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Synthesis of 2-aryl-3,3,3-trifluoropropanoic acids using electrochemical carboxylation of (1-bromo-2,2,2-trifluoroethyl)arenes and its application to the synthesis of β,β,β-trifluorinated non-steroidal *anti*-inflammatory drugs

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ABSTRACT

Electrochemical carboxylation of (1-bromo-2,2,2-trifluoroethyl)arenes resulted in an efficient fixation of carbon dioxide to give the corresponding 2-aryl-3,3,3-trifluoropropanoic acids in good yields, and the present reactions were successfully applied to the synthesis of β,β,β-trifluorinated non-steroidal *anti*-inflammatory drugs (NSAIDs).

1. Introduction

The use of carbon dioxide (CO_2) as a carbon source for chemical reaction is important and an attractive research topic in organic synthesis.[1] One useful and effective method for the reaction of CO_2 and organic compounds with a C–C bond formation involves an electrochemical process. Electrochemical fixation of CO_2 into organic molecules gives carboxylic acids. The fixation can be readily accomplished in high yields under neutral and mild conditions even under an atmospheric pressure of carbon dioxide when a reactive metal, such as magnesium or aluminum, is used as an anode in the electrolysis.[2,3] We have already reported the synthesis of useful carboxylic acids by electrochemical carboxylation (EC) of various organic compounds.[4] On the other hand, it is well known that fluorine-containing organic compounds have unique chemical and physical properties. The introduction of fluorine atoms into biologically-active compounds is also known to cause remarkable modification of their original activities.[5] Therefore, considerable attention has been paid to efficient and selective preparation methods of organofluorine compounds.[6] However, little attention has been paid to EC to afford fluorinated carboxylic acids. Fluorinated benzoic acids were synthesized by EC of trifluoromethyl or fluoroarylhalides.[3a,7] EC of α,α,α-trifluorotoluene[8] and (perfluoroalkyl)alkenes with a nickel catalyst[9] was reported to proceed with C–F bond cleavage to yield the corresponding fluorinated carboxylic acids. We also reported EC of α,α-difluorotoluenes[10] and pentafluoroethylarenes[11] to obtain α-fluorophenylacetic acids and 2-aryl-2,3,3,3-tetrafluoropropanoic acids, respectively. Their applications to the synthesis of α-fluorinated and α,β,β,β-tetrafluorinated non-steroidal *anti*-inflammatory drugs (NSAIDs) were also successfully carried out.[10,11] Although there have been several reports on EC of (1-haroethyl)arenes (1-arylethyl halides) and their application to the synthesis of NSAIDs,[2a,3a,12] to the best of our knowledge, our reports on EC using (1-haroethyl)arenes having fluorine atoms in an ethyl moiety[10,11] are the only examples and no further EC has been reported. We recently found that 2-aryl-3,3,3-trifluoropropanoic acids could be easily synthesized by efficient EC of (1-bromo-2,2,2-trifluoroethyl)arenes, and its application to the synthesis of trifluorinated NSAIDs was successfully carried out. We report herein the synthesis of β,β,β-trifluorinated NSAIDs by EC of (1-bromo-2,2,2-trifluoroethyl)arenes.

2. Results and discussion

2.1. Screening of reaction conditions

(1-Bromo-2,2,2-trifluoroethyl)benzene (**3**), a model substrate, could be easily prepared as shown in Scheme 1. Reduction of

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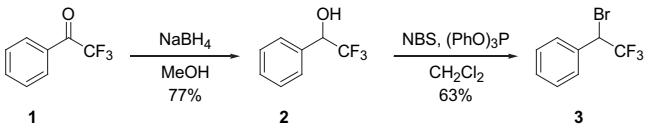
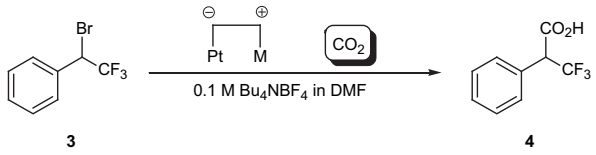


Scheme 1. Synthesis of (1-bromo-2,2,2-trifluoroethyl)benzene **3**.

commercially available 2,2,2-trifluoroacetophenone (**1**) with $NaBH_4$ in MeOH gave the corresponding alcohol **2** in 77% yield. Treatment of **2** with *N*-bromosuccinimide and triphenylphosphite in CH_2Cl_2[13] gave (1-bromo-2,2,2-trifluoroethyl)benzene (**3**) in 63% yield.

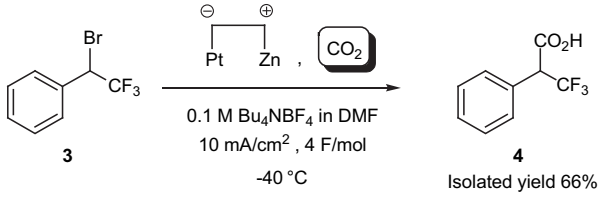
Firstly, screening of reaction conditions, including temperature, current density, electricity, and anode material, in EC was carried out using **3** as a substrate and the results are shown in Table 1. When a constant current electrolysis (10 mA/cm^2) of **3** in DMF containing 0.1 M Bu_4NBF_4 was carried out with 4 F/mol of electricity by using an undivided cell equipped with a Pt cathode and an Mg anode in the presence of CO_2 at 0 °C, expected 3,3,3-trifluoro-2-phenylpropanoic acid (**4**) was obtained in only 22% yield (entry 1). The reactions at lower reaction temperature resulted in increases of the yield of **4** to 60% at −40 °C (entries 2–5). Although no improvement in yield was realized by screening of current density and electricity (entries 6–9), the yield of **4** was improved up to 70% by changing the anode metal from Mg to Zn (entry 10). Concentration effect of the substrate **3** was also examined in EC using a Zn anode (entries 11–12). However, no further improvement in yield was realized. From these screenings, trifluoro-2-phenylpropanoic acid **4** was finally obtained in 66% isolated yield by EC of bromide **3** under optimized conditions as shown in Scheme 2 using an undivided cell

Table 1
Screening of reaction conditions in EC of **3**[a]



Entry	Temperature [°C]	Current Density [mA/cm^2]	Electricity [F/mol]	Anode Material (M)	Yield[b] [%]
1	0	10	4	Mg	22
2	−10	10	4	Mg	33
3	−20	10	4	Mg	40
4	−40	10	4	Mg	60
5	−60	10	4	Mg	58
6	−40	5	4	Mg	56
7	−40	20	4	Mg	23
8	−40	10	3	Mg	41
9	−40	10	5	Mg	44
10	−40	10	4	Zn	70
11[c]	−40	10	4	Zn	37
12[d]	−40	10	4	Zn	55

[a] All reactions were carried out using 1 mmol of bromide **3** in DMF (10 mL).
[b] Yields were determined by ^{19}F NMR.
[c] Reaction was carried out using 2 mmol of bromide **3** in DMF (10 mL).
[d] Reaction was carried out using 0.5 mmol of bromide **3** in DMF (10 mL).



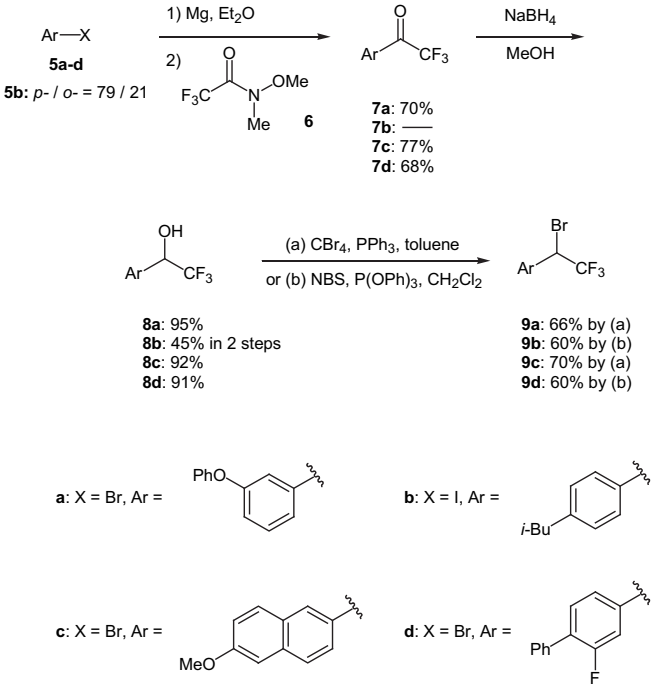
Scheme 2. EC of (1-bromo-2,2,2-trifluoroethyl)benzene **3** under optimized conditions.

equipped with a Pt plate cathode (2×2 cm^2) and a Zn plate anode (2×2 cm^2) (Scheme 2). This acceptable yield of **4** prompted us to apply the present EC to synthesis of β,β,β-trifluorinated NSAIDs.

2.2. Synthesis of β,β,β-trifluorinated NSAIDs by electrochemical carboxylation

2.2.1. Introduction. Several 2-arylpropanoic acids are known to inhibit various types of inflammation and are used as NSAIDs. On the other hand, it was mentioned above that introduction of fluorine atoms into biologically-active compounds often causes remarkable modification of their original activities. Actually, it has been reported that α-fluorination of NSAIDs results in modification of the balance of COX-1/COX-2 inhibitions and that the resulting α-fluorinated NSAIDs show a little *anti*-cancer activity.[14] For these reasons, α-fluorinated NSAIDs having a 2-aryl-2-fluoropropanoic acid moiety are suitable target molecules for organic synthesis, and several successful syntheses have been reported.[10,15] However, to the best of our knowledge, little attention has been paid to the synthesis of β,β,β-trifluoro-NSAIDs,[16] of which biological activities would also be anticipaited.

*2.2.2. Preparation of bromides **9** as precursors of β,β,β-trifluorinated NSAIDs.* Preparation of 1-bromo-2,2,2-trifluoroethylarenes **9** as precursors of β,β,β-trifluoro-NSAIDs was carried out as shown in Scheme 3. Aryl Grignard reagents, generated from the corresponding aryl halides **5**[17] and magnesium in ether, were reacted with Weinreb amide **6**[18] to give the corresponding aryl trifluoromethyl ketones **7**. Reduction of **7** with $NaBH_4$ in MeOH gave alcohols **8**. 1-Bromo-2,2,2-trifluoroethylarenes **9** were successfully obtained by treatment of alcohols **8** with (a) CBr_4 and Ph_3P in toluene[19] for **8a** and **8c** or with (b) NBS and $(PhO)_3P$ in CH_2Cl_2[13] for **8b** and **8d**.

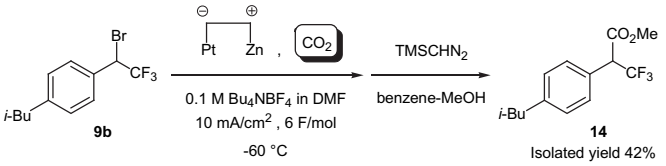


Scheme 3. Synthesis of 1-bromo-2,2,2-trifluoroethylarenes **9**.

2.2.3. Synthesis of β,β,β-trifluorofenoprofen. EC of 1-(1-bromo-2,2,2-trifluoroethyl)-3-phenoxybenzene (**9a**) under optimized conditions as described above resulted in efficient fixation of CO_2 at the benzylic position with a reductive cleavage of a C–Br bond to achieve synthesis of β,β,β-trifluorofenoprofen (**10**) in 70% yield

along with recovery of 17% of **9a** (entry 1 in Table 2). When 5 F/mol of electricity was supplied, the yield of **10** was slightly increased to 80% (entry 2). It should be noted that a small amount of difluorostyrene derivative **11** was observed in both cases in 3% and 4% ^{19}F NMR yields, respectively. Its formation was easily confirmed by a comparison of ^{1}H and ^{19}F NMR spectra of crude products with reported ones of similar difluorostyrenes.[20] Thus, one proton appeared at δ 5.24 (1H, dd, J=25.6 and 3.6 Hz) ppm in ^{1}H NMR and two fluorine atoms also appeared in ^{19}F NMR at δ −83.99 (1F, dd, J=31.3, and 3.6 Hz) and −81.70 (1F, dd, J=31.3, and 25.6 Hz) ppm. It is likely that the formation of **11** is caused by the elimination of a fluoride anion at the β-position from the corresponding benzyl anion generated by electroreductive cleavage of a C–Br bond. Actually, it is well known that β,β,β-trifluoroethyl carbanion species mostly release a fluoride ion spontaneously to give difluoroalkenes.[21] When a similar EC of **9a** was carried out at a higher temperature, 0 °C, the elimination of a fluoride ion was advanced to result in an increase in the yield of **11** and decrease in the yield of **10** (entry 3). On the other hand, it has been reported by us that a similar EC of 1-pentafluoroethyl-3-phenoxybenzene took place efficiently even at 0 °C to give α,β,β,β-tetrafluorofenoprofen in 82% yield without formation of trifluorostyrene.[11] These results indicated that a fluorine atom at the benzylic position in β,β,β-trifluoroethyl carbanion species plays an important role in its stability, although we do not have any explanation for this effect at present.

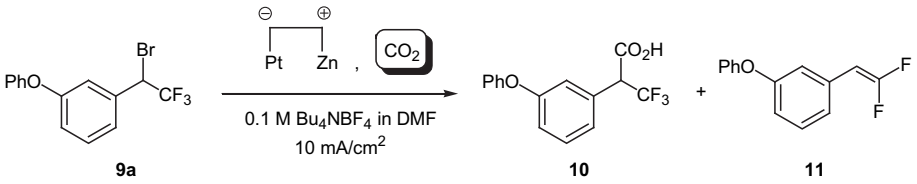
2.2.4. Synthesis of methyl esters of β,β,β-trifluoroibuprofen, -naproxen, and -flurbiprofen. EC of 1-(1-bromo-2,2,2-trifluoroethyl)-4-isobutylbenzene (**9b**) under conditions similar to those for entry 1 in Table 2 surprisingly gave desired carboxylic acid **12** in poor yield along with undesired 2,2-difluorostyrene **13** in 19% yield (entry 1 in Table 3). When the reaction was carried out at a lower temperature, −60 °C, the yield of **12** was improved to 57% along with a decrease in the yield of **13** to 9% (entry 2). Finally, EC of **9b** at −60 °C with 6 F/mol of electricity gave carboxylic acid **12** in 62% ^{19}F NMR yield (entry 3). Since other carboxylic acids were detected by ^{19}F NMR, the desired carboxylic acid was isolated as its methyl ester. Thus, treatment of crude products with trimethylsilyldiazomethane[22] in benzene and MeOH gave methyl ester of **12**, which was purified by column chromatography to give methyl 3,3,3-trifluoro-2-(4-isobutylphenyl)propanoate, β,β,β-trifluoroibuprofen methyl ester (**14**) in 42% isolated yield in two steps (Scheme 4).



Scheme 4. Synthesis of β,β,β-trifluoroibuprofen methyl ester (**14**).

We also investigated the synthesis of two other β,β,β-trifluorinated NSAIDs. Similar EC of 2-(1-bromo-2,2,2-trifluoroethyl)-6-methoxynaphthalene (**9c**) under 5 mA/cm^2 of constant current with 3 F/mol of electricity at −40 °C followed by esterification with trimethylsiliydiazomethane successfully afforded the desired methyl 3,3,3-trifluoro-2-(6-methoxynaphthalen-2-yl)propanoate, β,β,β-trifluoronaproxen methyl ester (**15**) in 48% yield in two steps. In a similar manner, methyl 3,3,3-trifluoro-2-(2-fluorobiphenyl-4-yl)-propanoate, β,β,β-trifluoroflurbiprofen methyl ester (**16**) could also be obtained in 59% yield by EC of **9d** under 5 mA/cm^2 of constant current with 4 F/mol of electricity at −40 °C followed by a similar esterification (Scheme 5).[23]

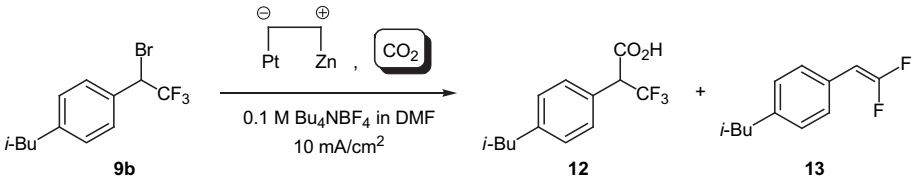
Table 2
Synthesis of β,β,β-trifluorofenoprofen (**10**) by EC of trifluoroethylarene **9a**



Entry	Electricity [F/mol]	Temperature [°C]	Yield [%]		Recovered **9a**[b] [%]
			10[a]	**11**[b]	
1	4	−40	70	3	17
2	5	−40	80	4	7
3	4	0	54	35	2

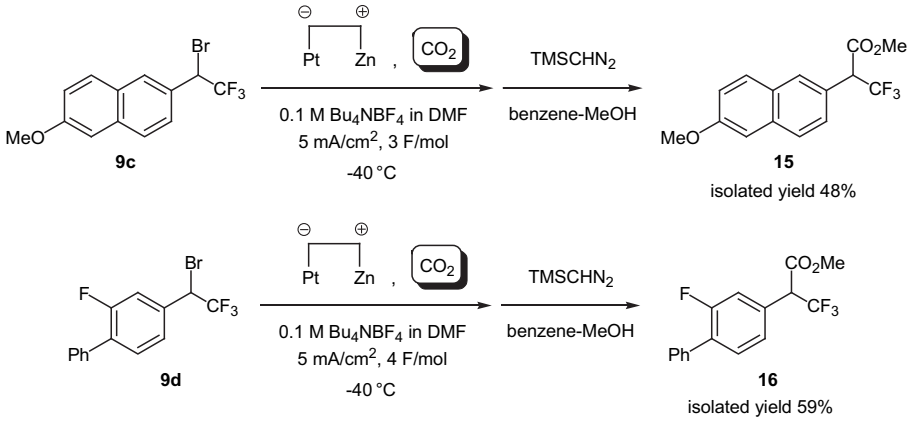
[a] Isolated yield.
[b] Determined by ^{19}F NMR.

Table 3
Synthesis of β,β,β-trifluoroibuprofen (**12**) by EC of **9b**

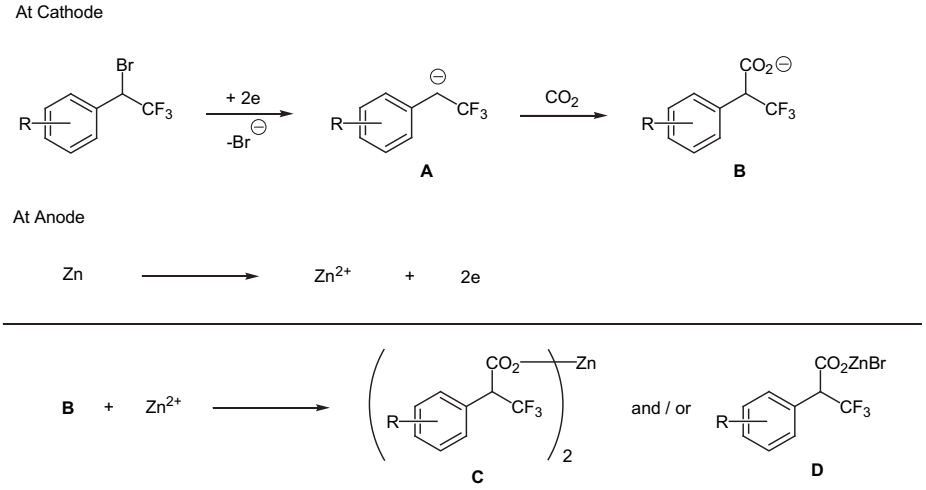


Entry	Electricity [F/mol]	Temperature [°C]	Yield[a] [%]		Recovered **9b**[a] [%]
			12	**13**	
1	4	−40	36	19	10
2	4	−60	57	8	11
3	6	−60	62	6	7

[a] Determined by ^{19}F NMR.



Scheme 5. Synthesis of β,β,β-trifluoronaproxen methyl ester (**15**) and β,β,β-trifluoroflurbiprofen methyl ester (**16**).

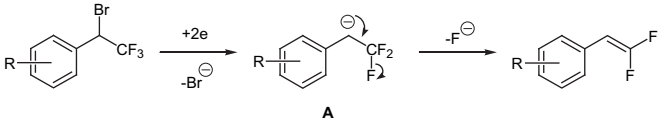


Scheme 6. Probable reaction mechanism.

2.3. Reaction mechanism

A probable reaction mechanism is shown in Scheme 6. At the cathode, two-electron reduction of the substrate results in C–Br bond cleavage at the benzylic position to generate benzylic anion **A** as an intermediate. In cyclic voltammetry of the typical benzyl bromide **3** used as a substrate, an irreversible reduction peak appears at −1.9 V Ag/Ag$^+$ and these results indicate that electrochemical reduction of the benzyl bromide would take place easily and smoothly. The anion **A** attacks CO_2 to give carboxylate ion **B**. On the other hand, at the anode, dissolution of zinc takes place to produce zinc ion, which captures carboxylate ion **B** to give zinc carboxylate **C** and/or **D**. Acid treatment in workup gives the corresponding carboxylic acid.

As mentioned earlier, β,β,β-trifluoroethyl anion is mostly known to release a fluoride ion spontaneously to give difluoroalkenes.[21] In the present EC, benzyl anion **A** thus generated has fluorine atoms at the neighboring carbon of an anion center. Elimination of a fluoride ion would proceed competitively to give difluorostyrene as a by-product, resulting in a decrease in yield of the expected product. When the EC of **9a** was carried out at 0 °C, the elimination of a fluoride ion producing difluorostyrene **11** was advanced in contrast to the reaction at −40 °C (Table 1). On the other hand, the reaction at −60 °C could suppress the elimination, resulting in an increase in the yield of acid **10**. These results indicated that the elimination of a fluoride ion from anion **A** would depend on its thermal conditions and would be closely related to its stability[21] (Scheme 7).



Scheme 7. Probable reaction mechanism affording difluoroalkene.

3. Conclusion

In conclusion, we have succeeded in synthesis of 2-aryl-3,3,3-trifluoropropanoic acids by the electrochemical reduction of (1-bromo-2,2,2-trifluoroethyl)arenes in the presence of CO_2 using a Pt cathode and a Zn anode. This new method was also shown to be effective for the synthesis of β,β,β-trifluorinated non-steroidal *anti*-inflammatory drugs.

4. Experimental section

4.1. General

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a JASCO FT/IR-410 spectrometer in neat form unless otherwise stated. ^{1}H (400 MHz), ^{13}C (100 MHz), and ^{19}F (372.5 MHz) NMR spectra were recorded in $CDCl_3$ with a JEOL ECX-400P FTNMR spectrometer. The chemical shifts, δ, are given in ppm with

tetramethylsilane (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F) as references, respectively. *J* values are in Hertz. MS spectra were determined using a JEOL JMS-T100GC (EI) and Thermo Scientific Exactive (ESI). Electrochemical reactions were carried out using Constant Current Power Supply (model 5944), Metronix Corp. Tokyo. CV was measured by Hokuto Denko HSV-100 with a Pt wire (φ 1 mm) and Ag/Ag^+ as a working electrode and a reference electrode, respectively. Column chromatography was carried out using Kanto Kagaku Silica gel 60 N with hexane/EtOAc as an eluent. All reagents and solvents were commercially available and were used as received without further purification. 1-Bromo-3-phenoxybenzene (**5a**)[17a] and 1-iodo-4-isobutylbenzene (**5b**, a 79/21 mixture of *p*-/*o*- isomers)[17b,c] were prepared by the reported procedure.

4.2. Preparation of aryl trifluoromethyl ketones: general procedure

To a flask that was charged with Mg (267 mg, 11 mmol) in dry Et_2O (10 mL) under N_2 was dropwise added a solution of aryl halide **5** (10 mmol) in dry Et_2O (5 mL) and a few drops of 1,2-dibromoethane. After the addition was completed, the mixture was refluxed for 1 h. The reaction mixture was then cooled to 0 °C and then Winereb amide **6**[18] (10 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was poured into 150 mL of 1 M HCl. The aqueous solution was extracted with Et_2O (3×30 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification with column chromatography gave aryl trifluoromethyl ketone **7**. In the case of reaction of **5b**, which is a mixture of regioisomers (*p*-/*o*-=79/21), isolation of the product **7b** was not carried out at this stage since it is difficult to separate **7b** and its regioisomer (*p*-/*o*-=92/8 by ^{1}H NMR).

*4.2.1. 2,2,2-Trifluoro-1-(3-phenoxyphenyl)ethanone (**7a**).* Isolated Yield: 70%. IR: 3071, 1721, 1581, 1489, 1444, 1245, 1204, 1146, 872, 754 cm^{-1}. ^{1}H NMR (400 MHz): δ 7.02–7.06 (m, 2H), 7.16–7.21 (m, 1H), 7.31–7.42 (m, 3H), 7.50 (t, *J*=8.0 Hz, 1H), 7.68 (s, 1H), 7.78 (d, *J*=7.8 Hz, 1H). ^{13}C NMR (100 MHz): δ 116.5 (q, *J*=291.2 Hz), 119.2 (q, *J*=1.9 Hz), 119.4, 124.4, 124.5 (q, *J*=2.4 Hz), 125.4, 130.1, 130.5, 131.3, 155.9, 158.2, 179.9 (q, *J*=35.3 Hz). ^{19}F NMR (372.5 MHz): δ −72.04 (s, 3F). HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_9F_3O_2$ 266.0555. Found 266.0555.

*4.2.2. 2,2,2-Trifluoro-1-(6-methoxynaphthalen-2-yl)ethanone (**7c**).* Isolated Yield: 77%. Mp: 64–66 °C IR (KBr): 2941, 1698, 1624, 1484, 1401, 1269, 1167, 1027, 902 cm^{-1}. ^{1}H NMR (400 MHz): δ 3.97 (s, 3H), 7.17 (d, *J*=2.4 Hz, 1H), 7.23–7.27 (m, 1H), 7.82 (d, *J*=8.9 Hz, 1H), 7.90 (d, *J*=9.1 Hz, 1H), 8.05 (d, *J*=8.7 Hz, 1H), 8.54 (s, 1H). ^{13}C NMR (100 MHz): δ 55.4, 105.8, 117.0 (q, *J*=291.6 Hz), 120.4, 125.0 (q, *J*=1.7 Hz), 125.0, 127.5, 127.6, 131.8, 132.9 (q, *J*=2.6 Hz), 138.4, 161.0, 180.0 (q, *J*=34.6 Hz). ^{19}F NMR (372.5 MHz): δ −71.16 (s, 3F). HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{19}F_3O_2$ 254.0555. Found 254.0553.

*4.2.3. 2,2,2-Trifluoro-1-(3-fluoro-4-phenylphenyl)ethanone (**7d**).* Isolated Yield: 68%. Mp: 54–56 °C IR (KBr): 3078, 1714, 1614, 1425, 1209, 1132, 848, 753, 739, 719, 699 cm^{-1}. ^{1}H NMR (400 MHz): δ 7.43–7.54 (m, 3H), 7.58–7.62 (m, 2H), 7.65 (d, *J*=7.8 Hz, 1H), 7.87 (d, *J*=10.9 Hz, 1H), 7.94 (d, *J*=8.2 Hz, 1H). ^{13}C NMR (100 MHz): δ 116.5 (q, *J*=290.9 Hz), 117.5 (dq, *J*=25.8, 1.9 Hz), 125.9–126.1 (m), 128.6, 128.9 (d, *J*=3.6 Hz), 129.0, 130.1 (d, *J*=7.2 Hz), 131.3 (d, *J*=3.6 Hz), 133.8 (d, *J*=1.4 Hz), 136.4 (d, *J*=13.8 Hz), 159.5 (d, *J*=251.1 Hz), 178.9 (qd, *J*=35.5, 2.2 Hz). ^{19}F NMR (372.5 MHz): δ −72.10 (s, 3F), −115.69 (m, 1F). HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_8F_4O$ 268.0511. Found 268.0508.

4.3. Preparation of 1-aryl-2,2,2-trifluoroethanol: general procedure

To a solution of aryl trifluoromethyl ketone (**1** or **7**, 10 mmol) in MeOH (10 mL) was added $NaBH_4$ (378 mg, 10 mmol) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was poured into 1 M HCl (200 mL). The resulting aqueous solution was extracted with Et_2O (3×30 mL) and the ethereal solution was dried over $MgSO_4$. Evaporation of the solvent followed by purification with column chromatography gave 1-aryl-2,2,2-trifluoroethanol **2** or **8**.

*4.3.1. 2,2,2-Trifluoro-1-phenylethanol (**2**)*[24,25]. Isolated Yield: 77%. ^{1}H NMR (400 MHz): δ 2.57 (d, *J*=4.4 Hz, 1H), 4.99–5.06 (m, 1H), 7.40–7.49 (m, 5H). ^{19}F NMR (372.5 MHz): δ −78.97 (d, *J*=6.7 Hz, 3F).

*4.3.2. 2,2,2-Trifluoro-1-(3-phenoxyphenyl)ethanol (**8a**)*[25]. Isolated Yield: 95%. ^{1}H NMR (400 MHz): δ 2.50 (d, *J*=4.6 Hz, 1H), 4.97–5.04 (m, 1H), 7.01–7.05 (m, 3H), 7.11–7.16 (m, 2H), 7.21 (d, *J*=7.8 Hz, 1H), 7.33–7.40 (m, 3H). ^{13}C NMR (100 MHz): δ 72.4 (q, *J*=32.4 Hz), 117.7, 119.1, 119.6, 122.0, 123.7, 124.1 (q, *J*=282.1 Hz), 129.9, 130.0, 135.8, 156.6, 157.5. ^{19}F NMR (372.5 MHz): δ −78.96 (d, *J*=6.7 Hz, 3F).

*4.3.3. 2,2,2-Trifluoro-1-(4-isobutylphenyl)ethanol (**8b**).* Isolated Yield: 45% from **5b** (two steps). IR (neat): 3398, 2957, 1270, 1171, 1129 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.90 (d, *J*=6.6 Hz, 6H), 1.81–1.92 (m, 1H), 2.48 (d, *J*=4.6 Hz, 1H), 2.49 (d, *J*=7.3 Hz, 2H), 4.96–5.03 (m, 1H), 7.19 (d, *J*=8.2 Hz, 2H), 7.38 (d, *J*=8.2 Hz, 2H). ^{13}C NMR (100 MHz): δ 22.3, 30.1, 45.1, 72.8 (q, *J*=32.4 Hz), 124.3 (q, *J*=281.7 Hz), 127.2, 129.4, 131.2, 143.3. ^{19}F NMR (372.5 MHz): δ −78.98 (d, *J*=6.7 Hz, 3F). HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{15}F_3O$ 232.1075. Found 232.1075.

*4.3.4. 2,2,2-Trifluoro-1-(6-methoxynaphthalen-2-yl)ethanol (**8c**)*[26]. Isolated Yield: 89%. Mp: 99–100 °C IR (KBr): 3262, 2941, 1632, 1610, 1490, 1392, 1268, 1175, 1129, 860, 690 cm^{-1}. ^{1}H NMR (400 MHz): δ 2.59 (d, *J*=4.5 Hz, 1H), 3.94 (s, 3H), 5.13–5.20 (m, 1H), 7.15 (d, *J*=2.4 Hz, 1H), 7.19 (dd, *J*=9.0, 2.4 Hz, 1H), 7.54 (d, *J*=8.6 Hz, 1H), 7.77 (d, *J*=8.7 Hz, 1H), 7.78 (d, *J*=8.7 Hz, 1H), 7.88 (s, 1H). ^{19}F NMR (372.5 MHz): δ −78.73 (d, *J*=6.7 Hz, 3F).

*4.3.5. 2,2,2-Trifluoro-1-(3-fluoro-4-phenylphenyl)ethanol (**8d**).* Isolated Yield: 91%. Mp: 63–64 °C. IR (KBr): 3389, 2939, 1582, 1489, 1422, 1255, 1132, 824, 698 cm^{-1}. ^{1}H NMR (400 MHz): δ 2.68 (d, *J*=4.6 Hz, 1H), 5.04–5.11 (m, 1H), 7.31–7.57 (m, 8H). ^{13}C NMR (100 MHz): δ 71.9 (qd, *J*=32.2, 1.4 Hz), 115.2 (d, *J*=24.8 Hz), 123.4 (d, *J*=2.9 Hz), 124.0 (q, *J*=282.3 Hz), 128.0, 128.5, 128.9 (d, *J*=3.1 Hz), 130.2 (d, *J*=13.6 Hz), 130.9 (d, *J*=3.8 Hz), 134.8, 134.9, 159.5 (d, *J*=248.9 Hz). ^{19}F NMR (372.5 MHz): δ −78.91 (d, *J*=6.7 Hz, 3F), −117.53 (m, 1F). HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{10}F_4O$ 270.0668. Found 270.0668.

4.3.6. Preparation of 1-bromo-2,2,2-trifluoroethylarenes: method A[13]. To a solution of 1-aryl-2,2,2-trifluoroethanol (**2**, **8b** or **8d**, 5 mmol) in CH_2Cl_2 (10 mL) was added *N*-bromosuccinimide (1.78 g, 10 mmol) and triphenylphosphite (3.10 g, 10 mmol), and then the mixture was stirred at 40 °C for 12 h. After evaporation of the solvent, ether (100 mL) was added to the residue and the insoluble solid was removed by filtration through Celite. Evaporation followed by purification with column chromatography gave 1-bromo-2,2,2-trifluoroethylarene **3**, **9b**, or **9d**.

*4.3.7. 1-(1-Bromo-2,2,2-trifluoroethyl)benzene (**3**).* Isolated Yield: 63%. IR (neat): 3072, 1259, 1166, 1112, 697 cm^{-1}. ^{1}H NMR (400 MHz): δ 5.12 (q, *J*=7.5 Hz, 1H), 7.37–7.44 (m, 3H), 7.48–7.54 (m, 2H). ^{13}C NMR (100 MHz): δ 47.1 (q, *J*=33.9 Hz), 123.5 (q, *J*=277.8 Hz), 128.9, 129.1, 130.0, 132.8. ^{19}F NMR (372.5 MHz): δ −71.06 (d, *J*=7.5 Hz, 3F). HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_8H_6BrF_3$ 237.9605. Found 237.9604.

*4.3.8. 1-(1-Bromo-2,2,2-trifluoroethyl)-4-isobutylbenzene (**9b**).* Isolated Yield: 60%. IR (neat): 2958, 2916, 1260, 1160, 1112, 678 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.91 (d, *J*=6.8 Hz, 6H), 1.81–1.93

(m, 1H), 2.49 (d, J=7.3 Hz, 1H), 5.11 (q, J=7.5 Hz, 1H), 7.16 (d, J=8.2 Hz, 2H), 7.40 (d, J=8.2 Hz, 2H). ^{13}C NMR (100 MHz): δ 22.2, 30.1, 45.1, 47.2 (q, J=34.1 Hz), 123.5 (q, J=277.8 Hz), 128.9, 129.6, 130.1, 144.0. ^{19}F NMR (372.5 MHz): δ −71.09 (d, J=7.5 Hz, 3F). HRMS (EI): m/z [M]$^+$ calcd for $C_{12}H_{14}BrF_3$ 294.0231. Found 294.0227.

*4.3.9. 2-Fluoro-4-(1-bromo-2,2,2-trifluoroethyl)biphenyl (**9d**).* Isolated Yield: 60%. Mp: 53–54 °C IR (KBr): 3063, 1422, 1256, 1168, 1105, 782, 688 cm^{-1}. ^{1}H NMR (400 MHz): δ 5.15 (q, J=7.4 Hz, 1H), 7.32–7.50 (m, 6H), 7.53–7.57 (m, 2H). ^{13}C NMR (100 MHz): δ 45.9 (qd, J=34.3, 1.9 Hz), 117.1 (dq, J=25.3, 1.0 Hz), 123.3 (q, J=278.0 Hz), 125.1 (dq, J=3.3, 1.0 Hz), 128.3, 128.6, 128.9 (d, J=3.1 Hz), 130.9 (d, J=13.6 Hz), 131.1 (d, J=4.1 Hz), 133.6 (dq, J=7.9, 1.0 Hz), 134.6 (d, J=1.4 Hz), 159.4 (d, J=249.9 Hz). ^{19}F NMR (372.5 MHz): δ −70.96 (d, J=7.4 Hz, 3F), −116.77 (m, 1F). HRMS (EI): m/z [M]$^+$ calcd for $C_{14}H_9BrF_4$ 331.9824. Found 331.9822.

4.3.10. Preparation of 1-bromo-2,2,2-trifluoroethylarenes: method B[19]. To a solution of triphenylphosphine (1.31 g, 5 mmol) in toluene (5 mL) was added a solution of 1-aryl-2,2,2-trifluoroethanol (**8a** or **8c**, 5 mmol) and carbon tetrabromide (1.66 g, 5 mmol) in toluene (10 mL). The mixture was then stirred at 60 °C for 15 h. After the solid had been removed by filtration, the filtrate was diluted with Et_2O (100 mL), washed with satd $NaHCO_3$ (2×40 mL), and dried over $MgSO_4$. Evaporation of the solvent and purification with column chromatography gave 1-bromo-2,2,2-trifluoroethylarene **9a** or **9c**.

*4.3.11. 1-(1-Bromo-2,2,2-trifluoroethyl)-3-phenoxybenzene (**9a**).* Isolated Yield: 66%. IR (neat): 3064, 1580, 1469, 1236, 894 cm^{-1}. ^{1}H NMR (400 MHz): δ 5.12 (q, J=7.5 Hz, 1H), 6.99–7.054 (m, 3H), 7.13–7.18 (m, 2H), 7.21–7.24 (m, 1H), 7.32–7.40 (m, 3H). ^{13}C NMR (100 MHz): δ 46.5 (q, J=34.3 Hz), 119.2, 119.3, 119.8, 123.3 (q, J=277.6 Hz), 123.6, 123.9, 129.9, 130.2, 134.5, 156.3, 157.7. ^{19}F NMR (372.5 MHz): δ −71.01 (d, J=7.4 Hz, 3F). HRMS (EI): m/z [M]$^+$ calcd for $C_{14}H_{10}BrF_3O$ 329.9867. Found 329.9867.

*4.3.12. 1-(1-Bromo-2,2,2-trifluoroethyl)-6-methoxynaphthalene (**9c**).* Isolated Yield: 70%. Mp: 78–79 °C. IR (KBr): 2961, 1631, 1255, 1175, 1107, 1029 cm^{-1}. ^{1}H NMR (400 MHz): δ 3.93 (s, 3H), 5.28 (q, J=7.5 Hz, 1H), 7.13–7.17 (m, 1H), 7.19 (dd, J=9.1, 2.6 Hz, 1H), 7.58 (d, J=8.5 Hz, 1H), 7.76 (t, J=8.2 Hz, 1H), 7.86 (s, 1H). ^{13}C NMR (100 MHz): δ 47.7 (q, J=34.3 Hz), 55.3, 105.6, 119.8, 123.5 (q, J=278.5 Hz), 126.1, 127.6, 127.7, 128.1, 128.8, 129.7, 135.1, 158.8. ^{19}F NMR (372.5 MHz): δ −70.75 (d, J=7.5 Hz, 3F). HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_{10}BrF_3O$ 317.9867. Found 317.9868.

4.4. Synthesis of 2-aryl-3,3,3-trifluoropropanoic acid by electrochemical carboxylation of 1-bromo-2,2,2-trifluoroethylarene followed by esterification: general procedure

A solution of 1-bromo-2,2,2-trifluoroethylarene (**3** or **9**, 1.0 mmol) in anhyd DMF (10 mL) containing Bu_4NBF_4 (0.1 M) was electrolyzed at 0 °C with a constant current (5 or 10 mA/cm^2) under an atmospheric pressure of bubbling carbon dioxide (flow rate of CO_2; ca. 50 mL/min). An undivided cell equipped with a Pt plate cathode (2×2 cm^2) and a Zn plate anode (2×2 cm^2) was used for the electrolysis. After an appropriate amount of electricity was passed (shown in schemes), the electrolyzed solution was poured into 1 M HCl (100 mL) and then extracted with Et_2O (3×30 mL).

*4.4.1. In the case of reaction of **3** or **9a**.* The combined ethereal solution was washed with satd $NaHCO_3$ (3×40 mL). The resulting aqueous solution was acidified with 3 M HCl and then extracted with Et_2O (3×30 mL). The combined ethereal solution was washed with satd brine and dried over $MgSO_4$. Evaporation of the solvent gave an almost pure 2-aryl-3,3,3-trifluoropropanoic acid **4** or **10**.

*4.4.2. In the case of reaction of **9b**, **9c**, or **9d**.* The combined ethereal solution was dried over $MgSO_4$ and was evaporated to give a crude product. To a solution of the crude product in benzene (7 mL) and MeOH (2 mL) was added 2 M solution of trimethylsilyldiazomethane[22] in Et_2O (1 mL) and the resulting solution was stirred at room temperature for 30 min. Evaporation followed by purification with column chromatography afforded methyl 2-aryl-3,3,3-trifluoropropanoate **14**, **15** or **16**.

*4.4.3. 3,3,3-Trifluoro-2-phenylpropanoic acid (**4**)[27].* Isolated Yield: 66%. ^{1}H NMR (400 MHz): δ 4.37 (q, J=8.5 Hz, 1H), 7.39–7.48 (m, 5H). ^{19}F NMR (372.5 MHz): δ −68.26 (d, J=8.5 Hz, 3F).

*4.4.4. 3,3,3-Trifluoro-2-(3-phenoxyphenyl)propanoic acid (**10**).* Isolated Yield: 80%. IR (neat): 3065, 2925, 1731, 1586, 1489, 1258, 1163, 1119, 909, 735 cm^{-1}. ^{1}H NMR (400 MHz): δ 4.32 (q, J=8.5 Hz, 1H), 7.00–7.05 (m, 3H), 7.11–7.20 (m, 3H), 7.32–7.39 (m, 3H). ^{13}C NMR (100 MHz): δ 55.1 (q, J=29.3 Hz), 119.2, 119.3, 119.8, 123.3 (d, J=280.2 Hz), 123.9, 123.9, 129.9, 130.3 (q, J=1.7 Hz), 130.3, 156.4, 157.9, 171.8 (q, J=2.6 Hz). ^{19}F NMR (372.5 MHz): δ −68.09 (d, J=8.5 Hz, 3F). HRMS (ESI): m/z [M−COOH]$^+$ calcd for $C_{14}H_{10}F_3O$ 251.0689. Found 251.0696.

*4.4.5. Methyl 3,3,3-trifluoro-2-(4-isobutylphenyl)propanoate (**14**).* Isolated Yield: 42% (two steps). IR: (neat) 2958, 1754, 1359, 1261, 1156, 1111, 1013 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.90 (d, J=6.6 Hz, 6H), 1.80–1.92 (m, 1H), 2.48 (d, J=7.2 Hz, 1H), 3.77 (s, 3H), 4.29 (q, J=8.6 Hz, 1H), 7.16 (d, J=8.1 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H). ^{13}C NMR (100 MHz): δ 22.3, 30.1, 45.0, 52.8, 55.0 (q, J=28.8 Hz), 123.7 (q, J=279.7 Hz), 126.5 (q, J=1.9 Hz), 129.1, 129.6, 143.0, 166.8 (q, J=2.9 Hz). ^{19}F NMR (372.5 MHz): δ −68.47 (d, J=8.6 Hz, 3F). HRMS (EI): m/z [M]$^+$ calcd for $C_{14}H_{17}F_3O_2$ 274.1181. Found 274.1181.

*4.4.6. Methyl 3,3,3-trifluoro-2-(6-methoxynaphthalen-2-yl)propanoate (**15**).* Isolated Yield: 48% (two steps). Mp: 107–109 °C IR (KBr): 2972, 1754, 1607, 1443, 1354, 1258, 1154, 1108, 857 cm^{-1}. ^{1}H NMR (400 MHz): δ 3.78 (s, 3H), 3.93 (s, 3H), 4.45 (q, J=8.5 Hz, 1H), 7.12–7.15 (m, 1H), 7.18 (dd, J=9.1, 2.6 Hz, 1H), 7.48 (d, J=8.4 Hz, 1H), 7.76 (dd, J=8.9, 3.8 Hz, 2H), 7.83 (s, 1H). ^{13}C NMR (100 MHz): δ 52.9, 55.2 (q, J=29.1 Hz), 55.3, 105.5, 119.6, 123.8 (q, J=280.0 Hz), 124.2 (q, J=1.9 Hz), 126.7, 127.6, 128.6, 129.0, 129.6, 134.7, 158.4, 166.8 (q, J=2.9 Hz). ^{19}F NMR (372.5 MHz): δ −68.20 (d, J=8.5 Hz, 3F). HRMS (EI): m/z [M]$^+$ calcd for $C_{15}H_{13}F_3O_3$ 298.0817. Found 298.0816.

*4.4.7. Methyl 2-(2-fluoro-3-phenylphenyl)-3,3,3-trifluoropropanoate (**16**).* Isolated Yield: 59% (two steps). IR (neat): 2958, 1754, 1271, 1164, 1112, 1014 cm^{-1}. ^{1}H NMR (400 MHz): δ 3.82 (s, 3H), 4.36 (q, J=8.5 Hz, 1H), 7.26–7.32 (m, 3H), 7.37–7.42 (m, 1H), 7.43–7.50 (m, 2H), 7.52–7.56 (m, 2H). ^{13}C NMR (100 MHz): δ 53.1, 54.7 (qd, J=29.6, 1.4 Hz), 117.3 (d, J=24.8 Hz), 123.4 (q, J=280.0 Hz), 125.6 (d, J=3.6 Hz), 128.1, 128.5, 128.9 (d, J=3.1 Hz), 130.0 (qd, J=8.1, 1.9 Hz), 130.2 (d, J=13.8 Hz), 131.2 (d, J=4.1 Hz), 134.8 (d, J=1.2 Hz), 159.6 (d, J=249.4 Hz), 166.1 (q, J=2.6 Hz). ^{19}F NMR (372.5 MHz): δ −68.11 (d, J=8.5 Hz, 3F), −117.01 (m, 1F). HRMS (EI): m/z [M]$^+$ calcd for $C_{16}H_{12}F_4O_2$ 312.0773. Found 312.0768.

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