Halogen Bonds

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Halogen-Bond-Induced Activation of a Carbon–Heteroatom Bond**

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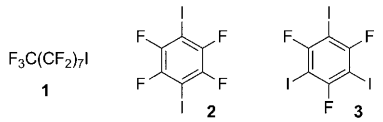
Dedicated to Professor Robert Weiss on the occasion of his 70th birthday

Halogen bonds are attractive noncovalent interactions between terminal halogen atoms in compounds of the type R-X (X = Cl, Br, I) and Lewis bases LB.[1–3] Reasonably strong halogen bonds are formed only when R is highly electronegative, as for example in the case of polyfluorinated alkyl or phenyl substituents (Scheme 1).[1,2] In these cases, a



Scheme 1. Commonly used polyfluorinated halogen-bond donors.

region of positive electrostatic potential is induced at the side of the halogen atom opposite to the R–X bond ("σ hole").[4] At the same time, the n→σ* charge transfer of the Lewis base with the halogen-bond donor R-X is also facilitated.[5] The electronic nature of the halogen-bond interaction causes an R–X···LB angle of approximately 180° and thus high directionality.[2a,b]

Although the interaction itself has been known for a long time,[5a,b] it has received increased interest only since the early 1990s.[2a,b,6] Aside from basic research, mainly studies towards the rational design of solids have been published,[2b,c,7] for instance concerning liquid crystals[8] and conductive materials.[9] In these investigations, strong halogen bonds (XBs) have often been obtained with halides as Lewis bases.[2a,10] There were also early indications for the occurrence of XBs in solution,[11] which have recently been confirmed.[3c,12] XB-based halide receptors, presented not long ago,[13] constitute a first application of this interaction in solution. In addition, Bolm et al. reported on the catalytic activity of XB donors like **1** (Scheme 1) in the reduction of quinoline derivatives.[14]

Lately, the potential of thiourea derivatives[15] to act as receptors for anions has been exploited increasingly for the activation of substrates and for asymmetric induction in *hydrogen-bond*-based organocatalytic reactions.[16,17] In these cases, the catalyst binds to halides,[17b,d] alkoxides,[17a] carboxylates,[17c] and other anions[17e] (which are usually liberated during the reaction). Despite the various analogies with hydrogen bonds, to the best of our knowledge no examples are known in which organic[18,19] *halogen-bond* donors have been used to activate organic substrates (apart from the case[14] mentioned above). As part of our investigations towards the use of halogen bonds in organic synthesis and organocatalysis, we herein report on the first activation of a carbon–heteroatom bond by novel (potentially bidentate) halogen-bond donors.

In view of the numerous examples of halogen-bond adducts with halide salts, our aim was to activate carbon–halogen bonds with strong XB donors. Coordination of the latter to the lone pairs of the terminal halogen atom should lead at least to the weakening of the respective C–X bond, if not, in the extreme case, to its heterolytic cleavage. Additional driving force for the overall reaction (e.g. the substitution of the halide by an added nucleophile) could be gained by the insolubility of the XB adduct formed by the XB donor and the halide salt. In the broadest sense, the XB donor would act as an organic Ag^+ equivalent.

We considered benzhydryl bromide[20] **4** (Table 1) to be an ideal test substrate to realize this idea, since its comparably labile C–Br bond can, for instance, be activated by Ag^+ salts.[21] Deuterated acetonitrile as the solvent should ensure good solubility, but should not exhibit a significant negative effect on the formation of XB adducts.[3c] In the absence of other reaction partners during the activation of the C–Br bond of **4**, the solvent would also assume the role of a nucleophile and would coordinate to the respective carbon atom. Hydrolysis of the resulting nitrilium intermediate by traces of water in the solvent would yield (deuterated) *N*-benzhydryl acetamide **5** in this variant of the Ritter reaction.[22] Without addition of an activating reagent, a solution of the pure bromide **4** in wet acetonitrile reacted to give only trace amounts of amide **5** after four days at room temperature (Table 1, entry 1). We first tested monodentate XB donors **2** and **3** (Scheme 1), but neither of them was able to induce the reaction (Table 1, entries 5 and 6).

Consequently we turned our attention to bidentate XB donors, only few of which are presently known.[13] Instead of a polyfluorinated backbone, we employed an alternative way to enhance the electrophilicity of XB donors: the C–I bonds in compounds *m*-**8** and *p*-**8** (Scheme 2) are electrostatically activated by the respective imidazolium cores.[23]

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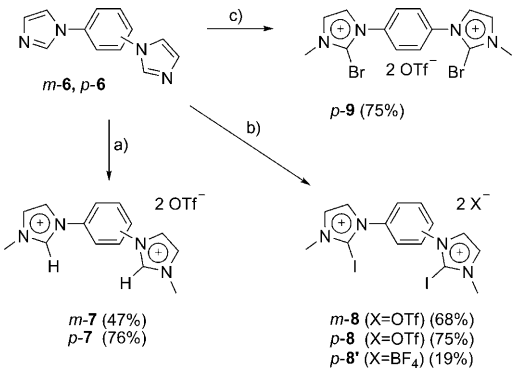
Table 1: Reactions of benzhydryl bromide **4** with various activating reagents in wet CD_3CN.

4 **5**

Entry	Activating reagent	(Equiv.)[a]	Additive[b]	Yield [%][c]
1	–	–	–	≤5
2	–	–	py	≤5
3	HOTf	0.05	–	12
4	HOTf	0.05	py	7
5	HOTf	1.0	–	25
6	NBu_4OTf	2.0	–	≤5
7	**2**	1.0	–	≤5
8	**3**	1.0	–	≤5
9	*p*-**7**	1.0	–	7
10	*p*-**7**	1.0	py	≤5
11	*p*-**8**	1.0	–	85 [88][d]
12	*p*-**8**	1.0	py	85
13	*m*-**7**	1.0	–	12
14	*m*-**7**	1.0	py	7
15	*m*-**8**	0.2	–	28
16	*m*-**8**	1.0	–	80 [71][d]
17	*m*-**8**	1.0	py	75
18	*p*-**8′**	1.0	–	97
19	*p*-**9**	1.0	–	54
20	**10**	2.0	–	49

[a] Equivalents of activating reagent (relative to **4**). [b] Additive: 0.1 equivalents of pyridine (relative to **4**); see text. [c] Yield of **5** after 96 h at room temperature according to ^{1}H NMR analysis (see the Supporting Information). [d] Yield of isolated product **5** in preparative experiments with CH_3CN.

Starting from the known[24] diimidazole *p*-**6** (and the analogously prepared *m*-**6**), we could obtain target compounds *m*-**8** and *p*-**8** by iodination and subsequent methylation in very good yields (Scheme 2). The corresponding noniodinated compounds **7** were prepared by direct methylation of **6**. All saltlike products could be isolated by simple recrystallization. The NMR spectra of both *m*-**8** and *p*-**8** show only one set of signals, indicating unhindered rotation of the imidazolium substituents. The result of the X-ray structural analysis of *p*-**8** is shown in Figure 1.[25] It represents the first structural analysis of a 2-iodoimidazolium derivative as a triflate salt. Particularly striking are the contacts of the XB donor with the triflate counterions (2.838 Å).[26] The respective distances are well below the sum of the van der Waals radii (3.50 Å),[27] which is already an indication of the high σ* acidity of *p*-**8**.



Scheme 2. Synthesis of the activating reagents. a) MeOTf (4 equiv), CH_2Cl_2; b) 1. *n*BuLi (2.6 equiv), THF, −78 °C; I_2 (2.4 equiv), THF, −78 °C; 2. MeOTf (4 equiv), CH_2Cl_2 (*m*-**8**, *p*-**8**) or 2. Me_3OBF_4 (2.5 equiv), CH_2Cl_2 (*p*-**8′**); c) 1. *n*BuLi (2.3 equiv), THF, −78 °C; CBr_4 (2.0 equiv), THF, −78 °C; 2. MeOTf (5.6 equiv), CH_2Cl_2.

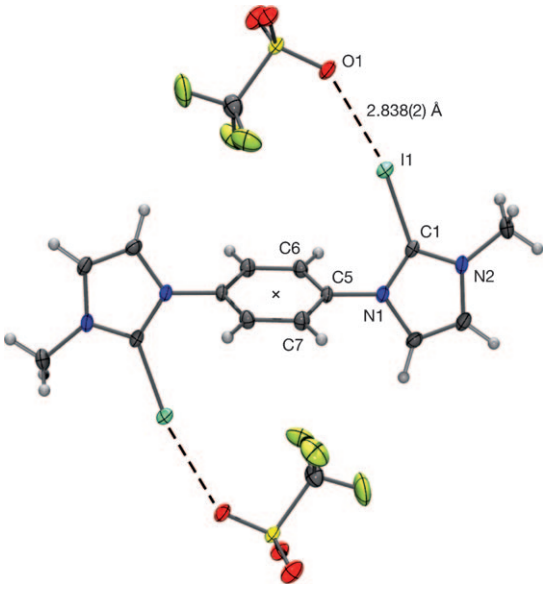


Figure 1. X-ray structural analysis of the XB donor *p*-**8** (ellipsoids at 50% probability); selected bond lengths [Å] and angles [°]: C1–I1 2.054(3), C1–N2 1.335(4), C1–N1 1.339(4), I1···O1 2.838(2); N1-C1-N2 107.9(2), C6-C5-N1-C1 62.7(4); x = center of inversion. Gray C, white H, yellow-green F, cyan I, blue N, red O, yellow S.

Both *p*-**8** and *m*-**8** activate benzhydryl bromide (Table 1, entries 11 and 16): according to ^{1}H NMR analysis, addition of *p*-**8** resulted in 85% conversion of **4** to **5**, while *m*-**8** still gave 80% yield of **5**. Side products or potential decomposition products of the activating reagent were not evident in the NMR spectra. The yields were confirmed in preparative experiments[28] and the NMR spectra of the product agree well with literature data on **5**.[29] When 20 mol% of *m*-**8** was added (Table 1, entry 15), a conversion of 28% was obtained according to NMR analysis; this points towards a stoichiometric effect of the activating reagent (including the background reaction). Maybe the XB donors **8** bind too strongly to the liberated bromide and are not available for further starting material **4**. This assumption is supported by the fact that the ^{13}C NMR signal of the iodine-carrying carbon atoms of *m*-**8** undergoes a shift from $\delta = 102.4$ ppm to $\delta = 110.2$ ppm in the course of the reaction (Figure 2). Comparative experiments with *m*-**8** indicate that this shift cannot be explained even by complete complexation with **5**; however, it is approximately reproduced with an equimolar amount of NBu_4Br. Incidentally, this ^{13}C NMR shift of *m*-**8** already points towards the contribution of halogen bonds in the activation of **4** (see below).

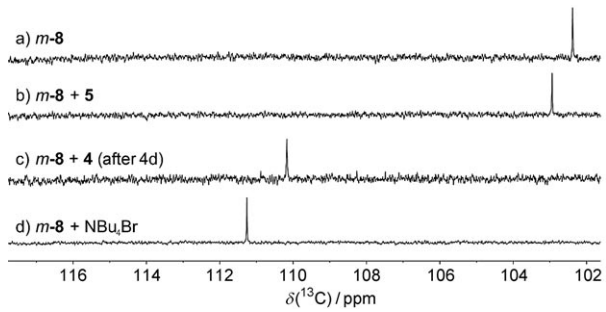


Figure 2. Signals of the iodine-carrying carbon atoms of *m*-**8** (^{13}C NMR spectra of solutions in CD_3CN): a) *m*-**8**, b) *m*-**8** and **5** (1:1), c) reaction solution after four days (see Table 1, entry 16), d) *m*-**8** and tetrabutylammonium bromide (1:1).

A critical aspect of investigations concerning the activation potential of XB donors is the risk that traces of acid (which might be hard to exclude) are the actual active reagent. As a consequence, experimental data could be misinterpreted. To rule out this alternative, a series of comparative kinetic measurements were performed (see also Table 1 and Figure 3). To begin with, addition of

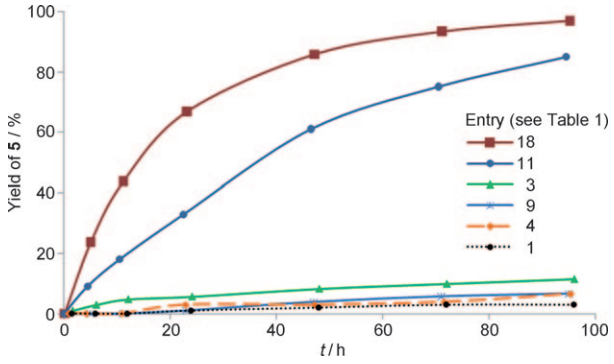


Figure 3. Yield-versus-time profile of selected reactions from Table 1, including the activation of **4** by *p*-**8** and appropriate reference experiments (*y* axis: yield of **5** based on ^{1}H NMR spectroscopy). For further plots see the Supporting Information.

5 mol% of HOTf led to a measurable, but comparably low yield of **5** (Table 1, entry 3). Moreover, this effect could be suppressed by addition of 10 mol% of pyridine (Table 1, entry 4), whereas *m*-**8** and *p*-**8** gave almost identical yields of **5** with the same additive (Table 1, entries 12 and 17).[30] Two equivalents of NBu_4OTf also did not induce any reaction (Table 1, entry 6).

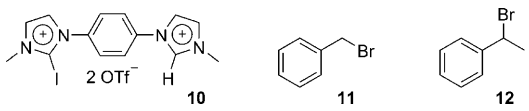
In addition, the non-iodinated compounds *m*-**7** and *p*-**7** activate **4** to a significantly lower extent (Table 1, entries 9 and 13; comparative experiments with pyridine as additive have also been performed in these cases). Since **7** and **8** differ only by the iodine substituents, these results are a strong indication that the iodine centers are causally related to the activation. If one also considers the NMR shifts reported above (Figure 2), the activation at hand can very likely be ascribed to halogen bonding.

In theory, **8** could also induce hydrolysis of acetonitrile, and the acetamide formed in this way over time could react with **4**. We can rule out this explanation, since even after several weeks no acetamide was detectable in solutions of *m*-**8** or *p*-**8** in CD_3CN (^{1}H and ^{13}C NMR spectra).

In further investigations regarding the mechanism of the reaction we could show that the HBr formed during the reaction is not active in an autocatalytic way. When one equivalent of HBr was added at the start of the reaction (with all other conditions maintained), only trace amounts of **5** had been formed after 96 h. Likewise, coordination of the XB donor to the HBr liberated during the reaction (and thus ultimately the generation of HOTf) cannot explain the activation of the substrate. Even in the (unrealistic) extreme case in which one equivalent of HOTf was added at the start of the reaction, **5** was generated in only 25% yield after 96 h (Table 1, entry 5).

In order to assess the influence of further structural variations of **8** on the effectiveness of the activation, we prepared both the dibromo derivative (*p*-**9**, Scheme 2) and the BF_4 analogue (*p*-**8′**) of *p*-**8**. As a result of the less coordinating nature of the counteranions (compared to triflate), the latter should feature increased electrophilicity at the iodine centers. As expected, *p*-**9** exhibited a markedly reduced activation potential (Table 1, entry 19), whereas the BF_4 salt *p*-**8′** was more effective than the triflate compound *p*-**8** (Table 1, entry 18). Figure 3, in particular, suggests a significant kinetic effect of the BF_4 counteranions.

The mono-iodinated imidazolium salt **10** (Scheme 3), which we synthesized for the purpose of comparison, generated **5** in only 49% yield after 96 h even when two



Scheme 3. Mono-iodinated XB donor **10** along with further substrates **11** (no activation by **8**) and **12** (after 96 h 40% conversion to the amide by *m*-**8**).

equivalents of the activating reagent were used (Table 1, entry 20). Although further studies regarding this matter are required, this already seems to indicate a bidentate coordination of XB donors **8**.[31]

Finally we tested the reactivity of benzyl bromide (**11**) and α-methylbenzyl bromide (**12**) in preliminary experiments (Scheme 3).[32] Under the reaction conditions corresponding to those specified in Table 1, no conversion of **11** was found with *m*-**8** or *p*-**8** after 96 h. In the case of **12** with *m*-**8**, however, formation of the respective amide in about 40% yield was observed after the same amount of time.

In summary, we could show that benzhydryl bromide **4** can be activated by the novel XB donors **8**. Comparative experiments with non-iodinated reference compounds and tests with added acids provide indications that halogen bonds are probably the basis for this effect. The successful conversion of substrate **12** also seems to point towards a broader applicability of this activation.

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charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[26] Shortest known (noncovalent) iodine–oxygen contact: 2.76 Å (L. Ouahab, F. Setifi, S. Golhen, T. Imakubo, R. Lescouëzec, F. Lloret, M. Julve, R. Swietlik, *C. R. Chim.* **2005**, *8*, 1286). Coordination of triflate to an I^{III} center: I–O = 2.89 Å (P. J. Stang, K. Chen, A. M. Arif, *J. Am. Chem. Soc.* **1995**, *117*, 8793).

[27] A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441. If one considers "polar flattening" (S. C. Nyburg, C. H. Faerman, *Acta Crystallogr. Sect. BA* **1985**, *41*, 274), a value of 3.30 Å is obtained.

[28] The activating reagent *m*-**8** or *p*-**8** could be re-isolated from the reaction solutions of the preparative-scale experiments in about 70% yield (as a mixture of salts with a counterion distribution of 90% triflate and 10% bromide).

[29] T. Maki, K. Ishihara, H. Yamamoto, *Org. Lett.* **2006**, *8*, 1431.

[30] Pyridine itself also reacts slowly with benzhydryl bromide to give the corresponding pyridinium salt (see, for example, Y. Pocker, *J. Chem. Soc.* **1959**, 3944), which we could also observe in the NMR spectra.

[31] Orientating DFT calculations indicate that bidentate coordination of *m*-**8** and *p*-**8** to a single halogen center is feasible (see the Supporting Information).

[32] On the basis of NMR experiments we have also obtained indications that **8** coordinates to other types of substrates (carbonyl compounds, imines) as well.

