

Condensed-Phase, Halogen-Bonded CF_3I and $\text{C}_2\text{F}_5\text{I}$ Adducts for Perfluoroalkylation Reactions**

Filippo Sladojevich, Eric McNeill, Jonas Börgel, Shao-Liang Zheng, and Tobias Ritter*

Abstract: A family of practical, liquid trifluoromethylation and pentafluoroethylation reagents is described. We show how halogen bonding can be used to obtain easily handled liquid reagents from gaseous CF_3I and $\text{CF}_3\text{CF}_2\text{I}$. The synthetic utility of the new reagents is exemplified by a novel direct arene trifluoromethylation reaction as well as adaptations of other perfluoroalkylation reactions.

Fluorinated organic molecules are increasingly useful in medicinal chemistry, agrochemistry, and materials science. Many recent advances in fluoroorganic chemistry^[1] are due to the development of safer, less toxic, or more selective reagents. Examples in perfluoroalkylation include the Rupprecht–Prakash reagent (Me_3SiCF_3),^[2] the Trifluoromethylator reagent ($[\text{CF}_3\text{Cu}]$),^[3] the Langlois reagent ($\text{CF}_3\text{SO}_2\text{Na}$),^[4] the Baran reagent $\text{Zn}(\text{SO}_2\text{CF}_3)_2$,^[5] the Umemoto reagent (*S*-(trifluoromethyl)dibenzothiophenium),^[6] and the Togni reagents.^[7] Perfluoroalkyl iodides, in particular CF_3I ,^[8–14] are useful and inexpensive sources of perfluoroalkyl fragments.^[1b,d,15] However, CF_3I and $\text{C}_2\text{F}_5\text{I}$ are gases, making accurate measurement cumbersome. Stock solutions of CF_3I cannot be stored without quick decline of the titer (see the Supporting Information). Here we introduce liquid-phase, halogen-bonded adducts of CF_3I and $\text{C}_2\text{F}_5\text{I}$ as perfluoroalkylation reagents. The reagents are stable at room temperature and can be conveniently manipulated. To the best of our knowledge, our report describes the first application of halogen bonding for organic reagent preparation, and the first X-ray crystal structure of a halogen-bonded CF_3I adduct. Using the easily manipulated halogen-bonded adducts, we have developed a novel direct arene C–H trifluoromethylation reaction. We also show the applicability of our new reagents as drop-in replacements for gaseous CF_3I and $\text{C}_2\text{F}_5\text{I}$.

Halogen bonding^[16] has been known since 1863^[17] and has found use in molecular recognition and supramolecular chemistry.^[18] However, halogen bonding has received relatively little attention from synthetic organic chemists^[9c,17j,19] compared to other non-covalent interactions such as hydro-

gen bonding. Trifluoromethyl iodide is a common trifluoromethylation reagent.^[8–14] Despite its utility and low cost (\$ 110 per mol from Oakwood Products), routine use by synthetic chemists has been challenging due to its boiling point of -22.5°C . The handling process is impractical, time consuming, and imprecise in the measurements of small quantities, when compared to the other more conveniently handled reagents mentioned above.

We have found that CF_3I and tetramethylguanidine (TMG) form a 1:1 adduct that is liquid at 23°C and can be dispensed accurately with a syringe (Figure 1). A 30 g batch of TMG- CF_3I stored in a glass vial with a Teflon seal at 0°C

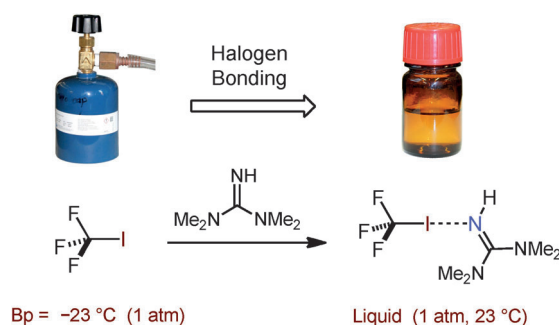


Figure 1. Formation of liquid TMG- CF_3I adduct via halogen bonding between CF_3I and tetramethylguanidine (TMG).

showed no signs of decomposition, loss in content of CF_3I , or pressure build-up over two months. This reagent is now commercially available.^[20] In addition to TMG, other Lewis bases can be used. Notably, the non-Brønsted-basic DMSO forms a 1:1 adduct with CF_3I . The presence of a second equivalent of DMSO imparts improved stability, making the preferred formulation $2\text{DMSO}\cdot\text{CF}_3\text{I}$. Like CF_3I , $\text{C}_2\text{F}_5\text{I}$ is a gas in most laboratory settings (bp $12\text{--}13^\circ\text{C}$) and forms a readily handled liquid adduct with TMG. We found that TMG- $\text{CF}_3\text{CF}_2\text{I}$ and DMSO- $\text{CF}_3\text{CF}_2\text{I}$ can be used in analogy to TMG- CF_3I and DMSO- CF_3I as pentafluoroethylation reagents.

Trifluoromethylated arenes are increasingly common structural motifs in pharmaceuticals and agrochemicals.^[21] Historically, trifluoromethyl arenes were synthesized via the Swarts reaction^[22] or cross-coupling.^[1e,15i,23] An attractive alternative to these methods is direct C–H trifluoromethylation by trifluoromethyl radical. Reagents such as CF_3SO_2^- salts,^[4,5] gaseous CF_3I ,^[8] $\text{CF}_3\text{SO}_2\text{Cl}$,^[24a] $(\text{CF}_3)\text{SiMe}_3$,^[24b–d] and Togni's reagent^[24e] have been used for this transformation. Some current methodologies are limited to specific substrate classes such as heterocycles, phenols, or anilines. Others

[*] Dr. F. Sladojevich, Dr. E. McNeill, J. Börgel, Dr. S.-L. Zheng, Prof. Dr. T. Ritter
Department of Chemistry and Chemical Biology
Harvard University
12 Oxford St., Cambridge, MA 02138 (USA)
E-mail: ritter@chemistry.harvard.edu
Homepage: <http://rittergroup.org>

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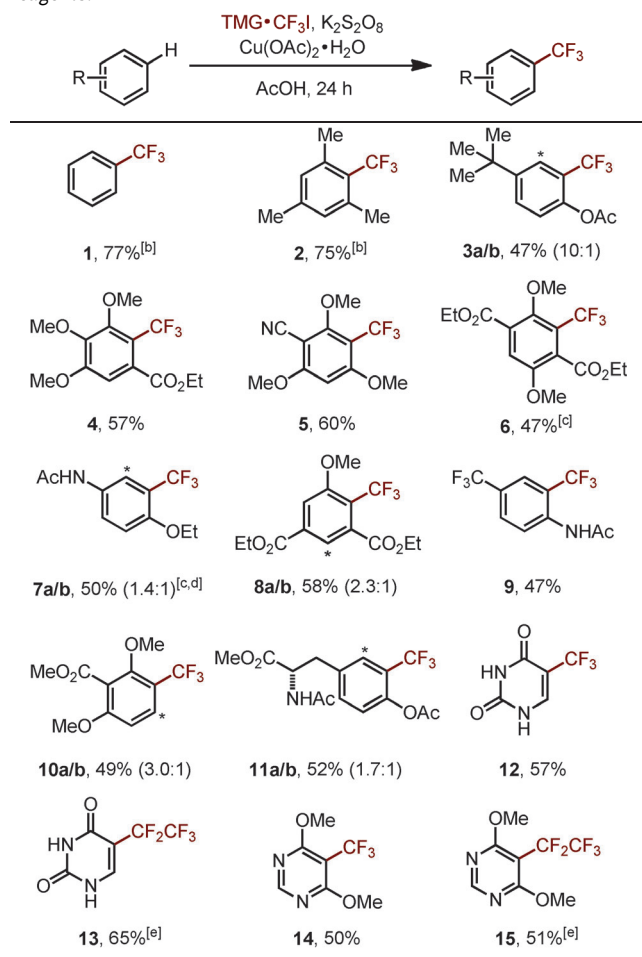
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require the use of reagents that are gaseous or corrosive, or require special apparatus to perform. We have developed a method for C–H trifluoromethylation that does not suffer from these limitations.

Utilizing liquid TMG·CF₃I, we were able to rapidly optimize conditions for direct arene trifluoromethylation. We found that electron-neutral to electron-rich arenes could be directly trifluoromethylated when treated with TMG·CF₃I, K₂S₂O₈, and Cu(OAc)₂·H₂O in acetic acid at 90 °C (Table 1).^[25] The reactions are conducted under ambient atmosphere and with no need for rigorous exclusion of moisture or specialized equipment.

The reaction conditions are compatible with common arene substituents, including ethers, esters, nitriles, and amides. The reaction is also effective with highly substituted arenes and electron-deficient heterocycles. The reagent TMG·CF₃CF₂I can be substituted for TMG·CF₃I to afford pentafluoroethylated products. Positional selectivities are

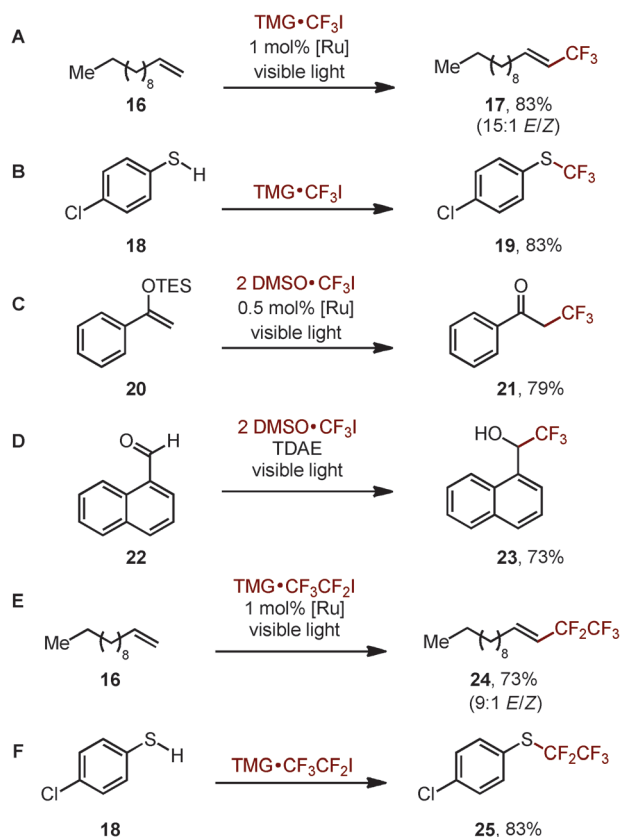
Table 1: Direct perfluoroalkylation of arenes using halogen-bonded reagents.^[a]



[a] Conditions: 2 equiv TMG·CF₃I, 4 equiv K₂S₂O₈, 2 equiv Cu(OAc)₂·H₂O, AcOH, 90 °C, 24 h. Yields of isolated products are shown unless otherwise specified. * indicates site of minor functionalization. [b] Yield determined by ¹⁹F NMR spectroscopy. [c] Reaction conducted at 120 °C. [d] 4 equiv tBuOOH and 0.2 equiv FeSO₄·7H₂O were utilized instead of K₂S₂O₈ and Cu(OAc)₂·H₂O. [e] TMG·CF₃CF₂I was utilized instead of TMG·CF₃I.

generally modest; generation of mixtures of positional isomers is common for direct arene trifluoromethylations.^[4,5,8,24] Direct arene trifluoromethylation using TMG·CF₃I is an effective and operationally simple method made possible by the condensed-phase nature of the reagent.

To further demonstrate the synthetic utility of TMG·CF₃I, we have explored its use as a drop-in replacement for gaseous CF₃I (Scheme 1). TMG·CF₃I can be used in Stephenson's



Scheme 1. Representative perfluoroalkylation reactions using halogen-bonded reagents. [Ru] = [Ru(bipy)₃]Cl₂·6 H₂O. TDAE = tetrakis(dimethylamino)ethylene.

photoredox-catalyzed oxidative olefin trifluoromethylation (Scheme 1 A).^[9b,e] Likewise, thiol trifluoromethylation can be accomplished with TMG·CF₃I (Scheme 1 B). In both cases, TMG acts as a base in addition to providing a liquid source of CF₃I.

In other cases, we found the presence of TMG to be detrimental. For example, TMG·CF₃I was not a suitable CF₃I surrogate for the MacMillan trifluoromethylation of enol ethers under photoredox catalysis.^[11h] However, 2DMSO·CF₃I proved effective both in the MacMillan trifluoromethylation and in the TDAE-mediated trifluoromethyl addition to aldehydes (Scheme 1 C and D, respectively). The ability of tetramethylguanidine to serve as one-electron reductant and/or H-atom donor may explain the differing reactivity of DMSO·CF₃I and TMG·CF₃I. We have also found that TMG·CF₃CF₂I is effective for pentafluoroethylation (Scheme 1 E and F).

To better understand our new reagents, we investigated the bonding in greater detail. The 1:1 stoichiometry of TMG·CF₃I was established by integration of the ¹H and ¹⁹F NMR signals against a 1-fluoro-3-nitrobenzene standard. When approximately 5 equivalents of CF₃I were condensed into a known amount of TMG at −23 °C, and the reaction mixture was warmed to 23 °C, CF₃I evaporated until a 1:1 liquid adduct (TMG·CF₃I) was formed. The experiment is consistent with a well-defined 1:1 adduct.

We were unable to characterize TMG·CF₃I by X-ray crystallography, but we obtained crystals of the TMEDA analog (Figure 2A). While the TMEDA·2CF₃I adduct behaves similarly to the TMG·CF₃I adduct (see the Supporting Information), the TMEDA-based crystalline solid became sticky with storage, making it less practical to handle than TMG·CF₃I. The iodine–nitrogen interaction, which we ascribe to halogen bonding, was unambiguously established by measuring an interatomic N···I distance of 2.80 Å, smaller than the sum of the van der Waals radii for N and I (3.53 Å). DFT calculations corroborated the experimentally determined N···I distance. With the validated DFT functionals, we found an N···I distance of 2.8 Å for TMG·CF₃I, and an interaction energy corrected for basis set superposition error (BSSE) of 9–10 kcal mol^{−1}, near the upper end of the 1–10 kcal mol^{−1} range for halogen bond strength.^[18] The calculated halogen bond strength is consistent with the temperature and storage stability of TMG·CF₃I.

Halogen bonding can be rationalized as a non-covalent polar interaction between halogen bond donors, such as CF₃I, and halogen bond acceptors, such as TMG.^[18h,j] The three filled lone pairs on iodine are almost purely s- and p-based orbitals, with little hybridization (Figure 2C); the C–I σ-bond has p_z character on iodine, and is polarized toward the electron-withdrawing CF₃ group. Thus, minimal electron density is observed in the outermost region of the iodine atom along the z axis of the C–I σ-bond; this region has been named the σ-hole^[26] (Figure 2D). The attractive interaction between a Lewis base such as TMG and the σ-hole contributes to halogen bonding.^[18h,j]

In conclusion, we have described the first use of halogen bonding to access reagents for organic synthesis. Stable, readily handled liquid adducts of CF₃I and CF₃CF₂I were prepared and used in perfluoroalkylation reactions. Using TMG·CF₃I, a novel arene C–H trifluoromethylation reaction has been developed. Given the strong interest in fluoro-organic compounds and perfluoroalkylation reagents, we anticipate that our reagents will be of use to the community both in wider accessibility of the rich chemistry of CF₃I and in development of novel reactions.

Experimental Section

General procedure for direct trifluoromethylation of arenes: Arene (0.250 mmol, 1.00 equiv), K₂S₂O₈ (270 mg, 1.00 mmol, 4.00 equiv), and Cu(OAc)₂·H₂O (100 mg, 0.500 mmol) were dissolved in glacial acetic acid (2.0 mL). TMG·CF₃I (0.100 mL, 0.500 mmol, 2.00 equiv) was added, the reaction vessel was sealed and heated to 90 °C for 24 h. The reaction mixture was diluted with saturated aqueous Na₂CO₃ (50 mL) and the resulting mixture extracted with ethyl acetate (3 × 25 mL). The combined ethyl acetate extracts were dried (MgSO₄) and

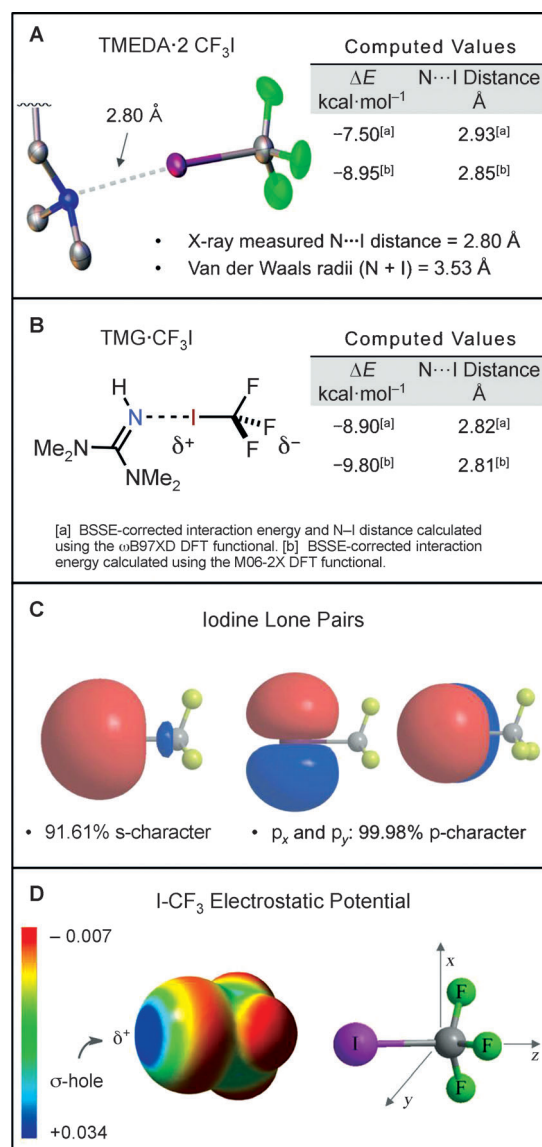


Figure 2. A) X-ray structure of TMEDA·2CF₃I; experimentally measured and calculated N···I distance; calculated interaction energy per CF₃I molecule. B) Calculated interaction energy and N···I distance for TMG·CF₃I. C) The two p-type and the s-type iodine lone pairs in CF₃I. D) Electrostatic potential map of CF₃I (in Hartrees) at the 0.001 electrons Bohr^{−3} isodensity surface highlighting the σ-hole region. See the Supporting Information for details on the DFT calculations.

concentrated in vacuo. The residue was purified by chromatography on silica gel.

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