mode) *m/z* (rel intensity) 385 ($[M(^{79}Br_2)+H]^+$, 50), 387 ($[M(^{79}Br\text{-}^{81}Br)+H]^+$, 100), 389 ($[M(^{81}Br_2)+H]^+$, 50). – HRMS (ESI, positive mode): *m/z*: calcd for $C_{10}Br_2F_3H_2O_3$ 384.8313, found 384.8323/$M+H]^+$.

Benzofurane 4: Yield: 14 %. – R_f = 0.30 (3:7 PE/EtOAc). – FTIR-ATR (neat): 3360, 1695, 1295, 1260, 1170 cm^{-1}. – ^1H NMR (300 MHz, [D_6]acetone, 25 °C): δ = 8.01 (s, 1H), 7.66 (s, 1H), 4.40 (q, ^3J = 7.2 Hz, 2H), 1.38 (t, ^3J = 7.2 Hz, 3H) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 158.3, 153.1, 149.3, 146.5, 124.3, 121.6, 113.5, 107.1, 92.4, 61.7, 14.3 ppm. – MS (DCI, positive mode) *m/z* (rel intensity) 363 ($[M(^{79}Br_2)+H]^+$, 50), 365 ($[M(^{79}Br\text{-}^{81}Br)+H]^+$, 100), 367 ($[M(^{81}Br_2)+H]^+$, 50). – HRMS (DCI, positive mode): *m/z*: calcd for $C_{11}Br_2H_9O_4$ 362.8868, found 362.8867 $[M+H]^+$.

7-Methoxy-3-trifluoromethylquinolin-2*(1H)*-one 6a: Using the general procedure and starting from *ortho*-aminocinnamic ester **5a**,[19] the expected quinoline **6a** was isolated as a white solid. – Yield: 34 %. – R_f = 0.20 (7:3 PE/EtOAc). – M.p. 196-199°C. – FTIR-ATR (neat): 3440, 2925, 1675, 1630, 1120 cm^{-1}. – ^1H NMR (300 MHz, [D_6]acetone, 25 °C): δ = 10.94 (bs, 1H, NH), 8.33 (s, 1H), 7.77 (d, ^3J = 8.8 Hz, 1H), 6.97 (d, ^4J = 2.4 Hz, 1H), 6.91 (dd, ^3J = 8.8 Hz & ^4J = 2.4 Hz, 1H), 3.92 (s, 3H) ppm. – ^{13}C NMR (75 MHz, [D_6]acetone, 25 °C): δ = 164.7, 158.7, 143.3, 141.0 (q, ^3J = 5.2 Hz), 132.1, 120.5 (q, ^1J = 265 Hz), 118.5 (q, ^2J = 31 Hz), 112.9, 112.3, 98.6, 56.1 ppm. – ^{19}F NMR (282 MHz, [D_6]acetone, 25 °C): δ = -65.50 ppm. – MS (ESI, positive mode) *m/z* (rel intensity) 244 ($[M+H]^+$, 60), 240 ($[M+Na]^+$, 70). – HRMS (ESI, positive mode): *m/z*: calcd for $C_{11}F_3H_9NO_2$ 244.0585, found 244.0585 $[M+H]^+$.

3-Trifluoromethylquinolin-2*(1H)*-one 6b: Using the general procedure and starting from *ortho*-aminocinnamic ester **5b**,[19] the expected quinoline **6b** was isolated as a white solid. – Yield: 53 %. – R_f = 0.20 (8:2 PE/EtOAc). – M.p. 192-195°C. – FTIR-ATR (neat): 3340, 2755, 1720, 1625 cm^{-1}. – ^1H NMR (300 MHz, [D_6]acetone, 25 °C): δ = 11.14 (bs, 1H, NH), 8.44 (s, 1H), 7.87 (dd, ^3J = 8.0 Hz & ^4J = 0.9 Hz, 1H), 7.69 (td, ^3J = 7.5 Hz & ^4J = 1.4 Hz, 1H), 7.48 (bd, ^3J = 8.3 Hz, 1H), 7.31 (td, ^3J = 8.0 Hz & ^4J = 1.0 Hz, 1H) ppm. – ^{13}C NMR (75 MHz, [D_6]acetone, 25 °C): δ = 158.4, 141.3 (q, ^3J = 5.6 Hz), 141.2, 133.7, 130.6, 123.7 (q, ^1J = 272 Hz), 123.6, 121.9 (q, ^2J = 30 Hz), 118.2, 116.1 ppm. – ^{19}F NMR (282 MHz, [D_6]acetone, 25 °C): δ = -66.10 ppm. – MS (DCI, positive mode) *m/z* (rel intensity) 214 ($[M+H]^+$, 100).

3,7-Ditrifluoromethylquinolin-2*(1H)*-one 6c: Using the general procedure (METHOD 1) and starting from *ortho*-aminocinnamic ester **5c**, the expected quinoline **6c** was isolated as a white solid. – Yield: 63 %. – R_f = 0.25 (9:1 PE/EtOAc). – M.p. 231-234°C. – FTIR-ATR (neat): 3305, 2920, 1685, 1575, 1325 cm^{-1}. – ^1H NMR (300 MHz, [D_6]acetone, 25 °C): δ = 11.32 (bs, 1H, NH), 8.57 (s, 1H), 8.13 (d, ^3J = 8.2 Hz, 1H), 7.81 (d, ^4J = 1.5 Hz, 1H), 7.60 (dd, ^3J = 8.2 Hz & ^4J = 1.2 Hz, 1H) ppm. – ^{13}C NMR (75 MHz, [D_6]acetone, 25 °C): δ = 158.1, 141.0, 140.7 (q, ^3J = 5.2 Hz), 139.6, 134.1 (q, ^2J = 33 Hz), 132.1, 124.6 (q, ^1J = 272 Hz), 124.3 (q, ^2J = 32 Hz), 123.3 (q, ^1J = 272 Hz), 119.5 (q, ^3J = 3.4 Hz), 113.2 (q, ^3J = 4.2 Hz) ppm. – ^{19}F NMR (282 MHz, [D_6]acetone, 25 °C): δ = -63.70, -66.56 ppm. – MS (ESI, positive mode) *m/z* (rel intensity) 214 (100), 282 ($[M+H]^+$, 40). – HRMS (ESI, positive mode): *m/z*: calcd for $C_{11}F_6H_6NO$ 282.0356, found 282.0354 $[M+H]^+$.

General procedure for the one-pot sequential synthesis of 3-trifluoromethylated coumarins 3a-e from salicylaldehydes: In a microwave reactor under argon were successively added

(carbethoxymethylene)triphenylphosphorane (1.05 equiv.), the salicylaldehyde (1.0 equiv.) and dry DMF as solvent (*ca.* 50 mL per g of salicylaldehyde). After stirring 24 h at room temperature, the reaction was monitored by TLC and proved complete. To the reaction mixture were then added copper(I) iodide (20 mol%) and TOGNI reagent **1** (2.0 equiv.). After stirring in the dark at 80°C for 7 h, the resulting mixture was diluted with 20 mL of diethyl ether and the resulting organic phase was washed with aqueous 1M $NaHCO_3$ (3 x 10 mL), brine (2 x 10 mL), dried over $MgSO_4$ and evaporated. Purification of the crude by column chromatography, eluting with an appropriate cyclohexane/EtOAc or cyclohexane/Et_2O mixture, afforded the desired trifluoromethylated product **3a,c,d** in pure form.

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Keywords: Coumarins • Trifluoromethylation • Radical Reactions • Fluorine • Carbostyrils

[1] For representative books dealing with fluorinated molecules, see: a) R. V. Prakash, *Organofluorine Compounds in Biology and Medicine,* Elsevier, Amsterdam, **2015**; b) V. G. Nenajdenko, *Fluorine in Heterocyclic Chemistry,* Springer, Berlin, **2014**; c) P. Kirsch, *Modern Fluoroorganic Chemistry – Synthesis, Reactivity, Applications,* 2nd Ed., Wiley, Weinheim, **2013**; d) V. A. Petrov, *Fluorinated Heterocyclic Compounds – Synthesis, Chemistry, and Applications,* Wiley, Weinheim, **2009**; e) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology,* Wiley, Chichester, **2009**; f) A. Tressaud, G. Haufe, *Fluorine and Health – Molecular Imaging, Biomedical Materials and Pharmaceuticals,* Elsevier, Amsterdam, **2008**; g) J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine,* Wiley, Hoboken, **2008**; h) K. Uneyama, *Organofluorine Chemistry,* Blackwell, Oxford, **2006**; i) P. Kirsch, *Modern Fluoroorganic Chemistry,* Wiley, Weinheim, **2004**; j) T. Hiyama, *Organofluorine Compounds – Chemistry and Applications,* Springer, Berlin, **2000**.

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[15] For details on the facile one-step Wittig-type preparation of *ortho*-hydroxycinnamic esters **2a-i** from salicylaldehydes, see the Supporting Information.

[16] We choose to continue this work with home-made Togni reagent because **1** is easy to prepare in large scale.

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[18] Further exploitation of this promising result will be reported elsewhere.

[19] For details on the two-step preparation of *ortho*-aminocinnamic esters **5a-c** from *ortho*-nitrobenzaldehydes, see the Supporting Information.

[20] Only trace amount of **3a** detected in TEMPO- and BHT-based inhibition experiments.

[21] For similar works dealing with *E*-stereoselective trifluoromethylation of C=C double-bonds, see Reference 9c and: a) A. Prieto, E. Jeamet, N. Monteiro, D. Bouyssi, O. Baudoin, *Org. Lett.* **2014**, *16*, 4770-4773; b) X.-P. Wang, J.-H. Lin, C.-P. Zhang, J.-C. Xiao, X. Zheng, *Beilstein J. Org. Chem.* **2013**, *9*, 2635-2640; c) H. Egami, R. Shimizu, Y. Usui, M. Sodeoka, *J. Fluorine Chem.* **2014**, *167*, 172-178.

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[23] In that case, the reaction time was extended to 24 h, with addition of CuI (10 mol %) and **1** (0.5 equiv) after 7 h to complete the reaction.

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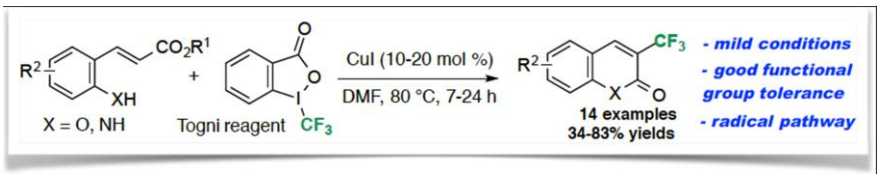

A method for the regioselective synthesis of 3-trifluoromethylated coumarins and carbostyrils *via* the direct trifluoromethylation of appropriately substituted *ortho*-functionalized esters is described. The reaction proceeds with Togni reagent as the CF_3 source under mild conditions and with good functional group tolerance.

Trifluoromethylation*

*Slim Chaabouni, Florent Simonet, Alison François, Souhir Abid, Chantal Galaup, and Stefan Chassaing**

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3-Trifluoromethylated Coumarins and Carbostyrils *via* Radical Trifluoromethylation of *ortho*-Functionalized Esters