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Perfluorobutylation of benzo(hetero)arenes in aqueous media

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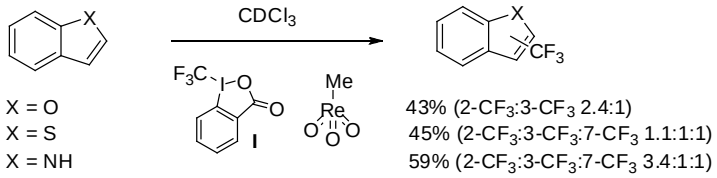
ABSTRACT

Perfluorobutylation of a series of benzo(hetero)aromatic compounds without formal leaving groups is achieved efficaciously in organic solvent-water mixtures under photostimulation. The methodology is compared with previously reported trifluoromethylation strategies of these nuclei in terms of product yields and regioselectivity. The reaction is a radical homolytic aromatic substitution process, where the perfluoroalkyl-substituted cyclohexadienyl radical intermediate is first oxidized and then a proton transfer sequence leads to the products.

Keywords: *radical reactions in aqueous media, C-H perfluoroalkylation, homolytic aromatic substitution, perfluoroalkylation, dibenzoheteroarenes.*

1. INTRODUCTION

A distinct division between innate perfluoroalkylation reagents, which accomplish substitution of aromatic nuclei without formal leaving groups, and those which substitute functionalized aromatic substrates can be established [1]. Among the former, the Langlois reagent [2], NaSO2Rf, has intensively been used under mild radical initiation conditions with tBuOOH affording perfluoroalkyl-substituted aromatic compounds in good yields in aqueous media.



Scheme 1. Usage of Togni´s reagent and methyl trioxorhenium as catalyst for the trifluoromethylation of heteroaromatic compounds.

Togni and collaborators have achieved the trifluoromethylation of a series of heteroaromatic compounds employing the hypervalent iodine reagent 1-(trifluoromethyl)-1,2-benziodoxol-3-(1H)-one (I) (Scheme 1) and methyl trioxorhenium as catalyst [3]. Very recently, this reagent (I) has been employed in the perfluoroalkylation of phenanthridines through a radical mechanism using dioxane as solvent, in the absence of methyl-trioxorhenium catalyst [3]. A review article highlighting important examples of radical trifluoromethylation and perfluoroalkylation reactions making use of these new reagents has recently been published [4]. Photocatalysts have also been employed to accomplish homolytic perfluoroalkylation reactions of aromatic and heteroaromatic compounds in organic solvents [5].

A photochemical method for achieving radical perfluoroalkylation reactions of aromatic nuclei in water and aqueous media through an ion-radical chain sequence, with aromatic compounds without formal leaving groups has recently been discussed [6]. This methodology turned out to be very suitable for electron-rich aromatic substrates, where an electron transfer (ET), and then proton transfer (PT) steps afford the substitution products.

We herein present a photoinduced method to obtain a direct C-H perfluorobutylation reaction of benzo(hetero)arenes in aqueous media, as a novel addition to the synthesis methods of perfluoroalkyl-substituted fused aromatics and heteroaromatic nuclei of biological and technological relevance. This methodology circumvents the use of transition metal reagents or catalysts and uses mild initiating techniques.

2. EXPERIMENTAL SECTION

Most of theseparation, irradiation, and purification procedures used in this study have been reported earlier [6].Some of the preparative TLC techniques employed a fluorous phase system, consisting of a mixture of 1-methyl-perfluorodecaline:iso-octane (1:1). NMR analyses were performed using CDCl3 as solvent or as noted otherwise. 2D-NMR experiments performed to assign 1H-1H, and 1H-13C connectivities include COSY-45, HSQC, HMBC, and HOESY and NOESY techniques. Irradiation of mixtures was carried out under conditions where only primary photoproducts were obtained, and in most cases the total substrate conversion was kept lower than 45%.

3-perfluorobutyl-1H-indole (6): Yellow oil, 17%, 6.1 mg. 1H-NMR (500 MHZ, CDCl3)δH ppm: 8.69 (s, 1H), 7.68 (d, J= 7.6 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.44-7.50 (m, 2H) and 7.11 (s, 1H). 13C-NMR (125 MHz, CDCl3) δC ppm: 137.5, 132.1, 126.1, 125.7, 124. 7, 121.8, 116.2 and 106.2. MS EI (70 eV) m/z (%): 335 (24), 167 (17), 166 (100), 83 (12) and 69 (11). 19F-NMR (470.4MHZ, CDCl3) δF (ppm): - 80.06, - 108.70, - 123.13 and

125.25. EI-HRMS Anal. Calcd. for C12H6F9N: 335.0357. Found: 335.0360.

2-perfluorobutyl-1H-indole (7): Yellow oil, 8%, 3.1 mg. 1H-NMR (500 MHZ, CDCl3) δH ppm: 8.43 (s, 1H), 7.70 (d, J: 8.1 Hz, 1H), 7.44-7.50 (m, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.21 (t, J= 7.9 Hz, 1H) and 6.98 (s, 1H). 13C-NMR (125 MHz, CDCl3) δC ppm: 137.4, 131.1, 129.2, 125.5, 122.5, 121.6, 120.4 and 106.9. 19F-NMR (470.4 MHZ, CDCl3) δF ppm: - 80.98, - 109.21, - 122.46, - 123.03 and 125.64. MS EI (70 eV) m/z (%): 336 (10), 335 (29), 316 (7), 197 (6), 166 (100), 119 (15), 83 (12) and 69 (14). EI-HRMS Anal. Calcd. for C12H6F9N: 335.0357. Found: 335.0358.

1-methyl-2-perfluorobutyl-1H-indole (8): Yellow oil. 35%, 11.5 mg. 1H-NMR (500 MHZ, CDCl3) δH ppm: 7.69 (d, J = 8.0Hz, 1H), 7.41 (d, J = 8.4Hz, 1H), 7.38 (t, J = 8.7Hz, 1H), 7.20 (dt, J = 1.3, 8.0 Hz, 1H), 6.97 (s, 1H) and 3.86 (s, 3H). 13C-NMR (125 MHZ, CDCl3) δC ppm: 139.4, 126.2, 125.5, 124.7, 122.3, 120.9, 110.1, 107.5 and 31.6. 19F-NMR (470.4 MHZ, CDCl3) δF ppm: - 80.92, - 105.27, - 121.50 and - 125.65. EI-HRMS Anal. Calcd. for C13H8F9N: 349.0513. Found: 349.0517.

2-perfluorobutyl-benzofuran (9): Yellow oil, 90%, 60 mg. 1H-NMR (500 MHZ, CDCl3) δH ppm: 7.69 (d, J = 7.80 Hz, 1H), 7.59 (dd, J = 8.42, 0.8 Hz, 1H), 7.48 (dt, J = 8.42; 1.2 Hz, 1H), 7.35 (dt, J = 7.72, 1.0 Hz, 1H) and 7.25 (1H, s). 13C-NMR (125 MHZ, CDCl3) δC ppm: 155.6, 126.9, 123.9, 122.3, 112.0 and 110.3. 19F-NMR (470.55 MHz, CDCl3) δF ppm: -80.56, -112.06, -123.37 and -126.11. EI-HRMS Anal. Calcd. for C12H5F9O: 336.0197. Found: 336.0167.

2-(perfluorobutyl)-1H-indene (10). Yellow Oil 66% yield, 44.2 mg isolated. 1H-NMR (500 MHz) δH ppm: 7.53-7.51 (m, 2H), 7.38-7.34 (m, 3H) and 3.66 (s, 2H). 13C-NMR (125 MHz) δC ppm: 144.3, 138.1, 138.0, 134.4, 127.9, 127.9, 124.2 and 38.6. 19F-NMR (470.4 MHz) δF ppm: -81.00, -107.65, -122.70 and -125.75. EI-HRMS Anal. Calcd. for C13H7F9: 334.0404. Found: 334.0400.

2-(perfluorobutyl)-benzo[b]thiophene (11) 21%, 1.95 mg isolated. 1H-NMR (500 MHz) δH ppm: 7.89 (d, 1 H), 7.72 (s, 1 H), 762 (d,1 H) and 7.46 (dt, 1 H). 13C-NMR (125 MHz) δC ppm: 140.7, 137.9, 131.4, 129.3, 128.3, 126.1 and 126.0. 19F-NMR (470.55 MHz, CDCl3) δF ppm: -80.59, -106.37, -122.12 and -125.69. Did not ionize in HRMS (ESI -TOF).

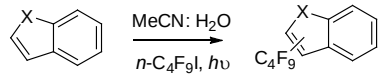
3-(perfluorobutyl)-benzo[b]thiophene (12) 15%, 2.79 mg. 1H-NMR (500 MHz) δH ppm: 7.91 (s, 1 H), 7.90 (d, 1H), 7.63 (d, 1H) and 7.48 (dt, 1 H). 13C-NMR (125 MHz) δC ppm: 141.4, 136.6, 131.9, 129.6, 126.6, 126.3 and 125.7. 19F-NMR (470.55 MHz, CDCl3) δF ppm: -80.79, -102.33, -122.12 and -125.69. Did not ionize in HRMS (ESI-TOF).

7-(perfluorobutyl)-benzo[b]thiophene (13) 13%, 1.75 mg isolated. 1H-NMR (500 MHz) δH ppm: 8.09 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.25 Hz, 1H), 7.63 (d, 1H), 7.50 (d, 1H) and 7.47 (dt, 1H). 13C-NMR (125 MHz) δC ppm: 141.3, 131.3, 129.5, 127.3, 125.7, 124.2 and 124.0 19F-NMR (470.55 MHz, CDCl3) δF ppm: -80.79, -108.11, -122.12 and -125.69. Did not ionize in HRMS (ESI-TOF).

6-(perfluorobutyl)-benzo[b]thiophene (14), not isolated, < 1%. 1H-NMR (500 MHz) δH ppm: 8.14 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.72 (d, 1H), 7.65 (d, J = 5.6 Hz, 1H) and 7.54 (d, 1H). 13C-NMR (125 MHz) δC ppm: 128.30, 126.62, 126.02, 125.55 and 123.44. 19F-NMR (470.55 MHz, CDCl3) δF ppm: -80.79, -109.84, -122.12 and -125.69. Did not ionize in HRMS (ESI-TOF).

3. RESULTS SECTION

When 1H-indole 1 is made to react(254-nm irradiation, 1 h) with n-C4F9I in a mixture of MeCN:H2O, we obtained the expected 3-perfluorobutyl-1H-indole (product 6, Scheme 1). Along with this product, the 2-substituted perfluorobutyl-indole was also observed (product 7, Scheme 1, Table 1, entry 1). However, the overall isolated substitution yield was rather low, that is25%. Both products, 6 and 7, were obtained in a relative ratio of 66:33, respectively. Indole 1 was recovered in 72% isolated yield.



X = NH, **1** 25% (*3*-C_4F_9 (**6**) **:** *2*-C_4F_9 (**7**) 2 : 1)
X = NMe, **2** 35% (*2*-C_4F_9 (**8**))
X = O, **3** 90% (*2*-C_4F_9 (**9**))
X = CH_2, **4** 66% (*2*-C_4F_9 (**10**))
X = S, **5** 49% (*2*-C_4F_9 (**11**) : *3*-C_4F_9 (**12**) : *7*-C_4F_9 (**13**) 1.6 : 1.1 : 1)

Scheme 2. Perfluorobutylation reactions of **1-5** in MeCN:water mixtures.

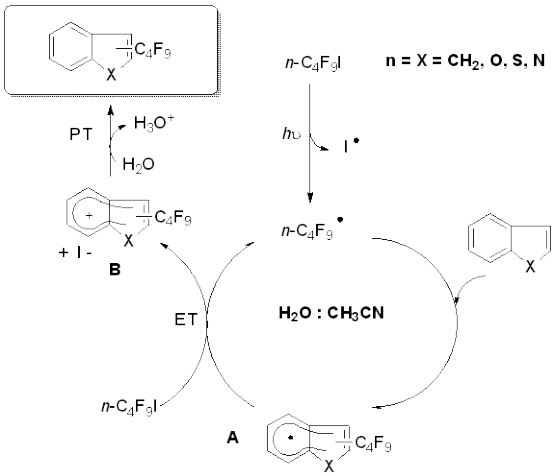
Further conversion of the starting material led to secondary photoproducts. In order to optimize reaction conditions, we varied the substrate and *n*-C_4F_9I concentrations with the purpose of maximizing product yields. This was achieved through plotting % substitution product versus n-C4F9I or substrate concentration at 254-nm irradiation (not shown) and obtained the best results asshown in column 3, Table 1. When reaction conditions are such that the absorption of substrates prevails at 254-nm irradiation wavelength, very low yields of substitution products were obtained. The highest substitution product yields were obtained when *n*-C_4F_9I was in excess with respect to substrate.When we subjected *N*-methyl indole **2** instead of 1*H*-indole 1 to the photoreaction in aqueous media with *n*-C_4F_9I, we obtained the perfluorobutyl-substituted product at the *2*- (product **8**) position of the ring in 35% yield. Product **8** was characterized by standard spectroscopic techniques. Indole **2** was recovered in 61% isolated yield. Further conversion of the starting material led to secondary photoproducts. Trifluoromethylation of 1*H*-indole and *N*-methyl indole at the *2*-,*3*-, and *7*- positions has recently been achieved by Togni and collaborators [7, 8] using $CHCl_3$ as solvent (Scheme 1). Their protocol renders a mixture of the *2*-,*3*-, and *7*-CF_3-substituted regioisomers that could not be separated, but identified by ^{19}F NMR spectroscopy as the isomeric mixture. (Do you mean Another methodology has recently been reported by Xiao *et al*. for the trifluoromethyl *ipso*-substitution of indole employing DMF as solvent [9].

When we subjected benzofuran **3** to react under photostimulation (254 nm) with *n*-C_4F_9I in MeCN:H_2O mixture, we exclusively obtained 2-(perfluorobutyl)-benzofuran **9** in 90% yield, as shown in Table 1, entry 3 (Scheme 2). Recently, Togni and collaborators have accomplished the trifluoromethylation of benzofuran and their heteroanalogs at the *3*- and *2*- positions with the Togni reagent, and methyltrioxorhenium as catalyst (Scheme 1)[7]. Their methodology, however, is not regioselective and renders the mixture of regioisomers that could not be separated but characterized by spectroscopic methods. 3-Trifluoromethyl-benzofuran has recently been synthesized by Sanford and collaborators using benzofuran-2ylboronic acid (a functionalized benzofuran ring) in the presence of $NaSO_2CF_3$, *tert*-butylhydroperoxide (TBHP) and a copper salt in 89% yield [10]. The photoinduced methodology, under our reaction conditions, seems to provide selectively the *2*-substituted perfluorobutyl benzofuran isomer in excellent yield (innate perfluoroalkylation).

When 1-*H*-indene **4** is made to react (254 nm) under similar reaction conditions, product **10** (Scheme 2, Table 1, entry 4) was obtained in 66% yield. Gassman and colleagues [11]have reported that the 2-perfluoroalkyl-substituted indene product could be obtained through a photoinduced perfluoroalkyl iodide addition that could not be isolated, but decomposed *in-situ* to the 2-perfluoroalkyl-substituted indene product through base-promoted dehydroiodination. Under our reaction conditions, however, no base was utilized to obtain product **10**, and the pH decreased gradually throughout the course of the reaction (Table 1, column 6). Benzo[*b*]thiophene **5** was also subjected to the photoinduced (254-nm) perfluorobutylation reaction in MeCN:H_2O to yield a mixture of regioisomers substituted at the *2*-, (product **11**), *3*-, (product **12**), and *7*-, (product **13**) positions of the benzo[*b*]thiophene ring with the C_4F_9 moiety in 49% overall yield that could not be isolated as single regioisomers but characterized in the reaction mixture (Table 1, entry 5) by multidimensional NMR techniques. These isomers (2-, *3*-, and *7*- C_4F_9 substituted benzothiophenes) were obtained in a relative ratio of 43:30:27, respectively. Togni and collaborators [7] attained the trifluoromethylation of benzothiophene with the Togni´s reagent, affording a mixture of the *2*-, *3*-, and *7*-CF_3 substituted regioisomers (innate trifluoromethylation, Scheme 1). However, this mixture of isomers could not be separated. Sanford and collaborators selectively synthesized the 2-trifluoromethyl-benzo[*b*]thiophene from benzo[*b*]thiophene-2-ylboronic acid (a functionalized benzothiophene ring) in the presence of $NaSO_2CF_3$, *tert*-butylhydroperoxide (TBHP) and a copper salt in 77% yield [10]. A minor isomer, accounting for less than 1% of the total yield of the mixture could be distinguished by the ^1H NMR spectrum of the chromatographed reaction mixture, which seems to correspond to another C_4F_9-regioisomer. Through a combination of 2D-NMR techniques, full spectral characterization of this isomer was possible in the mixture, and the identity of the compound was assigned as 6-(perfluorobutyl)-benzo[*b*]thiophene **14**. No ring-opening product was observed from the photoreactions of **1-5** with *n*-C_4F_9I under our reaction conditions. Addition of *n*-C_4F_9I provokes a decrease in fluorescence intensity, as observed in the Stern-Volmer plots (not shown). This quenching of fluorescence is in agreement with an electron-transfer process within the solvent cage, as has been proposed before [6]. The pH was monitored throughout the reaction for compounds **1-5**, (column 6, Table 1) with *n*-C_4F_9I either at 350-nm or at 254-nm irradiation. A significant decrease in pH was observed in all cases, as reaction progresses. Table 1, column 6 depicts the pH at the beginning and end of the reaction. This evidence is in accordance with a proton release in the course of the reaction, such as that observed in classical aromatic electrophilic substitution reactions, S_EAr.

Addition of di-*tert*butyl nitroxide (DTBN, 2% equiv), a well-known radical scavenger, at 254-nm irradiation in MeCN:H_2O mixtures, provoked a retardation of the reactions, purporting the presence of radicals as intermediates. Addition of *p*-dinitrobenzene(*p*-DNB), a known radical anion scavenger, did not affect the yields of the perfluoroalkyl group substitutions of the dibenzoarenes. The photoreactions carried out under basic conditions (pH ~ 10) did not show an enhancement in product yields. This would seem to imply that radical anions are not intermediates in these reactions. When 4-nitrodibenzofuran **15** was allowed to react with *n*-C_4F_9I in MeCN:H_2O mixtures either under 254-nm or 350-nm irradiation conditions, no substitution products were observed (Table 1, entry 6).

In previous photoinduced substitutions studies with R_fI [6] employing *N*,*N*-dimethyl-1-naphthylamine (DMNA) in water, we were able to detect the radical cation of DMNA in the presence of *n*-C_4F_9I from the UV-vis transient spectra obtained by Nanosecond Laser Flash Photolysis techniques at 355 nm excitation. This indicated an ET process to yield the radical cation of the substrate, and hence the dissociative radical anion of R_fI, under reaction conditions where absorption of aromatic substrates prevail.



Scheme 3. Proposed mechanism for the perfluorobutylation of benzo(hetero)arenes in aqueous mixtures.

Given the acceptor properties of R_fI, and the donor abilities of substrates **1-5**, a photoinduced ET sequence could be in operation, such as that postulated for aromatic amines [6]. The fact that 4-nitrodibenzofuran **15** does not react under our reaction conditions, might be indicative of the scarce electron donor ability of nitroarenes, or the poorly-stabilized Wheland intermediate. Notwithstanding, in the present study, when reaction conditions were changed to those where absorption of substrates ((hetero)arenes) prevail at 254-nm irradiation wavelength as

opposed to absorption of *n*-C_4F_9I (conditions where PET could take place), very low yields of substitution products were obtained. By increasing the amounts of *n*-C_4F_9I in the reaction mixtures, a steady increase in substitution product yield was obtained, suggesting that the reaction is initiated through homolysis of F_9C_4-I bond leading to $C_4F_9^{\bullet}$ radicals, and ulterior homolytic radical substitution of the benzo(hetero)arene. Indication of the proton release, is consistent with a (hetero)cyclohexadienyl-type radical intermediate that undergoes oxidation to a Wheland intermediate (σ-adduct).

At 254-nm irradiation, where most of the light is absorbed by *n*-C_4F_9I (see Table 1, column 6, footnote *b*), homolysis of F_9C_4-I bond produces perfluorobutyl radicals that add to the benzo(hetero)arene such as in Scheme 3 below, to yield the radical adduct intermediate **A**. The radical adduct **A** undergoes a sequence of ET to *n*-C_4F_9I (to afford cation intermediate **B**, Wheland intermediate, oxidation triggered through the favorableGibbs energy) and then the proton transfer (PT) steps to yield the substitution products in averaged good yields. We postulate that this mechanism is likely operative for substrates **1-5.**

Table 1. Optimized reaction conditions tested in the Hydrogen atom substitution (HAS) reaction of arenes with perfluoroalkyl halides in heterogeneous media under vigorous stirring

Entry	**Synthetic method**	**Substrates** (mmol)	**Solvent system,** (mL)[a]	**Product** (% yield)	$A_{substrate}$:A_{RfX}[b] $pH_{initial}/pH_{final}$[c]
1	**λ 254 nm**	**1** (0.2)**, *n*-C_4F_9I** (1.1)	**MeCN:H_2O** 1:1, (4)	(25) [d] **6** (66) [e] **7** (33) [e]	*1:1* [b] 5.5/3 [c]
2	**λ 254 nm**	**2** (0.2)**, *n*-C_4F_9I** (3.8)	**MeCN:H_2O** 1:1, (4)	**8** (35) [d]	*1:1* [b] 5.5/3 [c]
3	**λ 254 nm**	**3** (0.2)**, *n*-C_4F_9I** (5.8)	**MeCN:H_2O** 3:1, (4)	**9** (90) [d]	*1.3:1* [b] 5.5/3 [c]
4	**λ 254 nm**	**4** (0.2)**, *n*-C_4F_9I** (5.6)	**MeCN:H_2O** 3:1, (4)	**10** (66) [d]	*1:1* [b] 5.5/3 [c]
5	**λ 254 nm**	**5** (0.2), *n*-C_4F_9I (5.3)	**MeCN:H_2O** 3:1, (4)	(49) [d] **11** (43) [e] **12** (30) [e] **13** (27) [e] **14** (<1) [e]	*1:1* [b] 5.5/2 [c]
6	**MPL**[f] or **λ 254 nm**	**15** (0.2), *n*-C_4F_9I (5.3)	**MeCN:H_2O** 3:1, (4)	-	5.5/5.5[c] -

[a] Ar-deoxygenated solutions; [b] Absorbance ratio at the irradiation wavelength (254 nm or 365 nm) in pure organic solvent; [c] pH registered at the beginning of the reaction/pH registered at the end of the reaction; [d]isolated product yield; [e] relative regioisomer yield; [f] Medium pressure Hg lamp, unfiltered.

4. CONCLUSIONS

We herein present a substitution reaction on benzo(hetero)arenes in aqueous media with C4F9 moieties yielding perfluorobutyl group-substituted compounds in moderate to good yields. It is to be noted that these aromatic compounds have never been substituted before with perfluoroalkyl moieties by a direct methodology.

5. REFERENCES

[1] Ji, Y., Brueckl, T., Baxter, R. D., Fujiwara, Y. I., Seiple, B., Su, S., Blackmond, D. G., Baran, P. S., Innate C-H Trifluoromethylation of Heterocycles., *Proc.Natl. Acad. Sci*., *108*, 14411-14415, **2011**.

[2] Langlois, B. R., Laurent, E., Roidot, N., Trifluoromethylation of Aromatic Compounds with Sodium Trifluoromethanesulfinate Under Oxidative Conditions, *Tet. Lett*., *32*, 7525-7528, **1991**.

[3] (a) Mejía, E., Togni, A., Rhenium-Catalyzed Trifluoromethylation of Arenes and Heteroarenes by Hypervalent Iodine Reagents, *ACS Catalysis*, *2*, 521-527, **2012**. (b) Zhang, B., Mück-Lichtenfeld, C., Daniliuc, C. G., Studer, A., 6-Trifluoromethyl-Phenanthridines through Radical Trifluoromethylation of Isonitriles, *Angew. Chemie. Int. Ed*., *52*, 10792-10795, **2013**.

[4] Zhou, Q., Ruffoni, A., Gianatassio, R., Fujiwara, Y., Sella, E., Shabat, D., Baran, P. S., Direct Synthesis of Fluorinated Heteroarylether Bioisosteres, *Angew. Chemie. Int. Ed*., *52*, 3949-3952, **2013**.

[5] Nagib, D. A., MacMillan, D. W. C., Direct Trifluoromethylation of Aryl and Heteroaryl C–H Bonds, *Nature*, *480*, 224-228, **2011**.

[6] Barata-Vallejo, S., Martín Flesia, M., Lantaño, B., Argüello, J. E., Peñéñory, A. B., Postigo, A. Heterogeneous Photoinduced Homolytic Aromatic Substitution of Electron-Rich Arenes with Perfluoroalkyl Groups in Water and Aqueous Media – A Radical-Ion Reaction, *Eur. J. Org. Chem*., *2013*, 998-1008, **2013**.

[7] Niedermann, K., Frueh, N., Remo, S., Czarniecki, B., Verel, R., Togni, A., Direct Electrophilic N-Trifluoromethylation of Azoles by a Hypervalent Iodine Reagent, *Angew. Chemie.Int. Ed*., *51*, 6511-6515, **2012**.

[8] Wiehn, M. S., Vinogradova, E. V., Togni, A., Electrophilic Trifluoromethylation of Arenes and N-heteroarenes Using Hypervalent Iodine Reagents, *J. Fluorine Chem*., *131*, 951-957, **2011**.

[9] Zhang, C.-P., Wang, Z.-L-, Chen, Q.-Y., Gu, Zhang, Y.-C., Xiao, J.-C., Copper-Mediated Trifluoromethylation of Heteroaromatic Compounds by Trifluoromethyl Sulfonium Salts, *Angew. Chemie. Int. Ed*., *50*, 1896-1900, **2011**.

[10] (a) Ye, Y., Kunzi, S. A., Sanford, M. S., Practical Method for the Cu-Mediated Trifluoromethylation of Arylboronic Acids with CF_3 Radicals Derived from $NaSO_2CF_3$ and *tert*-Butyl Hydroperoxide (TBHP), *Org. Lett.*, *14*, 4979-4981, **2012**. (b) Li, Y., Wu, L., Neumann, H., Beller, M., Copper-catalyzed Trifluoromethylation of Aryl- and VinylboronicAcids with Generation of CF_3-radicals, *Chem. Comm*., *49*, 2628-2630, **2013**.

[11] Gassman, P. G., Ray, J. A., Wenhold, P. G., Mickelson, J. W., Synthesis of Perfluoroalkylated Indenes, *J. Org. Chem*., *56*, 5143-5146, **1991**.

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