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Silver-Mediated Methoxycarbonyltetrafluoroethylation of Arenes

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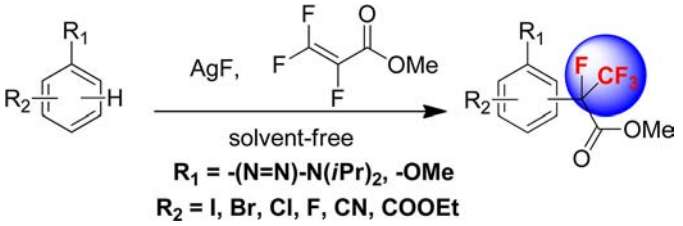
ABSTRACT



In the presence of silver(I) fluoride, highly fluorinated olefins react readily under solvent-free conditions with arenes via CH-substitution. This transformation could be used to synthesize various methoxycarbonyltetrafluoroethylated aromatic triazenes and anisoles under high functional group tolerance. The method could be applied to the synthesis of a formal fluorinated bioisostere of the NSAID flurbiprofen. To the best of our knowledge, this is the first example which uses highly fluorinated olefins for the perfluoroalkylation of aromatic substrates.

Despite the nearly complete absence of fluorine in natural products, a vast number of pharmaceuticals and agrochemicals are fluorinated compounds. Fluorine as well as fluorinated moieties offer unique chemical and physical properties, which can dramatically enhance the biological effectiveness of organic compounds and make them interesting in terms of bioisosteric replacement. Thus, numerous examples show that the introduction of fluorinated groups improve the metabolic activity, bioavailability, or lipophilicity of an active agent.[1] This explains why the interest in direct fluorination as well as direct perfluoroalkylation reactions has substantially grown over recent years. Especially the trifluoromethyl group plays an important role in modern synthetic organic

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(4) Examples of metal-mediated trifluoromethylation of halides: (a) Tomashenko, O. A.; Escudero-Adán, E. C.; Martínez Belmonte, M.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 7655. (b) Weng, Z.; Lee, R.; Jia, W.; Yuan, Y.; Wang, W.; Feng, X.; Huang, K.-W. *Organometallics* **2011**, *30*, 3229. (c) Kondo, H.; Oishi, M.; Fujikawa, K.; Amii, H. *Adv. Synth. Catal.* **2011**, *353*, 1247. (d) Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3793. (e) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679. (f) Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909.

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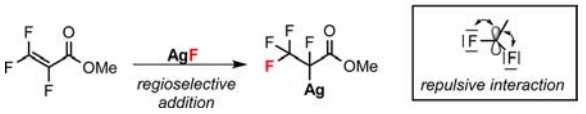
chemistry. Today, there are several protocols known that allow the introduction of this group into aromatic[2] and nonaromatic[3] systems. While most metal-mediated trifluoromethylation reactions require functionalized reactants (e.g. halides[4] or boronic acids[5]), radical trifluoromethylation reactions can be realized under a simple and straightforward CH-substitution.[6] However, when radical intermediates are involved, there is often a lack of selectivity. Recently, we could demonstrate that aromatic triazenes are suitable substrates for silver-mediated trifluoromethylation reactions.[7] These transformations were based on an "$AgCF_3$" species, which could be easily generated *in situ* and decompose to CF_3-radicals. In literature, the synthesis of silver perfluoroorganyls is well-documented but their applications as precursors for perfluoroalkyl radicals are limited.[8] Besides our work, only the Sanford group reported the use of $AgCF_3$ for the trifluoromethylation of aromatic compounds.[9] Both examples were based on a trimethylsilyl substituted CF_3-source.

Encouraged by our first results, we imagined that it should be possible to expand our protocol to other fluorinated silver species, which would allow the synthesis of new fluorinated arenes *via* a radical pathway.

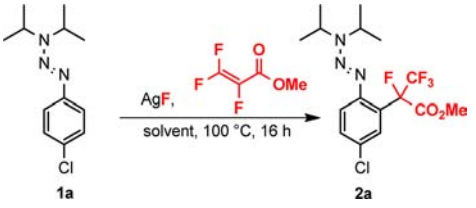
Scheme 1. Selective Addition of AgF to the Fluorinated Double Bond



In contrast to common perfluoroalkyl sources such as perfluoroiodides, TMS agents, or hypervalent iodine agents, the use of highly fluorinated olefins as a perfluoroalkyl source has not been well-investigated. Due to the repulsive interactions between the lone electron pairs of the fluorine substituent and the π-orbital of the sp^2-carbon, fluorinated olefins regioselectively add fluoride ions.[1a,10] In donor solvents like acetonitrile, this occurrence can be used to generate silver perfluoroorganyls by adding AgF regioselectively to the fluorinated double bond (Scheme 1).[8a−c] This regioselective addition is interesting, as it allows rapid access to secondary metal perfluoroalkyl species. However, fluoride abstraction of fluorinated olefins also enables the possibility of dimerization/oligomerization. This competing reaction limits the synthetic potential of these fluorinated compounds.[11] We assume that therefore metal-mediated perfluoroalkylation of organic compounds using highly fluorinated olefins has not yet been reported.[12]

We believed that a method allowing the usage of highly fluorinated olefins in simple aromatic substitution reactions would be interesting, as they would give access to complete new perfluoroalkylated arenes. Therefore, we started investigating this reaction using the commercially available methyl 2,3,3-trifluoroacrylate as a fluorinated olefin in the presence of silver(I) fluoride and the aromatic triazene **1a** (Table 1). While standard protocols for the synthesis of silver perfluoroorganyls use donor solvents like acetonitrile, in which dimerization/oligomerization of highly fluorinated olefins is the preferred reaction, our own observations with $AgCF_3$ showed that the trifluoromethylation of aromatic triazenes worked best in perfluorohexane as solvent. Although the conversion was not comparable to the one obtained for the trifluoromethylation reaction, the desired methoxycarbonyltetrafluoroethylated product could be obtained in 12% yield (entry 1).

Table 1. Optimization of the Methoxycarbonyltetrafluoroethylation of Aromatic Triazenes[a]



entry	MTA (equiv)	solvent	yield [%][b]
1	2	C_6F_{14}	12
2	3	C_6F_{14}	20
3	4	C_6F_{14}	43
4	2	–	38
5	4	–	49
6	4	DCE	13
7	4	MeCN	–

[a] Reaction conditions: **1a** (0.40 mmol), AgF (1.60 mmol), methyl 2,3,3-trifluoroacrylate (MTA), solvent (1 mL), 100 °C, 16 h. [b] Yields were determined by ^{19}F NMR using 2-fluoronitrobenzene or 2-fluoroaniline as the internal standard.

However, the yields could be increased by doubling the methyl 2,3,3-trifluoroacylate (MTA) equivalents (entry 3).

(6) (a) Wu, X.; Chu, L.; Qing, F.-L. *Tetrahedron Lett.* **2013**, *54*, 249. (b) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (c) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411. (d) Review: Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950.

(7) Hafner, A.; Bräse, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3713.

(8) Silverperfluoroorganyls: (a) Miller, W. T., Jr.; Burnard, R. J. *J. Am. Chem. Soc.* **1968**, *90*, 7367. (b) Burch, R. R.; Calabrese, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 5359. (c) Dyatkin, B.; Martynov, B.; Martynova, L.; Kizim, N.; Sterlin, S.; Stumbrevichute, Z.; Fedorov, L. *J. Organomet. Chem.* **1973**, *57*, 423. (d) Naumann, D.; Wessel, W.; Hahn, J.; Tyrra, W. *J. Organomet. Chem.* **1997**, *547*, 79. (e) Review: Tyrra, W.; Naumann, D. *J. Fluorine Chem.* **2004**, *125*, 823. (f) Tyrra, W. E. *J. Fluorine Chem.* **2001**, *112*, 149. (g) King, R. B.; Zipperer, W. C. *Inorg. Chem.* **1972**, *11*, 2119. (h) Zeng, Y.; Zhang, L.; Zhao, Y.; Ni, C.; Zhao, J.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 2955. (i) Kremlev, M. M.; Mushta, A. I.; Tyrra, W.; Naumann, D.; Fischer, H. T. M.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2007**, *128*, 1385. In fact, silver perfluoroorganyls are mostly used as transmetallation agents. Furthermore, only oxygenation, halogenation, elimination, and dimerization reactions are known. References 8h and 8i reported the use of $AgCF_3$ as the source of nucleophilic CF_3. However, these protocols do not use $AgCF_3$ as the precursor of CF_3 radicals.

(9) Ye, Y.; Lee, S. H.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 5464.

(10) Bartlett, P. D.; Wheland, R. C. *J. Am. Chem. Soc.* **1972**, *94*, 2145.

(11) Paleta, O.; Svoboda, J.; Dedek, V. *J. Fluorine Chem.* **1983**, *23*, 171.

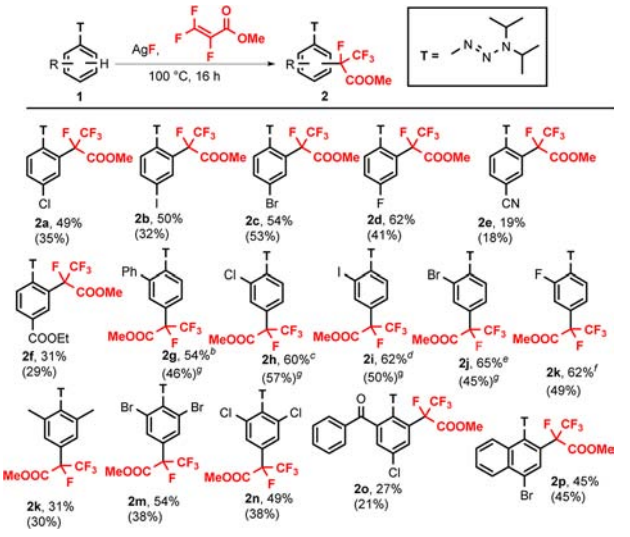
Lastly, we tried the reaction under neat (solvent-free) conditions, which further increased the yields to 49% (entry 5). When the reaction was carried out in dichloroethane, the yield dropped to 13% (entry 6), while in acetonitrile no conversion to the desired product occurred. Herein, dimerization/oligomerization of the fluoroolefin was observed as a major reaction (entry 7). Noteworthy, dimerization of MTA still occurred under solvent-free conditions, which did not allow the recovery of excess MTA, but could be significantly reduced.

With the optimized reaction conditions in hand, we further explored the scope of the methoxycarbonyltetrafluoroethylation reaction. As summarized in Scheme 2 several functionalized aromatic triazenes can be used for this kind of transformation. Most interestingly, this method tolerates various functional groups, e.g. iodides, bromides, chlorides, fluorides, nitriles and ethoxycarbonyl moieties. When *para*-substituted aromatic triazenes were used, the *ortho*-methoxycarbonyltetrafluoroethylated triazenes were always the major products. This is consistent with our observations during the trifluoromethylation reaction.[7] Surprisingly, *ortho*-substituted triazenes (e.g. **2g**–**2k**) yielded the *para*-methoxycarbonyltetrafluoroethylated triazenes as major products. In contrast to these results, the trifluoromethylation reaction showed a high *ortho*-selectivity with these substrates.[7]

We believe that this "loss" of *ortho*-selectivity can be explained by the steric hindrance of the silver organyl, which prevents any type of coordination to the triazene moiety. The reactions worked best when substitution at the *para*- and *ortho*-position was possible (up to 65%, **2j**). When the *para*-position was blocked (e.g. **2a**–**2f**), the yields dropped slightly to around 54% (**2c**) for halogenated triazenes. Aromatic triazenes bearing a strong electron-withdrawing group could be only methoxycarbonyltetrafluoroethylated in low yields (**2e**, **2f**). This circumstance could also explain why no disubstitution was observed. Thus, the electron-withdrawing effect of the methoxycarbonyltetrafluoroethyl group deactivates the aromatic core for a second substitution. Altogether, most yields were reasonable considering the electronic and steric properties of the silver perfluoroorganyl.

Aromatic triazenes offer various functionalization possibilities.[13] On one hand, they can be seen as protected diazonium salts; thus they can be converted into different

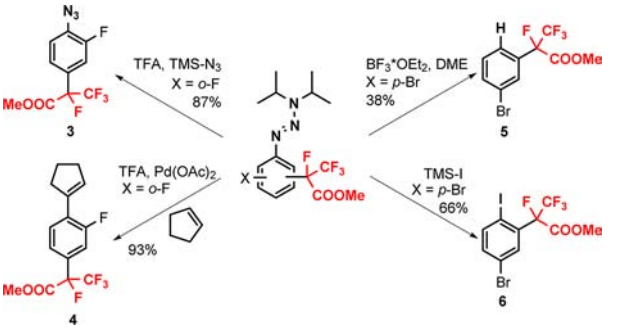
Scheme 2. Methoxycarbonyltetrafluoroethylation of Different Aromatic Triazenes[a]



[a] Reaction conditions: triazene **1** (0.40 mmol), AgF (1.60 mmol), methyl 2,3,3-trifluoroacrylate (MTA) (1.60 mmol), 100 °C, 16 h. Yields were determined by ^{19}F NMR using 2-fluoroaniline as the internal standard. Yields in parentheses are isolated yields. [b] *Ortho*/*para* = 1:10. [c] *Ortho*/*para* = 1:7.6. [d] *Ortho*/*para* = 1:6.8. [e] *Ortho*/*para* = 1:6.2. [f] *Ortho*/*para* = 1:14.5. [g] Mixture of *ortho*/*para*-isomer.

functional groups, e.g. halides,[14] azides,[15] nitriles,[16] or amines.[17] On the other hand, the triazene moiety allows further functionalization on the aromatic core like cross-coupling reactions.[14a,18]

Scheme 3. Conversion of the Triazene Moiety in Different Groups



Exemplarily, triazene **2k** was converted into the corresponding azide **3** and cross-coupled with cyclopentene (**4**), while triazene **2c** was converted into iodide **6** and defunctionalized to **5** (Scheme 3). This versatility combined with the methoxycarbonyltetrafluoroethylation reaction can be used for the synthesis of various compounds. Interestingly,

(12) In fact, only few examples are known in which highly fluorinated olefins are used for the perfluoroalkylation of arenes. These examples are either nucleophilic aromatic substitution reactions (e.g., Chambers, R. D.; Jackson, J. A.; Musgrave, W. K. R.; Storey, R. A. *J. Chem. Soc. (C)* **1968**, 2221.) or (mostly transition metal mediated) substitution reactions of the CF bond (e.g., Ohashi, M.; Kambara, T.; Hatanaka, T.; Saijo, H.; Doi, R.; Ogoshi, S. *J. Am. Chem. Soc.* **2011**, *133*, 3256.).

(13) Review: (a) Kimball, D. B.; Haley, M. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3338. (b) Bräse, S. *Acc. Chem. Res.* **2004**, *37*, 805.

(14) Representative transformations: (a) Liu, C.-Y.; Knochel, P. *Org. Lett.* **2005**, *7*, 2543. (b) Barbero, M.; Degani, I.; Diulgheroff, N.; Dughera, S.; Fochi, R. *Synthesis* **2001**, 2180. (c) Döbele, M.; Vanderheiden, S.; Jung, N.; Bräse, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5986.

(15) Liu, C.-Y.; Knochel, P. *J. Org. Chem.* **2007**, *72*, 7106–7115.

(16) Patrick, T. B.; Juehne, T.; Reeb, E.; Hennessy, D. *Tetrahedron Lett.* **2001**, *42*, 3553.

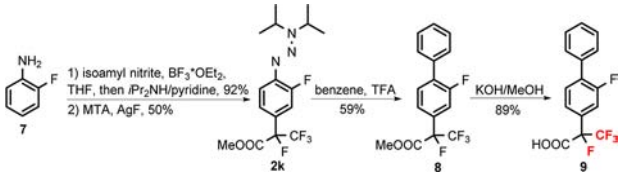
(17) Gross, M. L.; Blank, D. H.; Welch, W. M. *J. Org. Chem.* **1993**, *58*, 2104.

(18) Reingruber, R.; Vanderheiden, S.; Wagner, A.; Nieger, M.; Muller, T.; Es-Sayed, M.; Bräse, S. *Eur. J. Org. Chem.* **2008**, 3314.

(19) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.

most successful NSAIDs (nonsteroidal anti-inflammatory drugs), e.g. ibuprofen or flurbiprofen, possess an arylpropanoic acid group as the central structural motif.[19]

Scheme 4. Four-Step Synthesis of Flurbiperfluoroprofen (**9**)



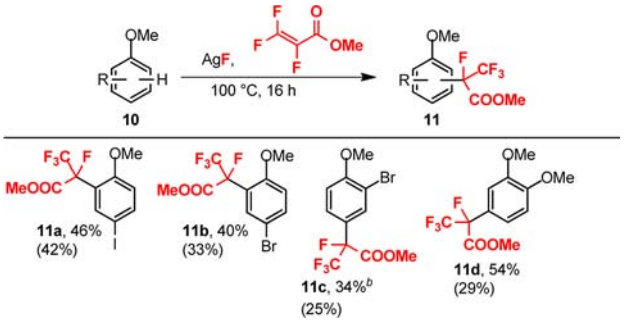
Due to the unique properties of fluorine substituents, much effort has been made to synthesize fluorinated profene analogues in terms of bioisosteric replacement.[20] To demonstrate the synthetic usefulness of our new method, we planned the synthesis of the corresponding flurbiperfluoroprofen (**9**), a tetrafluorinated analogue of the NSAID flurbiprofen. Starting from commercially available 2-fluoroaniline (**7**), this synthesis could be accomplished in 24% overall yield over four steps (Scheme 4). Noteworthy, the methoxycarbonyltetrafluoroethylation (step 2) could be upscaled to 500 mg with comparable isolated yields (50% vs 49%).

Furthermore, it was possible to expand this reaction to anisole derivatives. While electron-poor arenes such as nitrobenzene derivatives or aromatic nitriles showed no conversion at all under our conditions, electron-rich anisoles could be methoxycarbonyltetrafluoroethylated with similar yields compared to aromatic triazenes without further optimization of the reaction conditions (Scheme 5).

In conclusion, we herein report the silver-mediated methoxycarbonyltetrafluoroethylation of functionalized arenes by simple CH-substitution. This functionalization is based on the *in situ* generation of methoxycarbonyltetrafluoroethyl silver from commercially available silver(I) fluoride and

(20) For example: (a) Goj, O.; Kotila, S.; Haufe, G. *Tetrahedron* **1996**, *52*, 12761. (b) Schlosser, M.; Michel, D.; Guo, Z.-W.; Sih, C. J. *Tetrahedron* **1996**, *52*, 8257. (c) Rozen, S.; Hagooly, A.; Harduf, R. *J. Org. Chem.* **2001**, *66*, 7464. (d) Ricci, G.; Ruzziconi, R. *J. Org. Chem.* **2005**, *70*, 611.

Scheme 5. Methoxycarbonyltetrafluoroethylation of Different Anisoles[a]



[a] Reaction conditions: anisole **10** (0.40 mmol), AgF (1.60 mmol), MTA (1.60 mmol), 100 °C, 16 h. Yields determined by ^{19}F NMR using 2-fluoroaniline as the internal standard. Yields in parentheses are isolated yields. [b] *Ortho*/*para* = 1:1.8.

methyl 2,3,3-trifluoroacrylate (MTA). This perfluoroalkylation protocol tolerates a broad range of functional groups (e.g. iodides, bromides, nitriles), which combined with the versatility of the triazene group makes it interesting for the synthesis of various methoxycarbonyltetrafluoroethylated building blocks. Furthermore, we demonstrated the synthetic potential of this transformation through the synthesis of flurbiperfluoroprofen (a tetrafluorinated analogue of the NSAID flurbiprofen). In addition, we showed that this protocol is also suitable for the methoxycarbonyltetrafluoroethylation of anisole derivatives. To the best of our knowledge, this is the first example of the usage of highly fluorinated olefins for the perfluoroalkylation of aromatic substrates.

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Supporting Information Available. Experimental procedures and characterization and spectra data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.