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5-Iodo-1,2,3-triazolium-based multidentate halogen-bond donors as activating reagents†

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Bi- and tridentate polycationic halogen bond donors based on 5-iodo-1,2,3-triazolium groups have been synthesized by 1,3-dipolar cycloaddition reactions. These halogen-based Lewis acids have been evaluated as activators in a halide-abstraction benchmark reaction.

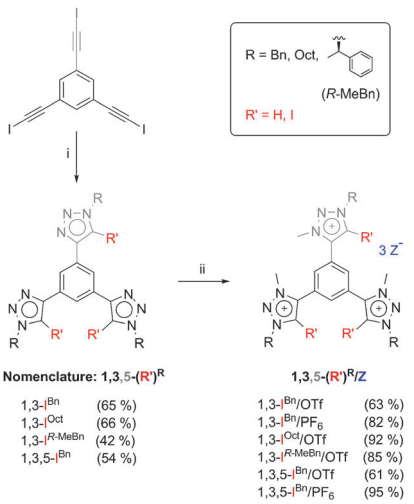
Halogen bonds ("XBs") are non-covalent interactions that occur between any kind of Lewis base and a Lewis-acidic component which features an electrophilic halogen atom.[1,2] In accordance with the nomenclature of hydrogen bonds (with which XBs share many similarities), such a Lewis acid is commonly, yet somewhat counter-intuitively, referred to as a "halogen-bond donor". Strong XB donors usually comprise either perfluorinated[2] or cationic backbones.[3] For a long time, XBs have mostly been investigated in the solid state,[4] whereas in recent years an increasing number of solution-phase studies have appeared.[5,6]

We have previously reported the use of strong XB donors in the cleavage of a carbon–bromine bond, employing bidentate halo-imidazolium-[7a] or halo-pyridinium-[7b] based activators. Due to the use of a strong lithiating reagent in the synthesis of the halo-imidazolium derivatives and the use of an azo-bridge as linkage of the two halo-pyridinium fragments, the design of XB donors with a denticity of three or more might present some challenges, at least with these parent structures. Promising alternatives in this respect are 5-iodo-1,2,3-triazolium moieties, whose principal structure can easily be obtained by the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and iodoalkynes.[8] Based on the pioneering work of Beer *et al.*, who recently introduced these groups as potent XB donors,[9] we consequently directed our attention to multidentate triazolium-based XB donors as further structurally different activators. Compared to our previous compounds, we presumed that these new systems would provide easier access to XB donors of higher denticity and might, ideally, constitute even stronger activators.

In the following, we present the synthesis and characterization of novel XB donors with two or three 5-iodo-1,2,3-triazolium groups. In addition, we test their effectiveness in our benchmark reaction for the activation of a carbon–bromine bond.

As shown in Scheme 1, Cu(I)-catalyzed cycloaddition reactions of 1,3-bis(iodoalkynyl)benzene with benzyl azide, *n*-octyl azide, and (*R*)-1-ethylphenylazide provided the corresponding bis(iodotriazolyl)benzene derivatives **1,3-I^{Bn}**, **1,3-I^{Oct}**, and **1,3-I$^{R–MeBn}$** in good yields. In the case of the sterically more demanding secondary azide, three equivalents of azide were needed to be used, as the reaction with two equivalents gave mainly the mono derivative (in 44% yield).

We chose to focus on a *meta*-substitution pattern since we had already shown for topologically related 1,3-bis(2-iodoimidazolium)benzene compounds that this geometric arrangement was ideal for a bidentate halide complexation.[7a,10] Subsequent regioselective methylation[11] with methyl triflate at the nitrogen atoms closest to the benzene core yielded the respective dicationic XB donors as triflate salts. We note that **1,3-I$^{R–MeBn}$/OTf** represents, to the best of our knowledge, the first synthetically obtained chiral XB donor.[12] This compound also exemplifies the fact that variously *N*-substituted multidentate XB donors



Scheme 1 Synthesis of XB donors: (i) CuI–TBTA (10 or 20 mol%), azide (2 or 3 eq.), THF, rt, 18 h; (ii) MeOTf (4 or 6 eq.), DCM, rt, 2 d. Anion exchange: $NaPF_6$ (3 or 4.5 eq.), MeOH, rt, 2 d. Yields for hexafluorophosphate salts refer to the anion exchange reaction.

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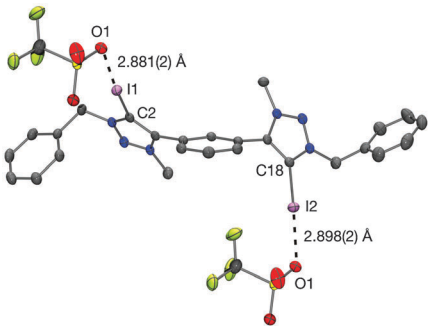


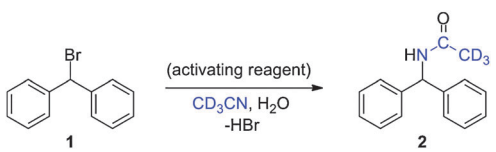
Fig. 1 ORTEP plot[13] of compound **1,3-I^{Bn}/OTf** in the solid state; hydrogen atoms are omitted for clarity; selected bond distances [Å] and angles [°]: I1–C2 = 2.055(2), I2–C18 = 2.058(2), C2–I1–O1 = 176.99(7), C18–I2–O1 = 169.44(8).

can be obtained by the present cycloaddition-based approach. In the case of **1,3-I^{Bn}/OTf**, the counterion could also be exchanged with hexafluorophosphate by anion metathesis in methanol.[10]

The result of a single-crystal X-ray structure determination of **1,3-I^{Bn}/OTf** is shown in Fig. 1.[13] In the solid phase, strong XBs were found between the iodine centers and, interestingly, the same oxygen atom of one triflate counterion, which thus bridges two dications. As is to be expected, the interaction distance is far below the sum of the van-der-Waals radii (3.50 Å),[14] and the C–I–O angle is close to linear. In the only previously known crystal structures of iodotriazolium compounds,[9b] Beer *et al.* also found a twofold coordination of the respective counterion, with notable differences in the I–X–I angle between X = I (approx. 80°) and X = Cl, Br (approx. 140–150°). In this respect, it is noteworthy that for **1,3-I^{Bn}/OTf**, the I–O–I angle is approx. 88°.

In order to obtain (previously unknown) tricationic XB donors with threefold denticity, we also reacted 1,3,5-tris-(iodoalkynyl)benzene with two organyl azides (Scheme 1). Despite several attempts under different reaction conditions, the dipolar cycloaddition of the trisubstituted benzene derivative with *n*-octyl azide did not yield the desired product. In contrast, the tris(triazolyl)benzene derivative **1,3,5-I^{Bn}** was obtained in good yield in the corresponding reaction with benzyl azide. Subsequent methylation with MeOTf gave the aspired XB donor **1,3,5-I^{Bn}/OTf**, the counterion of which could again be exchanged with hexafluorophosphate in excellent yield.

As a means of evaluating the Lewis acidity of the novel XB donors presented herein, we chose to compare them to our imidazolium- and pyridinium-based activators in the Ritter-type solvolysis of benzhydryl bromide (**1**) with acetonitrile (see Scheme 2). We recently established this transformation as a benchmark reaction to test for the carbon–bromine bond activation potential of XB donors, as it allows the exclusion of



Scheme 2 Benchmark reaction for the activation of a carbon–bromine bond by XB donors.

various other possible reagents (most notably traces of acid) as the actual activators.[7]

The yields of benzhydryl acetamide (**2**) that were obtained in the presence of stoichiometric amounts of various activators after 48 and 96 hours (under otherwise identical reaction conditions) are shown in Table 1. All experiments were conducted in the presence of 10 mol% of pyridine. For comparison, the corresponding non-iodinated analogues of the XB donors shown in Scheme 1 were also prepared by a similar synthetic route (see the ESI†).

Most importantly, while the non-iodinated analogue of **1,3-I^{Bn}/OTf** (*i.e.* **1,3-H^{Bn}/OTf**) induced only negligible formation of **2** (Table 1, entry 2), the latter was formed in high yield in the presence of the actual XB donor **1,3-I^{Bn}/OTf** (entry 3). As both activating reagents only differ in the iodine substituents, it is very likely that the observed activation is caused by halogen bonding. Thus, poly(iodotriazolium) compounds form a further class of XB-based "organic Ag^+ equivalents".[7a]

The influence of structural variations of these XB donors on the carbon–bromine activation potential became apparent in the benchmark reactions with **1,3-I^{Bn}/PF$_6$** and **1,3-I^{Oct}/OTf** (entry 6): although the hexafluorophosphate counterion is expected to be somewhat less coordinating than the triflate counterpart, the analogous XB donors with both counterions (**1,3-I^{Bn}/OTf** and **1,3-I^{Bn}/PF$_6$**) induced a very similar yield of **2** (entries 3 and 4). This implies that either the counterions are not blocking the electrophilic iodine centers or that the difference in Lewis basicity of the counterions triflate and hexafluorophosphate is too little to show any effect. In contrast, the *N*-octyl derivative **1,3-I^{Oct}/OTf** was a slightly less potent activator than its *N*-benzyl counterpart (entries 3 and 6). The reason for this difference remains unclear. We note that in both cases, the corresponding H-analogues **1,3-H^{Bn}/PF$_6$** and **1,3-H^{Oct}/OTf** again show negligible activation (see entry 5 and the ESI†).

In the case of the trisubstituted XB donors, there was once more a large difference between the iodinated and non-iodinated analogues: even though **1,3,5-H^{Bn}/OTf** (entry 7) did show a slight increase in the yield of **2** compared to the background reactivity (or **1,3-H^{Bn}/OTf**), this activation was far exceeded by

Table 1 Yield of **2** after 48 and 96 h in the presence of various XB donors and reference compounds as activating reagents (compare Scheme 2)[a]

#	Activating reagent	Yield of **2** [%] (48 h)	Yield of **2** [%] (96 h)
1	—	≤5	≤5
2	**1,3-H^{Bn}/OTf**	≤5	7
3	**1,3-I^{Bn}/OTf**	67	78
4	**1,3-I^{Bn}/PF$_6$**	64	82
5	**1,3-H^{Oct}/OTf**	8	11
6	**1,3-I^{Oct}/OTf**	48	62
7	**1,3,5-H^{Bn}/OTf**	8	15
8	**1,3,5-I^{Bn}/OTf**	≥ 95	≥ 95
9	**1,3,5-IBn/PF$_6$**	73	92
10	**3**	69	82
11	**4**	≥ 95	≥ 95

[a] Yields according to ^{1}H-NMR analysis. Stoichiometric amounts of the respective activating reagent were used. In all cases, 10 mol% of pyridine were present to exclude traces of acid as the actual activating reagent, compare ref. 7*a*. In the case of entry 11, one equivalent of cyclohexene was present to suppress a bromine-based activation mechanism, compare ref. 7*b*.

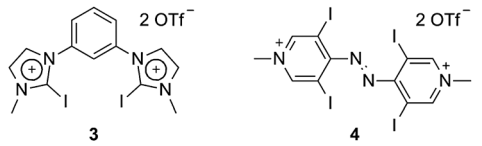


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Fig. 2 Imidazolium- and pyridinium-based multidentate XB donors.

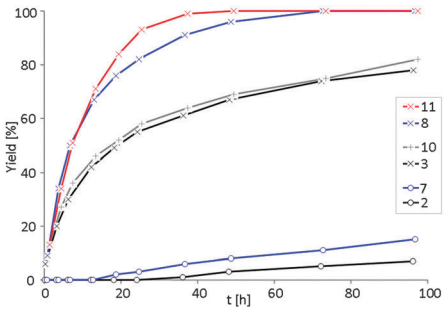

Fig. 3 Yield-*versus*-time profile of selected reactions from Table 1 (numbers for individual lines correspond to entries in Table 1). *Y*-axis: yield of **2** according to ^{1}H-NMR spectroscopy.

the iodinated equivalent **1,3,5-I^{Bn}/OTf** (entry 8), which gave a quantitative yield of **2** even after 48 hours. This also constitutes a marked increase compared to the bidentate analogue **1,3-I^{Bn}/OTf**, indicating that there might indeed be a tridentate binding to the bromine substituent in **1** and/or to the liberated bromide.[15] Strangely, the corresponding hexafluorophosphate salt **1,3,5-I^{Bn}/PF$_6$** (entry 9) was slightly less active than the triflate salt, opposite to the coordinating ability of the counterions. The same is true for the non-iodinated compound **1,3,5-H^{Bn}/PF$_6$** (compared to **1,3,5-H^{Bn}/OTf**, see the ESI†).

Finally, a comparison of **1,3-I^{Bn}/OTf** with the previously reported XB donors **3**[7a] and **4**[7b] (Fig. 2) was conducted. It became apparent that the topologically related imidazolium- and triazolium-based XB donors (*i.e.* **1,3-I^{Bn}/OTf** and **3**) possess a very similar activation potential (see entry 10). The tetra-iodinated (yet bidentate) azo compound **4** (entry 11), however, equaled the tridentate triazolium compound **1,3,5-I^{Bn}/OTf** in its carbon–bromine activation strength. This is further illustrated in the yield-*versus*-time profiles in Fig. 3.

In summary, we have synthesized 5-iodo-1,2,3-triazolium-based multidentate XB donors and tested their carbon–bromine activation potential in a benchmark reaction.[16] The presented synthetic route *via* dipolar cycloaddition reactions allows access to variously substituted derivatives, which was exemplified by the preparation of one of the first chiral XB donors as well as the synthesis of a tricationic one. While all new XB donors act as activators, we found little effect of the counterion, yet a noticeable influence of the *N*-substituent (in the *N*-octyl *versus* the *N*-benzyl variant). The bidentate XB donors equal our previously reported imidazolium-based compounds in their carbon–bromine activation potential, whereas the markedly stronger trifunctionalized compounds are analogous in activation strength to the recently introduced bidentate pyridinium-based XB donors.

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16 In order to get a first idea on the difference in potency between our novel tridentate activator **1,3,5-I^{Bn}/OTf** *versus* our bidentate activators **1,3-I^{Bn}/OTf** and **3** for more challenging substrates, we also tested their respective activation potential on a further test substrate: (1-bromoethyl)benzene (“α-methylbenzyl bromide”). Under identical reaction conditions, after four days at room temperature in CD_3CN we obtained yields of the corresponding amide of 35% (**3**), 25% (**1,3-I^{Bn}/OTf**), and 43% (**1,3,5-I^{Bn}/OTf**). Further investigations on the substrate scope are in progress.