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Diversity-Oriented Approach to CF_3CHF-, CF_3CFBr-, CF_3CF_2-, $(CF_3)_2CH$-, and $CF_3(SCF_3)CH$-Substituted Arenes from 1-(Diazo-2,2,2-trifluoroethyl)arenes

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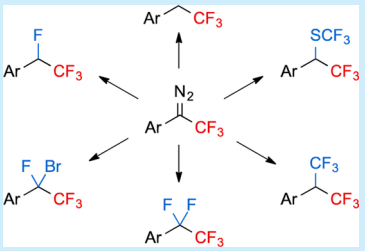
Supporting Information

ABSTRACT: Arenes substituted with perfluoroalkyl groups are attractive targets for drug and agrochemical development. Exploiting the carbenic character of donor/acceptor diazo compounds, a diversity-oriented synthesis of perfluoroalkylated arenes, for late stage fluorofunctionalization, is described. The reaction of 1-(diazo-2,2,2-trifluoroethyl)arenes with HF, F/Br, F_2, CF_3H, and CF_3SH sources give direct access to a variety of perfluoroalkyl-substituted arenes presenting with incremental fluorine content. The value of this approach is also demonstrated for radiochemistry and positron emission tomography with the [^{18}F]-labeling of CF_3CHF-, CF_3CBrF-, and CF_3CF_2-arenes from [^{18}F]fluoride.



Fluorine-containing arenes are an important class of aromatic motifs found in pharmaceuticals. Fluorine substitution affects docking interactions through contact with the protein and allows control over drug conformation; the presence of fluorine also influences physical and adsorption, distribution, metabolism, and excretion properties of a lead compound.[1] Fluorine substitution is equally prominent in agrochemicals that have progressed to the point where their chemical structures, physical properties, and site-specific binding make them difficult to distinguish from pharmaceutical drugs.[2] As a result, systematic fluorine scans emerge as a promising strategy in drug and agrochemical discovery. To date, most efforts have focused on late stage fluorination and trifluoromethylation of arenes.[3,4] Synthetic work leading to higher-order perfluoroalkyl motifs for evaluation in the context of drug and agrochemical performance is less documented. If we consider the established therapeutic value of the CF_3CF_2-containing drug Faslodex (fulvestrant), a selective estrogen receptor down-regulator indicated for the treatment of hormone receptor positive metastatic breast cancer.[5] The preparation of perfluoroalkyl-substituted arenes with incremental fluorine content for comparative studies of their biological properties remains a laborious and time-consuming process since no synthesis is available to synthesize CF_3CHF-, CF_3CBrF-, CF_3CF_2-, $(CF_3)(CF_3S)CH$-, and $(CF_3)_2CH$-arenes from a common precursor through late stage fluorofunctionalization (Figure 1).

With these considerations in mind, we posited that a diversity-oriented strategy exploiting the carbenic character of donor/acceptor diazo compounds would be an attractive alternative to conventional strategies for Rf-arene library

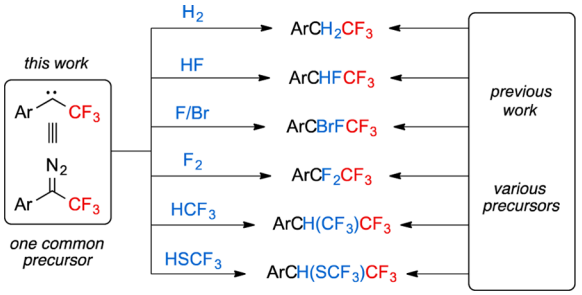


Figure 1. Branching pathway to perfluoroalkyl arenes: late stage fluorofunctionalization of 1-(diazo-2,2,2-trifluoroethyl)arenes.

synthesis.[6,7] 1-(Diazo-2,2,2-trifluoroethyl)arenes emerged as prime candidates for this purpose since these known compounds are readily accessible from the parent trifluoromethylketones,[8] via the corresponding tosylhydrazones,[9] and have been exploited in a range of transformations.[10] The absence of reports on fluorine incorporation prompted us to interrogate the reactivity of 1-(diazo-2,2,2-trifluoroethyl)arenes toward α,α-functionalization via *net* HF, F/Br, F_2, CF_3H, and CF_3SH addition. Successful implementation of this branching pathway approach would offer a direct route to a range of aryl-Rf motifs with precise control over incremental fluorine substitution with the number of fluorine (n) into the products varying from n = 4−6. Incidentally, the addition of H_2 onto 1-(diazo-2,2,2-trifluoroethyl)arenes readily expands the diversity

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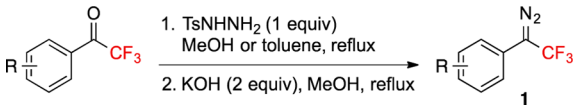
scope to CF_3CH_2-substituted arenes (n = 3). An additional motivation to study late stage fluorination of 1-(diazo-2,2,2-trifluoroethyl)arenes for reactions using fluoride is to explore [^{18}F]-labeling and applications in positron emission tomography. Successful [^{18}F]-labeling could facilitate studies probing the impact of higher-order fluorination of arenes on in vivo biodistribution and in the broader context of drug and agrochemical discovery.

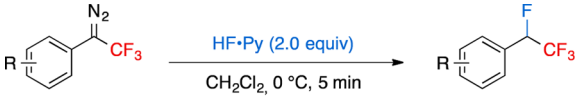
We began by preparing a selection of 1-(diazo-2,2,2-trifluoroethyl)arenes **1** applying an interrupted Bamford–Stevens reaction to a range of tosyl hydrazones; these precursors were obtained by reacting the corresponding aryl trifluoromethylketones with tosylhydrazide (Scheme 1).[11,12]

Scheme 1. Preparation of 1-(Diazo-2,2,2-trifluoroethyl)arenes 1



4-(1-Diazo-2,2,2-trifluoroethyl)-1,1′-biphenyl **1b** served as a model compound for validation of the various branching pathways toward distinct perfluoroalkyl motifs. We focused at first instance on hydrofluorination as a route to access 1,2,2,2-tetrafluoroethyl-substituted arenes.[13] Literature methods for the preparation of these poorly explored target compounds are scarce.[14] One approach is the fluorination of α-trifluoromethyl alcohols with diethylaminosulfur trifluoride, a reaction conducted in DCM at −70 °C.[14a] An alternative strategy consists of subjecting various (1-aryl-2,2,2-trifluoroethyl)hexyl sulfides to oxidative fluorodesulfuration with $Et_3N{\cdot}3HF$ and the oxidant IF_5.[14b] We found that the reaction of **1b** with HF·Py (HF ∼70%, pyridine ∼30%) at 0 °C afforded **2b** in 92% yield (Scheme 2). This reaction was extended to a range of diazo precursors leading to the hydrofluorinated products in yields reaching 99%.

Scheme 2. Hydrofluorination of 1-(Diazo-2,2,2-trifluoroethyl)arenes 1a–k

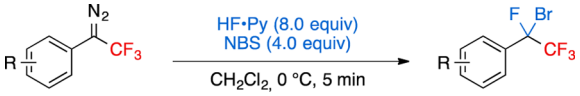


1a, R = H	52%[a]	**2a**
1b, R = 4-Ph	92%	**2b**
1c, R = 4-Me	77%	**2c**
1d, R = 4-NO_2	98%	**2d**
1e, R = 4-OMe	63%	**2e**
1f, R = 4-CO_2Me	90%	**2f**
1g, R = 4-Br	86%	**2g**
1h, R = 4-(C≡C-Cy)	96%	**2h**
1i, R = 3-(OC_7H_{15})	99%	**2i**
1j, R = 3-Br-4-F	79%	**2j**
1k, R = 3-OMe-4-F	86%	**2k**

[a]^{19}F NMR yield using fluorobenzene as internal reference.

To investigate the bromofluorination reaction,[13] **1b** was initially reacted with *N*-bromosuccinimide (2 equiv) and HF·Py (8 equiv) in Et_2O at 0 °C.[7a] Under these conditions, 50% conversion to the desired bromofluorinated product **3b** was reached after 24 h (Scheme 3). Further optimization of the reaction conditions led to the use of 4 equiv of NBS/HF·Py (1:2) in CH_2Cl_2 at 0 °C for full conversion after 5 min, with a yield of 81% of the isolated product **3b** (Scheme 3). The

Scheme 3. Bromofluorination of 1-(Diazo-2,2,2-trifluoroethyl)arenes 1a–i



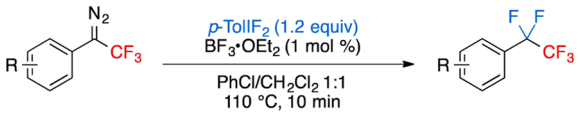
1a, R = H	59%[a]	**3a**
1b, R = 4-Ph	50%[a,b]	**3b**
1b, R = 4-Ph	81%	**3b**
1c, R = 4-Me	54%	**3c**
1d, R = 4-NO_2	67%	**3d**
1e, R = 4-OMe	54%	**3e**
1f, R = 4-CO_2Me	68%	**3f**
1g, R = 4-Br	65%	**3g**
1i, R = 3-(OC_7H_{15})	55%	**3i**

[a]^{19}F NMR yield using fluorobenzene as internal reference. [b]Reaction run in Et_2O with 2 equiv of NBS over 24 h.

reaction was applied successfully to a series of substituted arenes **3a–i** in yields ranging from 54 to 81%.[15]

The late stage *geminal* difluorination of 1-(diazo-2,2,2-trifluoroethyl)arenes as a route to pentafluoroethyl-substituted arenes was considered next. Current methods to install the CF_3CF_2 motif onto arenes rely on metal-catalyzed cross-coupling methodologies and the use of perfluorinated building blocks.[16] These processes are not trivial to exploit for [^{18}F]-labeling. We were pleased to find that the difluorination of **1b** was successfully performed in a sealed tube by action of (difluoroiodo)toluene (p-TolIF$_2$)[17] and 1 mol % of $BF_3{\cdot}OEt_2$ (added as a stock solution in CH_2Cl_2) in chlorobenzene at 110 °C (Scheme 4).[7g] These reaction conditions provided **4b** in

Scheme 4. Geminal Difluorination of 1-(Diazo-2,2,2-trifluoroethyl)arenes 1b,d,f,i



1b, R = 4-Ph	52%	**4b**
1d, R = 4-NO_2	46%	**4d**
1f, R = 4-CO_2Me	80%	**4f**
1i, R = 3-(OC_7H_{15})	37%	**4i**

52% isolated yield. The process was extended to diazo starting materials **1d**, **1f**, and **1i**, bearing electron-withdrawing or electron-donating functional groups, producing the pentafluoroethylarene products in moderate to good yields.

Hydrotrifluoromethylation was successfully accomplished by treating the model substrate **1b** with trimethyl(trifluoromethyl)silane[18] and CsF in the presence of CuI in NMP/H_2O (Scheme 5a).[7h] This reaction led to (1,1,1,3,3,3-hexafluoropropan-2-yl)arenes **5b**, **5f**, **5h**, and **5i** in moderate to very good yield. Using silver trifluoromethanethiolate ($AgSCF_3$) and CuCl instead of $TMSCF_3$ and CuI,[7j] we accessed (2,2,2-trifluoro-1-phenylethyl)(trifluoromethyl)sulfane **6b** in 77% yield via net hydrotrifluoromethylthiolation (Scheme 5b).[19] Following the same procedure, compounds **6h** and **6i** were also obtained, albeit in lower yields.

For completeness, we also considered the conversion of 1-(diazo-2,2,2-trifluoroethyl)arenes into CF_3CH_2-arenes.[20] Hydrogenation of **1b** was performed upon treatment with H_2 (1 atm) in MeOH in the presence of 10% of Pd/C (10% w/w) (Scheme 6). Under these conditions, **7b** and **7f** were isolated in 93 and 85% yield, respectively.

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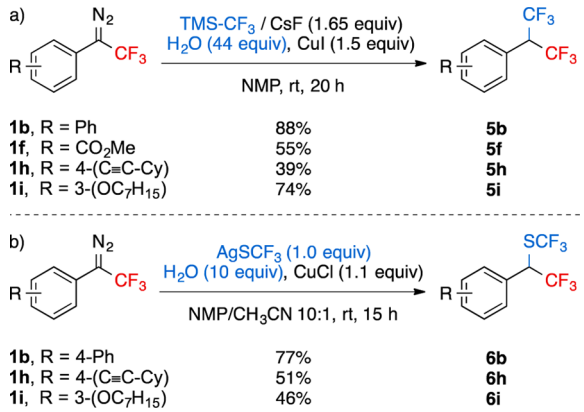
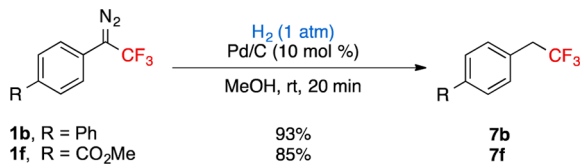
Scheme 5. Copper-Mediated HCF_3 and $HSCF_3$ Addition

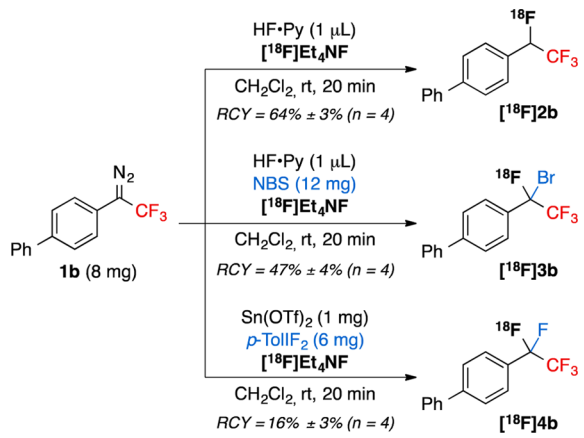


Scheme 6. Palladium-Catalyzed Hydrogenation of 1-(Diazo-2,2,2-trifluoroethyl)arenes 1b and 1f



Our ongoing interest in carbene reactivity for $[^{18}F]$ radiochemistry[21] prompted us to investigate 1-(diazo-2,2,2-trifluoroethyl)arenes as precursors to $[^{18}F]$-labeled CF_3CHF-, CF_3CBrF-, and CF_3CF_2-arenes using cyclotron-produced $[^{18}F]$fluoride (Scheme 7). To the best of our knowledge, there is no report in the literature on the labeling of these aromatic motifs; the radiochemistry available to date to access the nonaromatic CF_3CF_2-containing radiotracer EF5 does not employ $[^{18}F]$fluoride but requires $[^{18}F]F_2$ addition across the corresponding trifluoroalkene.[22]

Scheme 7. $[^{18}F]$-Labeling of CF_3CHF-, CF_3CBrF-, and CF_3CF_2-Arenes from $[^{18}F]$Fluoride



The reaction of **1b** (8 mg) with either $[^{18}F]KF/K_{222}$ or $[^{18}F]Et_4NF$ (~30 MBq), in DCM (300 μL) at room temperature for 20 min, gave none of the desired hydrofluorinated product, $[^{18}F]$**2b**, the only radioactive component present being unreacted $[^{18}F]$fluoride. When the reaction was performed using $[^{18}F]Et_4NF$ in the presence of 1 μL of HF·Py, $[^{18}F]$**2b** was formed in 64 ± 3% RCY (n = 4) as determined by radio-TLC and HPLC. $[^{18}F]KF/K_{222}$ led to product formation, but $[^{18}F]Et_4NF$ was used in subsequent fluorinations as it was found to give more consistent results. We next examined the bromofluorination of **1b** with NBS. Treatment of **1b** (8 mg) with $[^{18}F]Et_4NF$ (~30 MBq), NBS (12 mg), and HF·Py (1 μL) in DCM (300 μL) at room temperature for 20 min gave $[^{18}F]$**3b** in 47 ± 4% RCY (n = 4) in addition to $[^{18}F]$**2b** in 12 ± 2% RCY. As observed for the hydrofluorination, no reaction occurred in the absence of carrier-added HF·Py. The geminal difluorination of **1b** was carried out in the presence of p-$TolIF_2$ (6 mg) and $Sn(OTf)_2$ (1 mg) with $[^{18}F]Et_4NF$ in DCM to give pentafluoroethyl arene $[^{18}F]$**4b** in 16 ± 3% RCY. The hydrofluorinated product $[^{18}F]$**2b** was formed as additional separable labeled product in 7 ± 1% RCY. No additional HF·Py was required for this reaction to proceed.

In conclusion, a new strategy to generate $ArCHFCF_3$, $ArCBrFCF_3$, $ArCF_2CF_3$, $ArCH(CF_3)_2$, and $ArCH(CF_3)(SCF_3)$ was developed through formal α,α-difunctionalization of 1-(diazo-2,2,2-trifluoroethyl)arenes with nucleophilic F^-, CF_3^-, and CF_3S^- sources. Several salient features of this new approach include its diversity-oriented approach, simplicity of operation, and good substrate scope. Easy access to the unexploited or new motifs $ArCHFCF_3$ and $ArCH(CF_3)(SCF_3)$ may encourage studies aimed at delineating the particularities of these fluorinated groups, for example, through a combination of bond vector analysis and/or polarity and lipophilicity measurements. An additional feature of this diversity-oriented strategy is its bespoke design for $[^{18}F]$-labeling. We are aware that the carrier-added nature of the protocols we have developed may narrow the range of applications of this new $[^{18}F]$ technology, but to the best of our knowledge, this is the first report allowing for the labeling of CF_2CF_3 from $[^{18}F]$fluoride, not from $[^{18}F]F_2$. We also disclose the first examples of $[^{18}F]$-labeled $ArCHFCF_3$ and $ArCBrFCF_3$ motifs. These merits should find useful applications especially in the field of radiotracer development for clinical applications and for drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For reviews, see: (a) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992−1012. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881−1886. (c) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308−319. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (e) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359−4369. (f) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: New York, 2009. (g) *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*; Gouverneur, V., Muller, K., Eds.; Imperial College Press: London, 2012. (h) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432−2506. (i) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37−54.

(2) For reviews, see: (a) Theodoridis, G. In *Advances in Fluorine Science: Fluorine and the Environment—Agrochemicals, Archaeology, Green Chemistry & Water*; Tressaud, A., Ed.; Elsevier: Amsterdam, 2006; Vol. 2, pp 121−175. (b) Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16−29.

(3) For selected reviews on arene fluorination, see: (a) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, 1804−1821. (b) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929−2942. (c) Campbell, M. G.; Ritter, T. *Org. Process. Rev. Dev.* **2014**, *18*, 474−480.

(4) For selected reviews on arene trifluoromethylation, see: (a) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475−4521. (b) Liu, T.; Shen, Q. *Eur. J. Org. Chem.* **2012**, *34*, 6679−6687. See also ref 1i.

(5) Robertson, J. F. R.; Come, S. E.; Jones, S. E.; Beex, F.; Kaufmann, M.; Makris, A.; Nortier, J. W. R.; Possinger, K.; Rutqvist, L.-E. *Eur. J. Cancer* **2005**, *41*, 346−356.

(6) For general reviews on diazo compounds, see: (a) Regitz, M.; Maas, G. In *Diazo Compounds: Properties and Syntheses*; Academic Press: Orlando, FL, 1986. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160. (c) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: Chichester, UK, 1998. (d) Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev.* **2009**, *38*, 3061−3071.

(7) For selected examples of fluorofunctionalization of diazo compounds, see the following. For hydro- and/or halofluorination: (a) Olah, G. A.; Welch, J. *Synthesis* **1974**, 896−898. (b) Takeuchi, Y.; Takagi, K.; Yamaba, T.; Nabetani, M.; Koizumi, Y. *J. Fluorine Chem.* **1994**, *68*, 149−154. (c) Doherty, G.; Cook, A. Patent WO 2008/024746 A1, 2008. (d) Pasceri, R.; Bartrum, H. E.; Hayes, C. J.; Moody, C. J. *Chem. Commun.* **2012**, *48*, 12077−12079. (e) Qin, C.; Davies, H. M. L. *Org. Lett.* **2013**, *15*, 6152−6154. (f) Yadav, A. K.; Srivastava, V. P.; Yadav, L. D. S. *Chem. Commun.* **2013**, *49*, 2154−2156. For difluorination: (g) Tao, J.; Tran, R.; Murphy, G. K. *J. Am. Chem. Soc.* **2013**, *135*, 16312−16315. For hydrotrifluoromethylation: (h) Hu, M.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2012**, *134*, 15257−15260. For hydrotrifluoromethylthiolation: (i) Wang, X.; Zhou, Y.; Ji, G.; Wu, G.; Li, M.; Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2014**, 3093−3096. (j) Hu, M.; Rong, J.; Miao, W.; Ni, C.; Han, Y.; Hu, J. *Org. Lett.* **2014**, *16*, 2030−2033. (k) Lefebvre, Q.; Fava, E.; Nikolaienko, P.; Rueping, M. *Chem. Commun.* **2014**, *50*, 6617−6619. For bis(trifluoromethylthiolation), see ref 7k.

(8) For a review on trifluoromethylketones, see: Kelly, C. B.; Mercadantea, M. A.; Leadbeater, N. E. *Chem. Commun.* **2013**, *49*, 11133−11148.

(9) For the preparation of 1-(diazo-2,2,2-trifluoroethyl)arenes, see: (a) Shepard, R. A.; Wentworth, S. E. *J. Org. Chem.* **1967**, *32*, 3197−3199. (b) Shi, G.; Xu, Y. *J. Fluorine Chem.* **1990**, *46*, 173−178.

(10) For examples of functionalization of 1-(diazo-2,2,2-trifluoroethyl)arenes, see: (a) Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. Lett.* **2007**, *9*, 2625−2628. (b) Uehara, M.; Suematsu, H.; Yasutomi, Y.; Katsuki, T. *J. Am. Chem. Soc.* **2011**, *133*, 170−171. (c) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364−5367. (d) Wang, X.; Xu, Y.; Deng, Y.; Zhou, Y.; Feng, J.; Ji, G.; Zhang, Y.; Wang, J. *Chem.—Eur. J.* **2014**, 961−965.

(11) Overall yields for the synthesis of diazo compounds **1** are generally modest.

(12) All diazo compounds reported in this paper were purified by silica gel column chromatography, stored in a freezer under air, and, in our hands, found to be stable for months. See Supporting Information for details.

(13) For a comparative study employing the corresponding aryl diazo esters, see Supporting Information.

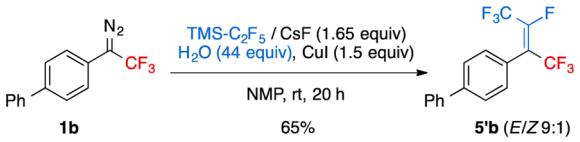
(14) For other methods leading to $ArCHFCF_3$, see: (a) Anilkumar, R.; Burton, D. J. *Tetrehedron Lett.* **2003**, *44*, 6661−6664. (b) Tahara, R.; Fukuhara, T.; Hara, S. *J. Fluorine Chem.* **2011**, *132*, 579−586.

(15) To the best of our knowledge, only one method for the synthesis of the $ArCFBrCF_3$ motif has been reported to date. See: Winter, R. W.; Dodean, R.; Smith, J. A.; Anilkumar, R.; Burton, D. J.; Gard, G. L. *J. Fluorine Chem.* **2005**, *126*, 1202−1214.

(16) For alternative methods towards $ArCF_2CF_3$, see: (a) Langlois, B. R.; Roques, N. *J. Fluorine Chem.* **2007**, *128*, 1318−1325. (b) Büttner, S.; Lubbe, M.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2008**, *64*, 7968−7976. (c) Kremlev, M. M.; Tyrra, W.; Mushta, A. I.; Naumann, D.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2010**, *131*, 212−216. (d) Tahara, R.; Fukuhara, T.; Hara, S. *J. Fluorine Chem.* **2011**, *132*, 579−586. (e) Schareina, T.; Wu, X.-F.; Zapf, A.; Cotté, A.; Beller, M. *Top. Catal.* **2012**, *55*, 426−431. (f) Serizawa, H.; Aikawa, K.; Mikami, K. *Org. Lett.* **2014**, *16*, 3456−3459. (g) Litvinas, N. D.; Fier, P. S.; Harwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 536−539. (h) Zatolochnaya, O. V.; Gevorgyan, V. *Org. Lett.* **2013**, *15*, 2562−2565. (i) Cui, L.; Matusaki, Y.; Tada, N.; Miura, T.; Uno, B.; Itoh, A. *Adv. Synth. Catal.* **2013**, *355*, 2203−2207. (j) Mormino, M. G.; Fier, P. S.; Hartwig, J. F. *Org. Lett.* **2014**, *16*, 1744−1747.

(17) For a review, see: (a) Yoneda, N. J. *Fluorine Chem.* **2004**, *125*, 7−17. For a recent example, see: (b) Arrica, M. A.; Wirth, T. *Eur. J. Org. Chem.* **2005**, 395−400. See also ref 7g.

(18) The use of $TMSC_2F_5$ in place of $TMSCF_3$ led to the formation of olefin **5′b**.



1b 65% **5′b** (*E*/*Z* 9:1)

(19) Klabunde, K. J.; Burton, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 820−828.

(20) For recent methods towards $ArCH_2CF_3$, see: (a) Kawai, H.; Furukawa, T.; Nomura, Y.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2011**, *13*, 3596−3599. (b) Zhao, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 1033−1036. (c) Zhu, L.; Liu, S.; Douglas, J. T.; Altman, R. A. *Chem.—Eur. J.* **2013**, 12800−12805. (d) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 2477−2480. (e) Qiao, Y.; Si, T.; Yang, M.-H.; Altman, R. A. *J. Org. Chem.* **2014**, *79*, 7122−7131 and references therein.

(21) Huiban, M.; Tredwell, M.; Mizuta, S.; Wan, Z.; Zhang, X.; Collier, T. L.; Gouverneur, V.; Passchier, J. *Nat. Chem.* **2013**, *5*, 941−944.

(22) EF5: [2-(2-nitro-1*H*-imidazol-1-yl)-*N*-(2,2,3,3-pentafluoropropyl)acetamide]. (a) Evans, S. M.; Fraker, D.; Hahn, S. M.; Gleason, K.; W. Jenkins, W. T.; Jenkins, K.; Hwang, W.; Zhang, P.; Mick, R.; Koch, C. J. *Int. J. Radiat. Oncol. Biol. Phys.* **2006**, *64*, 922−927. (b) Dolbiera, W. R., Jr.; Lia, A.; Koch, C. J.; Shiuec, C.; Kachurb, A. V. *Appl. Radiat. Isot.* **2001**, *54*, 73−80. (c) Ziemer, L. S.; Evans, S. M.; Kachur, A. V.; Shuman, A. L.; Cardi, C. A.; Jenkins, W. T.; Karp, J. S.; Alavi, A.; Dolbier, W. R., Jr.; Koch, C. J. *Eur. J. Nucl. Med.* **2003**, *30*, 259−266.

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