Letter

Fluorobissulfonylmethyl Iodides: An Efficient Scaffold for Halogen Bonding Catalysts with an sp3-Hybridized Carbon-Iodine Moiety

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Fluorobissulfonylmethyl Iodides: An Efficient Scaffold for Halogen Bonding Catalysts with an *sp*³-Hybridized Carbon-Iodine Moiety

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ABSTRACT: *The halogen-bond donors FBSM-I and FBDT-I, which contain an sp³-hybridized carbon-iodine (C_{sp3}–I) moiety, were designed and synthesized. The highly electron-withdrawing nature of the fluorobissulfonyl-methane scaffold leads to the generation of σ-holes on the surface of the iodine atoms in FBSM-I and FBDT-I. Mukaiyama aldol reactions and hydrogen-transfer reductions are efficiently catalyzed by FBSM-I and FBDT-I under neutral and mild reaction conditions. The driving force for these transformations should be the halogen bonding induced by FBSM-I and FBDT-I, which was confirmed by DFT calculations, single-crystal X-ray diffraction analyses, and NMR titrations.*

KEYWORDS: *halogen bonding, fluorobissulfonyl methane, fluorine, iodine, organocatalysis*

Halogen bonds refer to non-covalent interactions between an electrophilic region associated with a halogen atom and a Lewis basic moiety.[1] While halogen bonding interactions have traditionally been investigated predominantly in the context of crystal engineering, current research avenues encompass many areas with applications in liquid crystals, supramolecular assemblies, medicinal chemistry, and organic synthesis.[1] Especially the use of halogen bonding in organocatalysis has recently gained substantial attention.[2] Although much research efforts have been devoted to this topic, most halogen-bond catalysts (donors) are limited to those containing an *sp*²-hybridized carbon-iodine (C_{sp2}–I) moiety, as in *e.g.* aryl iodides (Figure 1a) and imidazolium iodides (Figure 1b).[3] One example of a halogen-bond catalyst that contains an *sp*-hybridized carbon-iodine (C_{sp}–I) moiety has also been reported (Figure 1c).[4] However, halogen-bond donors that contain an *sp*³-hybridized carbon-iodine (C_{sp3}–I) moiety are extremely rare,[5] despite the potential structural variation including chiral structures that would arise from tetra-substituted asymmetric carbon centers.

1-Fluoro-1,1-bis(phenylsulfonyl)methane (FBSM)[6] and 2-fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide (FBDT)[7] represent synthetic equivalents of monofluoromethide species, and these compounds have been employed in a wide range of nucleophilic monofluoromethylation reactions that include asymmetric catalytic reactions (Figure 1d).[7,8] We speculated that iodinated analogues of FBSM and FBDT, *i.e.*, 1-fluoro-1-iodobis(phenylsulfonyl)methane (FBSM-I, **1a**)[9] and 2-fluoro-2-iodo-1,3-benzodithiole-1,1,3,3-tetraoxide (FBDT-I, **1b**) could potentially be useful halogen-bond donors due to the poor electron density of the central sp³-hybridized carbon (Figure 1e). We herein disclose fluorobissulfonylmethyl iodides such as FBSM-I and FBDT-I as an efficient scaffold for halogen-bonding catalysts with a C_{sp3}–I moiety.

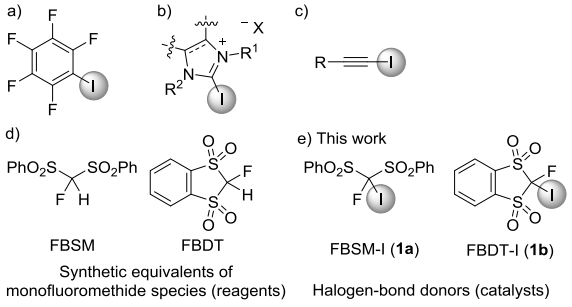


Figure 1. a-c) Structures of reported halogen-bond donors. d) FBSM and FBDT as synthetic equivalents of monofluoromethide species. e) Halogen-bond donors FBSM-I (**1a**) and FBDT-I (**1b**).

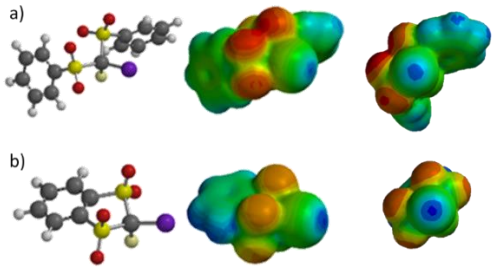
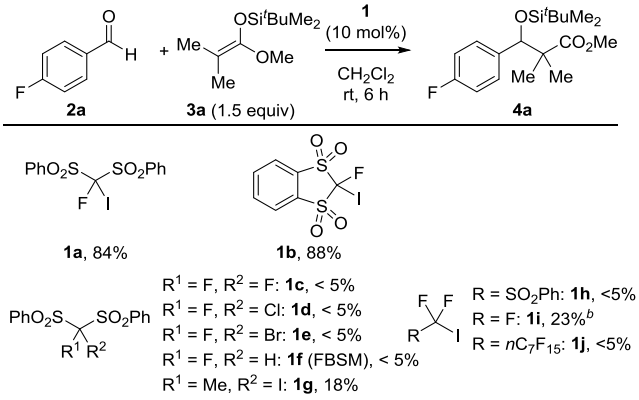


Figure 2. Optimized structures and mappings of the electrostatic potential for a) **1a** and b) **1b**. All calculations were performed at DFT/B3LYP/6-311+G(d,p) level of theory using Spartan14.

Treating FBSM and FBDT with iodine and cesium carbonate in acetonitrile at room temperature resulted in the formation of FBSM-I (**1a**) and FBDT-I (**1b**) as stable off-white solids in 95% and 92% yield, respectively (Scheme S1). To evaluate the po-

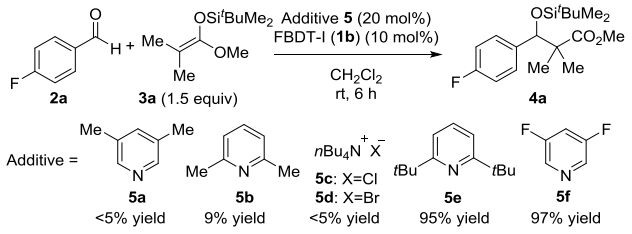
tential of **1a** and **1b** as halogen-bond donors, electronic potential maps were generated using DFT calculations at the DFT/B3LYP/6-311+G(d,p) level of theory, which clearly revealed the existence of σ-holes, *i.e,* electron-deficient areas, on the surface of the iodine atoms (Figure 2).

Encouraged by the results of the DFT calculations, we next attempted to use **1a** and **1b** as halogen-bond donors in a catalytic Mukaiyama aldol reaction[10] between aldehyde **2a** and silyl ketene acetal **3a** to furnish **4a**. As expected, aldol product **4a** was obtained in high yield when 10 mol% of **1a** or **1b** were employed as catalysts. The cyclic fluorobissulfonylmethyl Iodide **1b** afforded a slightly higher yield than acyclic fluorobissulfonylmethyl Iodide **1a**. When analogues of **1a** that contain F (**1c**), Cl (**1d**), Br (**1e**) or H (**1f**, FBSM) atoms instead of iodine were employed as catalysts, the reaction did not proceed and only **2a** was recovered after 6 h. The presence of a fluorine atom in **1a** and **1b** should be vital to obtain high yields, given that the yield decreased dramatically using **1g.** The replacement of the sulfonyl group in **1a** with fluorine (**1h**) resulted in a low product yield, similar to when perfluoroalkyl iodides such as CF_3I (**1i**) and $nC_8F_{17}I$ (**1j**) were used (Scheme 1).



Scheme 1. Mukaiyama Aldol Reaction between 2a and 3a in the Presence of Catalytic Amounts of Halogen-bond Donors 1 or Related Compounds[a]

[a]The reaction between 2a (0.20 mmol) and 3a (0.30 mmol) was carried out in the presence of 1 (0.020 mmol) in CH_2Cl_2 (0.2 mL) at room temperature. Yields were calculated based on the ^{19}F NMR data of the crude reaction mixture using $PhCF_3$ as an internal standard. [b]An excess of CF_3I was used.

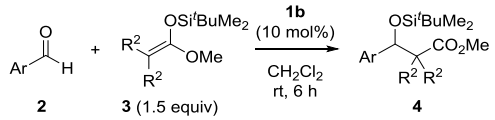


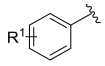
Scheme 2. Effect of Additives (5) on the Mukaiyama Aldol Reaction between 2a and 3a Catalyzed by 1b.

The addition of catalytic amounts (20 mol%) of halogen-bond acceptors such as 3,5-lutidine (**5a**), 2,6-lutidine (**5b**), tetrabutylammonium chloride ([nBu$_4$N]Cl, **5c**) and tetrabutylammonium bromide ([nBu$_4$N]Br, **5d**) significantly suppressed the **1b**-catalyzed Mukaiyama aldol reaction. On the other hand, sterically demanding 2,6-di-*t*-butylpyridine (**5e**) and less basic 3,5-difluoropyridine (**5f**) did not affect the reaction. These results strongly support the notion that **1b** acts as a halogen-bond donor (Scheme 2).

Subsequently, we examined the substrate scope of the **1b**-catalyzed Mukaiyama aldol reaction with respect to various aromatic aldehydes (**2**) (Table 1). Halogen (entries 1-3), alkyl (entries 4 and 5), phenyl (entry 6), and methoxy substituents (entries 7 and 8) on the arylaldehydes **2** were tolerated under the applied conditions, and the products (**4**) were obtained in high yield. Electron-withdrawing cyano and trifluoromethyl groups on the aromatic ring of **2** decreased the yield (entries 9–11). The transformation of sterically demanding naphthyl and heteroaryl aldehydes also proceeded smoothly (entries 12-14), while *n*-octyl aldehyde 2n did not react under these reaction conditions (entry 15).

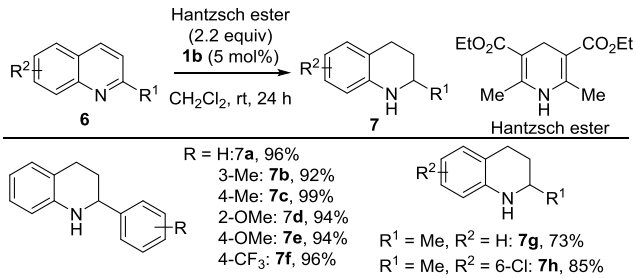
Table 1. Substrate Scope for the Mukaiyama Aldol Reaction between 2 and 3 Catalyzed by 1b[a]



Entry	Ar	R^1	2	R^2	3	4	Yield (%)
1		4-F	**2a**	Me	**3a**	**4a**	87
2		3-Br	**2b**	Me	**3a**	**4b**	94
3		4-Br	**2c**	Me	**3a**	**4c**	80
4		4-Me	**2d**	Me	**3a**	**4d**	89
5		4-*t*Bu	**2e**	Me	**3a**	**4e**	87
6		4-Ph	**2f**	Me	**3a**	**4f**	97
7		2-OMe	**2g**	Me	**3a**	**4g**	98
8		4-OMe	**2h**	Me	**3a**	**4h**	99
9		4-OAc	**2i**	Me	**3a**	**4i**	59
10		4-CN	**2j**	Me	**3a**	**4j**	73
11		4-CF_3	**2k**	Me	**3a**	**4k**	49
12	2-naphthyl	-	**2l**	Me	**3a**	**4l**	98
13	2-naphthyl	-	**2l**	H	**3b**	**4m**	87
14	2-thienyl	-	**2m**	Me	**3a**	**4n**	98
15	*n*-octyl	-	**2n**	Me	**3a**	**4o**	-

[a]The reaction between aldehyde **2** (0.20 mmol) and silyl ketene acetal **3** (0.30 mmol) was carried out in the presence of **1b** (0.020 mmol) in CH_2Cl_2 (0.2 mL) at room temperature for 6 h. The yields refer to isolated yields.

Table 2. Reduction of Quinolones 6 with a Hantzsch Ester Catalyzed by 1b[a]



[a]Reduction of quinolones **6** (0.20 mmol) by a Hantzsch ester (0.44 mmol) in the presence of **1b** (0.010 mmol) in CH_2Cl_2 (2.8 mL) at room temperature. Yields refer to isolated yields.

To investigate the further versatility of **1b** as a halogen-bond donor, we carried out the catalytic hydrogen-transfer reduction of quinolone derivatives **6** with a Hantzsch ester[3b, 5] in CH_2Cl_2 using 5 mol% of **1b** (Table 2). The targeted C2-alkylated or -

arylated tetrahydroquinolines (**7**) were obtained in good to excellent yield independent of the substitution at the aromatic ring with electron-donating or -withdrawing groups.

In order to ascertain the effect of halogen bonding on these reactions, single-crystal X-ray diffraction analyses of **1a** and **1b** were examined. Interestingly, the crystal structures of **1a** and **1b** clearly show intermolecular halogen-bonding interactions between the iodine atoms and the oxygen atoms of one sulfonyl group (Figure 3). The I-O bond distances are unequivocally shorter than the corresponding sum of van der Waals radii, and the C_1–I_1–O_1 angles are close to 180°, which represent ideal conditions for halogen-bonding interactions.[11]

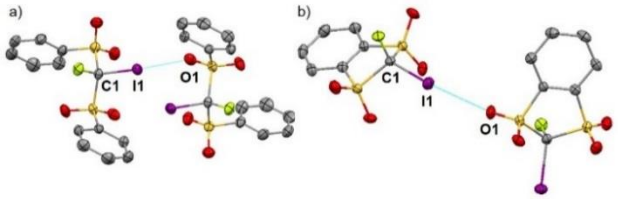


Figure 3. X-ray crystallographic structures of a) **1a** (CCDC 1834149) and b) **1b** (CCDC 1834152), which show halogen bonding between I_1–O_1 (**1a**: 2.93 Å; **1b**: 2.97 Å); thermal ellipsoids set to 50% probability and hydrogen atoms omitted for clarity.

Considering that the **1b**-catalyzed Mukaiyama aldol reaction was inhibited by the addition of by halogen-bond acceptors such as 3,5-lutidine (**5a**) (Scheme 2), we then attempted to examine complexation between **1a** or **1b** and **5a**. Recrystallization of 1:1 mixtures of **1a** or **1b** and **5a** from CH_2Cl_2/*n*-hexane resulted in the formation of 1/1 complexes of **1a**/**5a** or **1b**/**5a.** Single-crystal X-ray diffraction analyses these complexes clearly revealed halogen-bonding interactions (Figure 4), wherein **5a** indeed serves as a halogen-bond acceptor. Both I_1-N_1 bonds (**1a**/**5a**: 2.64 Å; **1b**/**5a**: 2.62 Å) are shorter than the corresponding I_1-O_1 bonds (**1a**: 2.93 Å; **1b**: 2.97 Å) shown in Figure 3, which suggests that the aromatic nitrogen moiety in **5a** is a stronger halogen-bond acceptor than the sulfonyl group in **1a/b**. The C_1-I_1 bonds in **1**/**5a** are elongated compared to those in **1** (**1a**: 2.13 Å; **1b**: 2.11 Å; **1a**/**5a**: 2.18 Å; **1b**/**5a**: 2.15 Å), which strongly supports halogen bonding between I_1 and N_1.

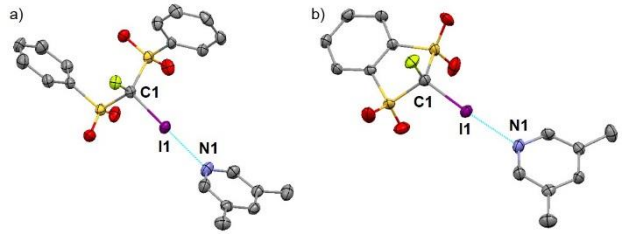


Figure 4. X-ray crystallographic structures for the 1/1 halogen-bonding complexes of a) **1a**/**5a** (CCDC 1834147) and b) **1b**/**5a** (CCDC 1834148); I_1-N_1 bonds (**1a**/**5a**: 2.64 Å; **1b**/**5a**: 2.62 Å); thermal ellipsoids at 50% probability and hydrogen atoms omitted for clarity.

Encouraged by this clear evidence for the presence of halogen bonding induced by **1a**,**b** in the solid state, we subsequently attempted to observe halogen bonding in solution. Based on the fact that [*n*Bu$_4$N]Cl (**5c**) inhibited the aldol reaction catalyzed by **1b** (Scheme 2), NMR titration experiments on **1a**, **1b**, and **1c** in $CDCl_3$ in the presence of [*n*Bu$_4$N]Cl were carried out, whereby difluorinated **1c** was used as a control (Figure 5). After the titration, the ^{19}F NMR signals were significantly up-field shifted (> −9 ppm) in the case of **1a** and **1b**. On the other hand, the titration of **1c** revealed only a small shift (< 0.4 ppm) of its ^{19}F NMR peak under identical conditions. This result indicates that the iodine atoms in **1a** and **1b** interact with the chloride anion (Cl^-) in [*n*Bu$_4$N]Cl, while the fluorine atoms in **1a-c** do not engage in any significant interactions with the chloride. The shapes of the peaks of **1a** and **1b** changed from sharp to broad and sharp again with increasing amount of [*n*Bu$_4$N]Cl during the titration, which suggests an equilibrium between monomeric **1a,b** and halogen-bonding complexes **1a,b**/Cl^- in solution.

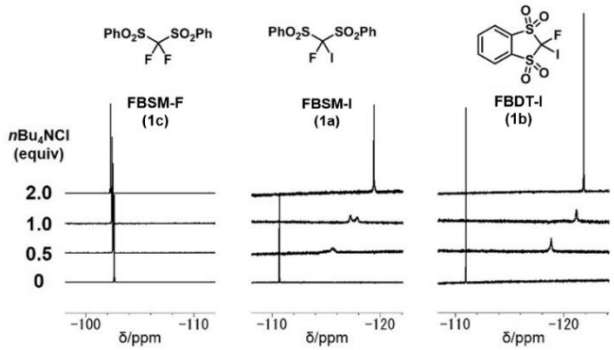


Figure 5. ^{19}F NMR titration of **1a-c** with [*n*Bu$_4$N]Cl in $CDCl_3$.

Peak shifts in the ^{13}C NMR spectra of **1b** were also observed, whereby the carbon atom at the α-position relative to the iodine atom showed the largest shift (+1.58 ppm) after the addition of 1.0 equiv of [nBu$_4$N]Cl (Figure 6). This result is consistent with previous reports on halogen-bond donors.[12] Slight peak shifts of the other peaks might be due to the effects of the sulfonyl group in **1b** to act as a Lewis base or halogen-bond acceptor.

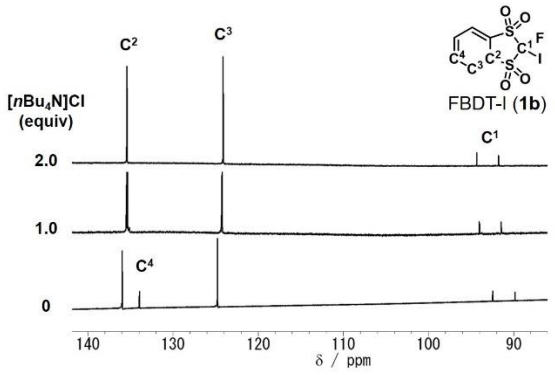
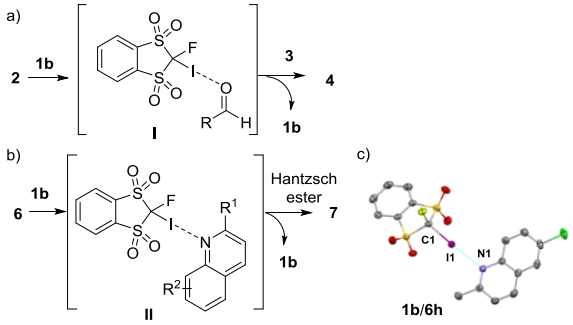


Figure 6. ^{13}C NMR titration of **1b** with [*n*Bu$_4$N]Cl in $CDCl_3$.

Based on the results obtained from solid-state and solution experiments, a plausible reaction pathway is shown in Scheme 3. Initially, **1b** should act as a Lewis acid to activate the carbonyl group in aldehydes **2** or the nitrogen atom in quinolines **6** to form a halogen-bonding complex (**I**/**II**). Then, the nucleophile (**3**) or hydride could attack the substrates (**2**/**6**) in **I** or **II** to form the desired product (**4**/**7**) (Scheme 3a, b). Although we failed to obtain evidence for the activation of aldehydes (**2**) by halogen bonding induced by **1b**, the formation of 1/1 halogen bonding complex **II** of **1b** with **6h** (**1b**/**6h**) was confirmed by single-crystal X-ray diffraction analysis, which revealed strong halogen bonding between the iodine atom of **1b** and the nitrogen atom of quinoline **6h** (Scheme 3c).



Scheme 3. (a) Plausible Reaction Intermediates I or II for the Mukaiyama Aldol Reactions and (b) Hydrogen Transfer Reactions, Using a Catalytic Amount of 1b. (c) X-ray Crystallographic Structure of 1/1 Halogen Bonding Complex 1b/6h (CCDC 1834151); Thermal Ellipsoids at 50% Probability and Hydrogen Atoms Omitted for Clarity.

In conclusion, we have disclosed the new halogen-bond donors FBSM-I and FBDT-I, which contain sp^3-hybridized carbon-iodine bonds (C_{sp3}–I). Both FBSM-I and FBDT-I efficiently catalyze the Mukaiyama aldol reaction of aldehydes with silyl enol ethers and the hydrogen-transfer reduction of quinolines with a Hantzsch ester to furnish the corresponding products in high yield. The highly electron-withdrawing nature of the fluorobissulfonyl-methane scaffold results in the formation of σ-holes on the surface of the iodine atoms in FBSM-I and FBDT-I, and these were examined by DFT calculations. Halogen-bonding interactions induced by FBSM-I and FBDT-I were confirmed in the solid state using single-crystal X-ray diffraction analyses, and in solution using ^{19}F and ^{13}C NMR titration experiments.[13] Considering that the structural variation of previously reported halogen-bond donors are essentially limited to iodo-compounds with a sp^2-hybridized carbon-iodine bond (C_{sp2}–I), our fluorobissulfonylmethyl iodide scaffold for halogen-bond donors should present an attractive alternative for the design of new halogen-bond catalysts that contain a tetra-substituted chiral carbon center. Further applications of this concept for the design of novel chiral halogen-bond donors for enantioselective reactions are currently under investigation. Besides, **1a** is used for radical addition of terminal alkenes under reaction conditions,[9] it might be possible to show a unique usage of **1** as both a catalyst and a reactant in a tandem process using a stoichiometric amount of 1, i.e., **1**-catalyzed aldol reactions of substrates with a terminal alkene followed by the radical addition of **1** to the terminal alkene moiety of the substrates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: .

Experimental details, analytical data (HRMS), and copies of ^1H, ^{13}C and ^{19}F NMR spectra.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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(13) We observed that < 30% of **1b** (FBDT-I) was lost after the completion of Mukaiyama Aldol reaction and detected FBDT and α-iodinated ester by ^{19}F NMR and GC. The results indicate that **1b** acts not only as a catalyst but also as an electrophilic iodinating reagent for silyl ketene acetal **3**. We also confirmed the by-product, α-iodinated ester (10mol%), cannot catalyze the Mukaiyama Aldol reaction.

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