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Preorganization: A Powerful Tool in Intermolecular Halogen Bonding in Solution

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Dedicated to Professor Jean-Marie Lehn on the occasion of his 80th birthday

Preorganization is a powerful tool in supramolecular chemistry which has been utilized successfully in intra- and intermolecular halogen bonding. In previous work, we had developed a bidentate bis(iodobenzimidazolium)-based halogen bond donor which featured a central trifluoromethyl substituent. This compound showed a markedly increased catalytic activity compared to unsubstituted bis(iodoimidazolium)-based Lewis acids, which could be explained either by electronic effects (the electron withdrawal by the fluorinated substituent) or by preorganization (the hindered rotation of the halogen bonding moieties). Herein, we systematically investigate the origin of this increased Lewis acidity via a comparison of the two types of compounds and their respective derivatives with or without the central trifluoromethyl group. Calorimetric measurements of halide complexations indicated that preorganization is the main reason for the higher halogen bonding strength. The performance of the catalysts in a series of benchmark reactions corroborates this finding.

1. Introduction

The fields of noncovalent organocatalysis and anion recognition are nowadays shaped by various noncovalent interactions, of which hydrogen bonding was the dominating one for a long time.[1] Lately, however, other interactions[2] such as anion-π,[3] chalcogen bonding,[4] pnictogen bonding[5] and halogen bonding[6] are receiving steadily increasing interest. The latter in particular is by now relatively widely used,[7] as it offers several advantages over hydrogen bonding: the possibility to tune the binding strength via a simple exchange of the Lewis acidic center, the sometimes high solubility in apolar solvents, and especially the high directionality.[8] As a result, numerous applications of halogen bonding are by now known in solid-state chemistry and crystal engineering.[9]

Halogen bonding (XB) is the interaction of a Lewis acidic halogen substituent, called halogen bond donor (XB donor), and a Lewis basic center. Halogen substituents on sufficiently electronegative backbones feature an anisotropic electron distribution with a region of positive electrostatic potential (σ-hole)[8a,10] at the elongation of the R–X bond. In addition, particularly for strong XBs, n→σ* orbital overlap will also contribute to the overall interaction energy (Figure 1). For weak XBs, on the other hand, dispersion effects will play an increasing role.[7a,11]

In the last 15 years, applications of XB have also been developed for solution-phase processes, particularly for anion binding and recognition.[8b,9b,12] Pioneering work in this field was reported by Resnati, Metrangolo et al. in 2005 in the form of the first heteroditopic receptor involving XB (**1 a**, Figure 2) which however bound in a monodentate fashion to the anions.[13] The first truly multidentate system was published by Taylor and co-workers in 2010, which was again based on polyfluorinated XB donor motifs(**1 b**, Figure 2).[14] Further halogen bond receptors were developed in the groups of Beer,[15] Ghosh[16] and Berryman,[17] who incorporated imidazolium moieties into

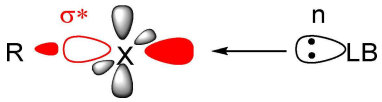
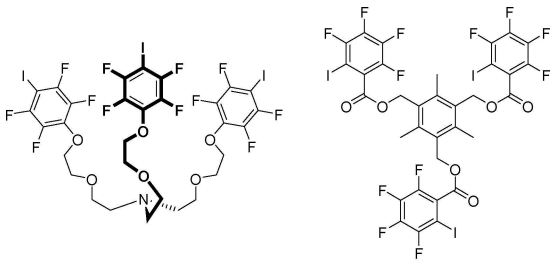


Figure 1. Halogen bonding as n→σ* interaction involving the anti-bonding orbital of the R–X bond and a lone pair of the Lewis base (LB). R = backbone, X = halogen.



1a **1b**

Figure 2. Heteroditopic XB-based tripodal receptor **1 a** as reported by the group of Resnati and Metrangolo as well as tripodal receptor **1 b** by the group of Taylor.

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macrocyclic systems as well as in bi- and tripodal preorganized[18] host molecules, yielding enhanced binding strength to halide anions.[19]

During the last decade, several other host motifs were established as anion receptors, which utilized triazolium, carbazole, catenane and rotaxane moieties, or a combination of them.[20] Particularly interlocked rotaxane systems, which bear triazolium and imidazolium moieties, were widely used in that context.[21] In parallel, different approaches were followed by the groups of Molina, Schubert and Berryman. Molina et al. showed in 2014 that open chain halogen bond donors can be preorganized via π-π-stacking (**2**, Figure 3), resulting in strong binding to $HP_2O_7^{2-}$ in acetone.[22] Schubert and co-workers demonstrated in 2015 that it is possible to rigidify XB donors via internal hydrogen bonds to triazolium substituents (**4**, Figure 3), thereby increasing the binding strength to halides by about a factor of 30.[23] Recently, the group of Berryman introduced preorganization via internal hydrogen bonding to iodine substituents (**5**, Figure 3).[24] To this end, they exploited the anisotropic charge distribution of halogen substituents and coordinated the belt of higher electron density with a hydrogen bond donating amine group, which lead to an order of magnitude stronger binding of chloride, bromide and iodide.

With respect to halogen bond based organocatalysis, fewer examples are known compared to anion recognition, although the number is steadily increasing.[6a,c,7b] First studies were published in the early 2000 s reporting quinoline reductions and halide abstraction reactions by Bolm et al. and our group.[25] Today, several examples for carbon-halide bond,[26] carbonyl,[27] imine[28] and double bond[29] activations are known, but the concept of preorganization is, in this context, far less established than it is for anion recognition. To the best of our knowledge, the first such example was published in 2015 by our group:[30] rotationally locked, cationic bisimidazolium-based halogen bond donors **3** (Figure 3) showed superior activity over "non-locked" analogues (Figure 4, $\mathbf{9}^{Im\text{-}OTf}$). More precisely, when the catalyst loading was reduced to 0.5 mol-%, similar yields were obtained as with 10 mol-% of the non-preorganized imidazolium systems.[30] This trend was also found in a Michael addition reaction[31] as well as in an intramolecular Nazarov cyclisation reaction.[32] Compared to the "unlocked" XB donor $\mathbf{9}^{Blm\text{-}BArF4}$ (Figure 4), "locked" catalyst $\mathbf{9}^{Blm\text{-}CF3\text{-}BArF4}$ (Figure 4) accelerated the conversion rate in the Michael addition reaction by up to 50 times and in the Nazarov cyclisation by up to 15 times. In these comparisons, it is assumed that the CF_3 group exerts only steric effects (preventing rotation of the heterarene sidearms) and not also electronic ones. Since trifluoromethyl is obviously a strongly electron-withdrawing group, this hypothesis needs to be verified. In addition, no data on the effect of preorganization had been obtained for other reactions than the ones previously mentioned. Thus, the aim of this study was twofold: on the one hand, we applied preorganized and non-preorganized XB donors to several further reactions. On the other hand, we systematically investigated the effect of the CF_3 group, inter alia by extending our portfolio with a CF_3-marked analogue of a freely rotating imidazolium-based catalyst (see Scheme 1). In this context, next to a comparison of catalytic

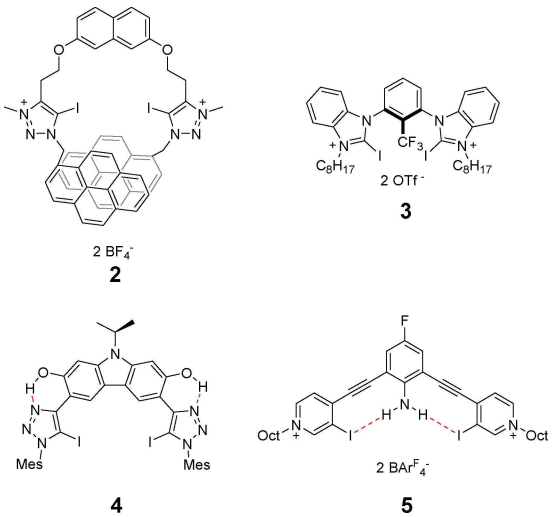


Figure 3. Schematic representation of Molina's π-π-locked triazolium receptor **2**, our rotationally locked halogen bond donor **3**, Schubert's hydrogen bonded triazolium receptor **4** and Berryman's intramolecular hydrogen-bonded halogen-bond-based pyridinium receptor **5**.

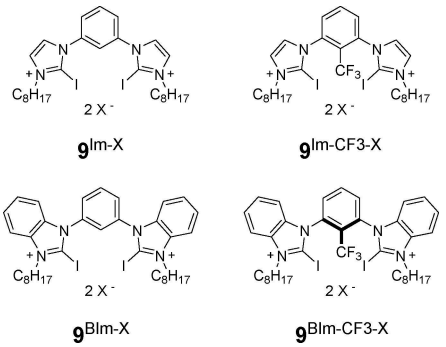
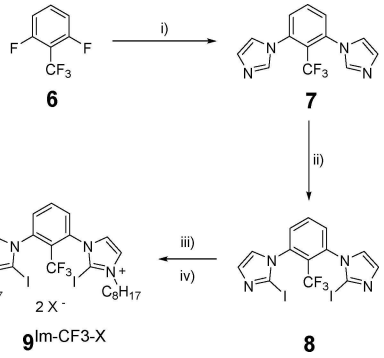


Figure 4. Overview of all halogen bond donors **9** used in this study. *Top*: 1,3-bis(iodoimidazolium)-based compounds. *Bottom*: 1,3-bis(iodobenzimidazolium)based compounds. X = OTf or BAr^F_4. The nomenclature provides information on the counter anion, the presence or absence of the CF_3 group and on whether an imidazolium (Im) or benzimidazolium moiety (Blm) was used.



Scheme 1. i) 2.5 eq. imidazole, 10 eq. K_3PO_4, DMF (0.18 M), 72 h, 135 °C, yield: 40 %; ii) 2.4 eq. lithium diisopropylamide, 2.4 eq. iodine (0.65 M THF solution), THF (0.04 M), 24 h, −78 °C→RT, yield: 25 %; iii) 4.0 eq. octyl triflate, dry DCM (0.05 M), 72 h, RT, yield: 51 %; iv) 2.4 eq $TMABAr^F_4$, dry DCM (0.1 M), 72 h, RT, yield: 77 %.

performance, we were also interested in the binding strengths of preorganized vs. non-preorganized systems to simple halide anions as reference substrates. For that purpose, ITC titration experiments were performed in different solvents.

2. Results and Discussion

2.1. Synthesis of a CF_3-Marked XB Donor

To complete the library of our bis(benz)imidazolium based halogen bond donors, the CF_3-marked analogue $\mathbf{9}^{Im\text{-}CF3\text{-}OTf}$ of 1,3-bisimidazolium $\mathbf{9}^{Im\text{-}OTf}$ was synthesized. Its synthesis route followed a sequence (Scheme 1) already published for its 1,3-bisbenzimidazolium analogue (**3**, Figure 3) and started from commercially available 1,3-difluoro-2-trifluoromethylbenzene (**6**).[30] The first step involves a nucleophilic aromatic substitution (S_NAr) which afforded the neutral 1,3-bisimidazole compound **7** in 40% yield. After deprotonation of compound **7** with lithium diisopropylamide and subsequent addition of elemental iodine, the twofold iodinated compound **8** was obtained. The evaluation of ^{1}H NMR, ^{19}F NMR, ^{13}C NMR and GC/MS data showed no signs of a rotational barrier for the imidazolium moieties around the C-N bond, which indicates that the CF_3 group has no preorganizing effect to this framework structure. A comparison of the ^{1}H NMR data of intermediate **8** to that of the non-alkylated precursor of $\mathbf{9}^{Im\text{-}X}$ (Figure 4), which lacks the CF_3 group but is otherwise identical, displayed no crucial difference in the chemical shifts of the imidazolium protons. This is a first indication that the CF_3 group induces no substantial electron withdrawal from the sidearm moieties.

Finally, compound **8** was alkylated with octyl triflate, which afforded the cationic halogen bond donor $\mathbf{9}^{Im\text{-}CF3\text{-}OTf}$. Previous publications clearly found that for the activation of neutral compounds, counter anions more weakly coordinating than triflate are necessary.[27a,32] Thus, an exchange to the corresponding BAr^F_4 salt was performed via simple metathesis with $TMABAr^F_4$, affording $\mathbf{9}^{Im\text{-}CF3\text{-}BArF4}$.[27a,28b,31,33]

2.2. ITC Titration Experiments

With XB donor $\mathbf{9}^{Im\text{-}CF3}$ now complementing the three already published variants $\mathbf{9}^{Im}$ as well as $\mathbf{9}^{BIm}$ and $\mathbf{9}^{BIm\text{-}CF3}$ (Figure 4), a comparison of their halogen bonding strength should reveal the effect of the central CF_3 group: the latter should exert a similar electronic effect in $\mathbf{9}^{Im\text{-}CF3}$ and $\mathbf{9}^{BIm\text{-}CF3}$, while it only leads to preorganization (hindered rotation) in the latter. Thus, if both $\mathbf{9}^{Im\text{-}CF3}$ and $\mathbf{9}^{BIm\text{-}CF3}$ outperform their non-CF_3-bearing analogues, there is likely a strong electronic effect of the CF_3 moiety, and if only $\mathbf{9}^{BIm\text{-}CF3}$ outperforms $\mathbf{9}^{BIm}$ (but $\mathbf{9}^{Im}$ and $\mathbf{9}^{Im\text{-}CF3}$ perform similarly), the difference is mostly due to preorganization.

To compare the binding strength of the triflate salts of all halogen bond donors **9** shown in Figure 4, isothermal calorimetric titrations (ITC) were performed with tetra-*n*-octylammonium or tetra-*n*-butylammonium halides in either acetonitrile, chloroform or methylene chloride. In THF, either precipitation of the $[\mathbf{9}^{OTf}\cdot X]$ complexes or deiodination of the bis(benz)imidazolium moieties was observed. MTBE was ruled out as solvent due to low solubility of host and guest (e.g. $\mathbf{9}^{Im\text{-}CF3\text{-}OTf}$: <0.50 mM; $(n\text{Oct})_4\text{Cl}$: <5.0 mM). The titration results are summarised below in Table 1 and Figure 5.

As tetraalkylammonium salts are commonly hygroscopic, the unknown water content of the ammonium halides used is a possible source of error. To probe for the influence of residual water on the measured binding affinities, an ITC titration was done using a guest solution prepared under inert conditions with pre-dried $(n\text{Bu})_4\text{Cl}$ (entry 2). Compared to ITC titrations utilizing non-dried halide salts, a marginal 0.9 kJ·mol^{-1} stronger binding was noted, hence all further titrations were performed at ambient conditions.

The bidentate nature of the halide binding with all XB donors $\mathbf{9}^{OTf}$ is apparent from the stoichiometries observed in the titrations: only 3 of 34 titrations are outside a range of $0.90 \leq n \leq 1.10$.

Of all the compounds titrated, XB donor $\mathbf{9}^{BIm\text{-}CF3}$ shows the highest affinity towards halides, with the overall binding free energy ($\Delta G°$) ranging from -35.4 up to -39.4 kJ·mol^{-1}. The donors $\mathbf{9}^{BIm}$ (-30.0 up to -36.4 kJ·mol^{-1}) and $\mathbf{9}^{Im}$ (-31.9 up to -35.5 kJ·mol^{-1}) do have comparable affinities, whereas $\mathbf{9}^{Im\text{-}CF3}$

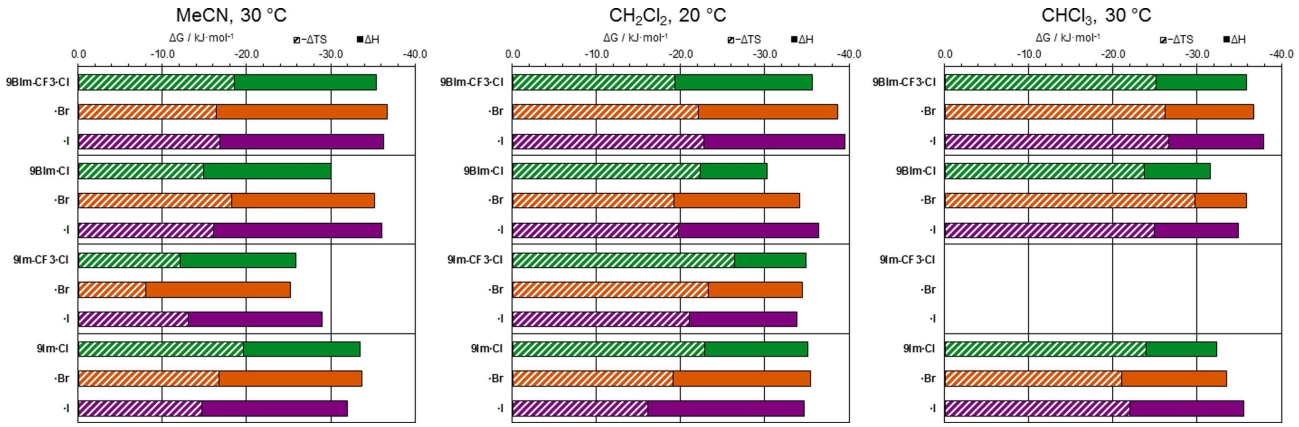


Figure 5. Bar graph representation of the binding energies (ΔG) of the **9**·X adducts.

Table 1. Binding constant K, energy terms ΔG°, ΔH° and −TΔS° as well as stoichiometries n collected from ITC experiments.

	Entry	9^{-OTf}	X^-	K [M^{-1}]	ΔG° [kJ·mol^{-1}]	ΔΔG° (X^-–Cl^-) [kJ·mol^{-1}]	ΔH° [kJ·mol^{-1}]	-TΔS° [kJ·mol^{-1}]	[%] of -TΔS° in ΔG°	n
CH_3CN, 30 °C	1	$9^{Blm-CF3}$	Cl	$1.23\cdot10^6$	−35.4	0.0	−16.8	−18.5	52%	1.08
	2*		Cl	$1.82\cdot10^6$	−36.3	−0.9	−19.7	−16.6	46%	0.88
	3		Br	$2.06\cdot10^6$	−36.6	−1.3	−20.2	−16.4	45%	0.91
	4		I	$1.74\cdot10^6$	−36.2	−0.8	−18.6	−12.9	41%	0.92
	5	9^{Blm}	Cl	$1.49\cdot10^5$	−30.0	0.0	−15.2	−14.8	49%	1.05
	6		Br	$1.11\cdot10^6$	−35.2	−5.1	−17.0	−18.1	52%	0.94
	7		I	$1.61\cdot10^6$	−36.0	−5.9	−20.0	−16.0	44%	0.94
	8	9^{Im-CF3}	Cl	$2.79\cdot10^4$	−25.8	0.0	−13.8	−12.1	47%	1.27
	9		Br	$2.18\cdot10^4$	−25.2	+0.6	−17.2	−7.9	32%	1.01
	10		I	$9.72\cdot10^4$	−29.0	−3.1	−15.9	−13.1	45%	0.80
	11	9^{Im}	Cl	$5.71\cdot10^5$	−33.4	0.0	−13.9	−19.5	58%	1.10
	12		Br	$6.25\cdot10^5$	−33.7	−0.3	−17.1	−16.6	49%	0.94
	13		I	$3.17\cdot10^5$	−31.9	+1.5	−17.3	−14.6	46%	0.96
$CHCl_3$, 30 °C	14	$9^{Blm-CF3}$	Cl	$1.41\cdot10^6$	−35.7	0.0	−10.7	−25.0	70%	1.03
	15		Br	$2.02\cdot10^6$	−36.6	−0.8	−10.4	−26.1	71%	0.99
	16		I	$3.24\cdot10^6$	−37.9	−2.1	−11.3	−26.5	70%	0.99
	17	9^{Blm}	Cl	$2.69\cdot10^5$	−31.5	0.0	−7.9	−23.6	75%	0.91
	18		Br	$1.41\cdot10^6$	−35.8	+4.3	−6.1	−29.7	83%	0.89
	19		I	$1.01\cdot10^6$	−34.8	+3.3	−9.9	−24.9	71%	0.97
	20	9^{Im-CF3}	*insoluble*							
	21	9^{Im}	Cl	$2.58\cdot10^5$	−32.3	0.0	−8.4	−23.9	74%	1.05
	22		Br	$5.53\cdot10^5$	−33.4	−1.1	−12.4	−20.9	63%	1.00
	23		I	$1.26\cdot10^6$	−35.5	−3.2	−13.5	−22.0	62%	0.99
CH_2Cl_2, 20 °C	24	$9^{Blm-CF3}$	Cl	$2.22\cdot10^6$	−35.6	0.0	−16.3	−19.3	54%	0.94
	25		Br	$7.42\cdot10^6$	−38.5	−2.9	−16.4	−22.1	57%	1.00
	26		I	$1.03\cdot10^7$	−39.4	−3.8	−16.7	−22.7	58%	1.00
	27	9^{Blm}	Cl	$2.29\cdot10^5$	−30.2	0.0	−7.9	−22.2	74%	1.05
	28		Br	$1.15\cdot10^6$	−34.1	−3.9	−14.9	−19.1	56%	0.95
	29		I	$2.91\cdot10^6$	−36.4	−6.2	−16.7	−19.6	54%	0.99
	30	9^{Im-CF3}	Cl	$1.57\cdot10^6$	−34.8	0.0	−8.4	−26.4	76%	0.92
	31		Br	$1.28\cdot10^6$	−34.3	+0.5	−11.1	−23.2	68%	1.04
	32		I	$1.02\cdot10^6$	−33.7	+1.1	−12.7	−21.0	62%	1.07
	33	9^{Im}	Cl	$1.78\cdot10^6$	−35.1	0.0	−12.2	−22.8	65%	0.98
	34		Br	$2.00\cdot10^6$	−35.4	−0.3	−16.4	−19.0	54%	1.00
	35		I	$1.47\cdot10^6$	−34.6	+0.4	−18.5	−16.1	46%	0.99

*$(nBu)_4Cl$ was dried prior to use and its guest solution prepared using Schlenk techniques.

shows a somewhat reduced binding energy (−25.2 up to −34.8 kJ·mol^{-1}).

A direct comparison of the binding energies of $9^{Blm-OTf}$ and $9^{Blm-CF3-OTf}$ confirms in almost all cases the hypothesis that preorganization leads to superior binding strength. The highest constant *K* measured was the binding of $9^{Blm-CF3-OTf}$ to iodide in methylene chloride with $1.03\cdot10^7$ M^{-1}. Under the same conditions, the affinity of $9^{Blm-OTf}$ towards iodide decreased by almost one order of magnitude ($2.91\cdot10^6$ M^{-1}). A higher electron deficiency induced by trifluoromethylation cannot explain the superior binding strength found: $9^{Im-CF3-OTf}$ shows lower binding free energies to halides than 9^{Im-OTf} in all tested solvents. Therefore, the electronic contribution of electron-withdrawing CF_3 substituents to the overall halogen bonding

strength is negligible. In fact, a decrease of the binding free energies is observed. Interestingly, the solubility of the bisimidazolium compound $\mathbf{9}^{Im\text{-}OTf}$ is reduced when a CF_3 groups is present in the structure, which could affect the halide binding capabilities of $\mathbf{9}^{Im\text{-}CF3\text{-}OTf}$. However, no precipitation was observed in the ITC experiments mentioned above.

In view of prior results,[34] a preference for harder anions and therefore an increased affinity in the order $I^- < Br^- < Cl^-$ could be expected, yet a minor trend in the opposite direction was observed. While for all XB donors with the exception of $\mathbf{9}^{Im\text{-}CF3\text{-}OTf}$, the binding free energies $\Delta G°$ increase when going from chloride to bromide, this trend continues with iodide only for benzimidazolium donors (see $\Delta\Delta G°(X^-–Cl^-)$). However, as $\Delta\Delta G°$ values can only be considered significant when exceeding 3 kJ·mol^{-1},[35] no clear binding trend towards any halides can be derived from these data.

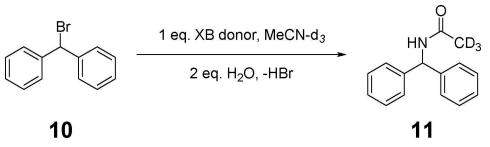
As already found in earlier titrations,[34] the entropic term $-T\Delta S°$ heavily contributes to the overall binding energy, exceeding 50% for most of the energy terms ($\Delta G°$) found (exceptions: entries 1–4, 7–10, 12, 13, and 35). The average distribution of the entropic term over all measurements in a given solvent increase from acetonitrile (47%) over methylene chloride (60%) to chloroform (71%), correlating to the relative polarities of the solvents in their inverse order.[36] With a few exceptions, however, the overall binding strength does not appear to be affected by the choice of solvent: XB donor $\mathbf{9}^{Im\text{-}CF3}$ shows halide affinities increased by $\Delta\Delta G°_{CH2Cl2\text{-}MeCN} = +9.0$ (Cl^-), +9.2 (Br^-) and +4.8 (I^-) kJ·mol^{-1}, respectively. The binding towards iodides is also notably stronger for $\mathbf{9}^{Bim\text{-}CF3}$ ($\Delta\Delta G°_{CH2Cl2\text{-}MeCN}$: +7.9; $\Delta\Delta G°_{CHCl3\text{-}MeCN}$: +6.3 kJ·mol^{-1}) and for $\mathbf{9}^{Im}$ ($\Delta\Delta G°_{CH2Cl2\text{-}MeCN}$: +2.7; $\Delta\Delta G°_{CHCl3\text{-}MeCN}$: +3.6 kJ·mol^{-1}). All other $\Delta\Delta G°$ values do not exceed ±2.0 kJ·mol^{-1}, which by and large points to an enthalpy-entropy compensation effect.

2.3. Halogen Bond Organocatalysis – Preface

Overall, the titration studies confirmed that *syn*-locked $\mathbf{9}^{Bim\text{-}CF3\text{-}OTf}$, compared to non-locked $\mathbf{9}^{Bim\text{-}OTf}$, shows a stronger binding to halide anions. Furthermore, they refuted the possibility that a mere electronic effect of the CF_3-group is responsible for that observation (via the comparison of the binding constants of $\mathbf{9}^{Im\text{-}CF3\text{-}OTf}$ and $\mathbf{9}^{Im\text{-}OTf}$, Table 1). To see whether the same trends are seen for the catalytic activity of XB donors **9** (Figure 4), we then moved our focus to catalysis studies using several benchmark reactions described below.

2.3.1. Halide Abstraction Reactions in Halogen Bond Catalysis

First, we focused on the activation of benzhydryl bromide (**10**, Scheme 2) with stoichiometric amounts of XB donors $\mathbf{9}^{OTf}$ (Figure 4), since this reaction a) has virtually no background reactivity, b) can be easily followed via ^{1}H NMR spectroscopy, c) is unaffected by the presence of Brønsted acids and d) was already activated by several halogen bond donors with success.[25d] In these examples, reaction times of 2–4 days in presence of $\mathbf{9}^{Im\text{-}OTf}$ and a triazolium catalyst were necessary to yield full conversion to compound **11**.[25b,c]



10 **11**

Scheme 2. Solvolysis reaction of benzhydryl bromide (**10**) in deuterated acetonitrile in the presence of selected halogen bond donors. For satisfactory and reproducible results, it is necessary to have exactly 2 eq. water present. The reaction time is 9.5 h.

First, we reproduced our results with catalyst $\mathbf{9}^{Im\text{-}OTf}$: as reported,[25b] after 96 h reaction time a conversion >90% was obtained. Next, preorganized bisbenzimidazolium catalyst $\mathbf{9}^{Bim\text{-}CF3\text{-}OTf}$ was applied in the reaction, which resulted in nearly full conversion to product **11** within 9.5 h reaction time (Table 2, Entry 5 and Figure 6). After the same period, only 56% of **11** were obtained in presence of $\mathbf{9}^{Im\text{-}OTf}$ (Table 2, Entry 3). With the unsubstituted bisbenzimidazolium catalyst $\mathbf{9}^{Bim\text{-}OTf}$, 72% conversion to **11** was observed, while with CF_3-marked bisimidazolium compound $\mathbf{9}^{Im\text{-}CF3\text{-}OTf}$, a conversion of 56% was determined, similar to the one with $\mathbf{9}^{Im\text{-}OTf}$ (Table 2, Entries 4/2).

This data represents further evidence that the CF_3 group has only a steric effect on the activating properties of the XB

Table 2. ^{1}H NMR conversion of benzhydryl bromide (**10**) to amide **11** activated by XB donors **9** and the determined relative rate accelerations.

Entry	XB donor[a]	Conversion to **11** [%][b,c]	k_{rel}[d]
1	/	<5	1
2	$\mathbf{9}^{Im\text{-}CF3\text{-}OTf}$	56	150
3	$\mathbf{9}^{Im\text{-}OTf}$	56	225
4	$\mathbf{9}^{Bim\text{-}OTf}$	72	540
5	$\mathbf{9}^{Bim\text{-}CF3\text{-}OTf}$	90	1000

[a] 1 eq. of the respective XB donor was used. [b] The reaction time was 9.5 h. [c] Determined via integration of selected signals of the starting material vs. the product in the ^{1}H NMR spectrum. [d] Referenced values to the background reactivity after approximately 0.6 h reaction time.

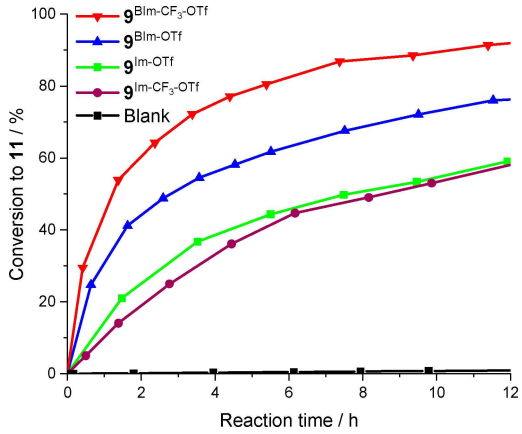
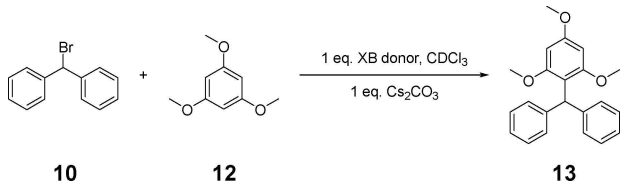


Figure 6. Conversion vs. time profile for the activation of benzhydryl bromide (**10**) in presence of different halogen bond activators (monitored via ^{1}H NMR spectroscopy).

donors, as $9^{Im\text{-}CF3\text{-}OTf}$ should otherwise be superior to $9^{Im\text{-}OTf}$. Finally, relative rate constants k_{rel} were determined for all catalysts (Table 2), which revealed an acceleration of 1000 with $9^{BIm\text{-}CF3\text{-}OTf}$ compared to the background reaction and an acceleration by more than 6 times compared to the weakest activator $9^{Im\text{-}CF3\text{-}OTf}$. Encouraged by these first promising results, we next studied the benzhydrylation of trimethoxy benzene (**12**) with benzhydryl bromide (**10**), shown in Scheme 3.

Although this reaction is analogous to the solvolysis of benzhydryl bromide (**10**) in acetonitrile, it was chosen for several reasons: a) due to its similarity, it should follow comparable trends for the activity of our XB donors, which could be considered as a confirmation of the previous results, b) because a different solvent is used, it is possible to probe for any influence of solvents onto the overall activity of our catalysts and c) as monocationic, pyridinium-based halogen



Scheme 3. Reaction between benzhydryl bromide (**10**) and trimethoxy benzene (**12**) in dry, deuterated chloroform.

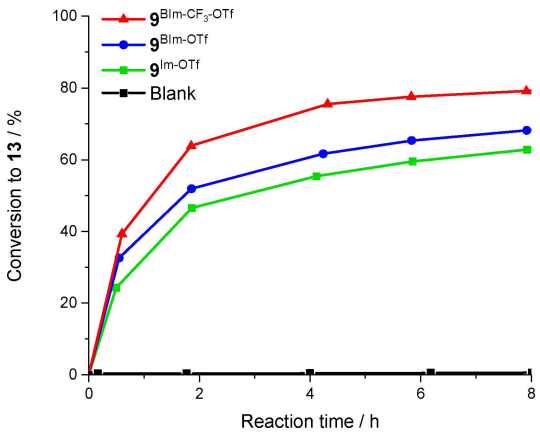
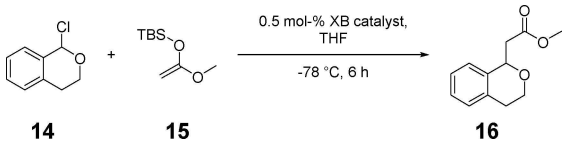


Figure 7. Conversion vs. time profile for the acylation of trimethoxy benzene (**12**) with benzhydryl bromide (**10**) in presence of different halogen bond activators (followed by ^{1}H NMR spectroscopy). Activator $9^{Im\text{-}CF3\text{-}OTf}$ could not be tested in the reaction due to solubility issues.

Table 3. ^{1}H NMR conversions and relative rate constants for the benzhydrylation of trimethoxy benzene (**12**) with benzhydryl bromide (**10**) in presence of selected halogen bond activators.

Entry	XB donor[a]	Conversion to **13** [%][b,c]	k_{rel}[d]
1	/	< 5	1
2	$9^{Im\text{-}OTf}$	62	210
3	$9^{BIm\text{-}OTf}$	68	250
4	$9^{BIm\text{-}CF3\text{-}OTf}$	79	290

[a] 1 eq. of the respective catalyst was used. [b] The reaction time was 8 h. [c] Determined via integration of selected signals of the starting material vs. the product in the ^{1}H NMR spectrum. [d] Referenced values to the background reactivity after approximately 0.6 h reaction time.



Scheme 4. Reaction of 1-chloroisochroman (**14**) with ketene silyl acetal **15** in presence of different halogen bond donors. No background reaction at −78 °C in THF is observed.

bond donors were already successfully employed in this reaction – resulting in up to 90% conversion within 12 h reaction time – (benz)imidazolium-based structures should be activating as well.[26a] In line with our earlier study,[26a] Cs_2CO_3 was added to the reaction to rule out hidden Brønsted acid catalysis.

Since twofold, cationic bis(benz)imidazolium catalysts should be stronger activators than pyridinium based structures, we set our observation time to a period of 8 h. In Figure 7, a conversion vs. time profile is shown. Again, $9^{BIm\text{-}CF3\text{-}OTf}$ is the strongest activator, followed by its freely rotatable analogue $9^{BIm\text{-}OTf}$ and the imidazolium compound $9^{Im\text{-}OTf}$ (see also Table 3).

Catalyst $9^{Im\text{-}CF3\text{-}OTf}$ could not be tested in the reaction due to solubility issues. With all catalysts, conversions towards compound **13** were determined to be between 62–79% (Table 3). With catalyst $9^{BIm\text{-}CF3\text{-}OTf}$, a relative rate acceleration of 290 was determined compared to background reactivity, whereas with the weakest activator $9^{Im\text{-}OTf}$, a 210-fold acceleration was observed (Table 3). Compared to previous results of the solvolysis of benzhydryl bromide (**10**), only relatively subtle differences in the relative accelerations were found, with the best XB donor $9^{BIm\text{-}CF3\text{-}OTf}$ being only 1.4 times more active than the weakest one ($9^{Im\text{-}OTf}$). The order of activity of the XB donors was not affected by the solvent, however.

Both reactions discussed so far have the disadvantage that stoichiometric amounts of the respective catalysts are necessary in order to obtain adequate yields. Therefore, we next focused on catalytic applications of these Lewis acids. As first test reaction for this purpose, the activation of 1-chloroisochroman (**14**, Scheme 4) was chosen, as several features qualify it as an ideal benchmark reaction: a) it had already been activated by halogen bonding, b) there is no background reactivity at −78 °C, c) several reference compounds (e.g. elemental iodine, HOTf, cationic hydrogen bond donors)[25e,30] are inactive in this reaction and d) very low catalyst loadings are necessary.[25e,30] With merely 0.5 mol-% of $9^{BIm\text{-}CF3\text{-}OTf}$, a strong activation had already been observed, and thus we focused in the following on this reaction set-up.[30]

After a period of 6 h, 55% of **16** was isolated with $9^{BIm\text{-}CF3\text{-}OTf}$ as catalyst, while the yield markedly decreased to 25% when the non-preorganised catalyst $9^{BIm\text{-}OTf}$ was employed (Table 4, Entries 5 and 4). This again demonstrates the superiority of the preorganized halogen bond donor. Besides that, with imidazolium catalysts $9^{Im\text{-}OTf}$ and $9^{Im\text{-}CF3\text{-}OTf}$ only 17% yield of compound **16** were isolated (Table 4, Entries 2 and 3). The comparable performance of these two catalysts shows again that the CF_3

group does not have a pronounced electron withdrawing influence on the catalysts.

2.3.2. Neutral Compound Activation in Halogen Bond Catalysis

Up to this point, only examples for halide abstraction reactions were discussed, because it is known from many publications in the field of anion recognition,[12b,c,34,37] that XB donors strongly interact with halide anions.

However, many applications in organocatalysis target the activation of neutral compounds, and thus we further investigated the catalytic activity of XB donors **9** (Figure 4) in reactions involving carbonyl or nitro compounds. Previous studies in halogen-[32] and chalcogen bond[33b] organocatalysis highlighted the relevance of non-coordinating counter anions to achieve satisfying yields and the necessity to work with dry solvents to suppress a competitive interaction with water. To this end, the BAr^F_4 counter anion (Figure 8) was used multiple times with great success in our group, but also applications of the BF_4, PF_6 or NTf_2 anion are known.[7b]

As first test reaction, we focused on the Diels Alder reaction of cyclopentadiene (**17**) and methyl vinyl ketone (**18**, Scheme 5).[26b,27a] Moreover, Diels Alder reactions are powerful tools in organic synthesis, as large ring systems with several stereogenic centers can be formed in a single step.[38] To achieve high conversions under mild conditions, Lewis acids are commonly added. In 2014, this reaction was already successfully preformed in presence of 20 mol-% of XB donor $\mathbf{9}^{Im\text{-}BArF4}$ as catalyst.[27a] First orientating experiments were repeated with a catalyst load of 20 mol-%, but after the first measurement point (approximately after 20 min), each catalyst ($\mathbf{9}^{BArF4}$, Figure 4) had yielded full conversion to product **19**. Possible explanations for the lower activity of catalyst $\mathbf{9}^{Im\text{-}BArF4}$ in previous publications could be an inhibition of the catalyst by water, or the presence of $\mathbf{9}^{Im\text{-}OTf}$ residues as artifact of an incomplete anion exchange, which equally inhibits the iodine centers. A reduction of the catalyst loading to 2.5 mol-% did not show any improvement: after 20 min reaction time, nearly full conversion for each catalyst again was observed. Finally, the catalyst load was reduced to 0.5 mol-%, which finally lowered the catalysts activity enough so that only in presence of the strongest catalyst $\mathbf{9}^{BIm\text{-}CF3\text{-}BArF4}$, nearly full conversion to compound **19** was observed within one hour (Table 5, Entry 5 and Figure 9). With the simple imidazolium catalysts $\mathbf{9}^{Im\text{-}BArF4}$ and $\mathbf{9}^{Im\text{-}CF3\text{-}BArF4}$, approximately 22–25% conversion to compound **19** was found, whereas with bisbenzimidazolium variant $\mathbf{9}^{BIm\text{-}BArF4}$, a conversion of 92% was observed in the same period (Table 5, Entries 2, 3 and 4).

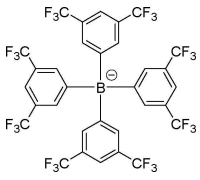
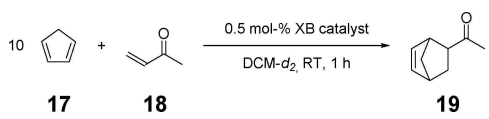


Figure 8. Structure of the $BAr^F_4{}^-$ counter anion.



Scheme 5. Diels-Alder reaxtion of cyclopentadiene (**17**) and methyl vinyl ketone (**18**) in presence of selected halogen bond donors. Cyclopentadiene was freshly prepared by cracking of dicyclopentadiene at 250 °C.

Table 4. Yield of compound **16** in the reaction between 1-chloroisochroman (**14**) and ketene silyl acetal **15** in presence of different halogen bond donors.

Entry	XB donor[a]	Yield of **16** [%][b,c]
1	/	< 5
2	$\mathbf{9}^{Im\text{-}CF3\text{-}OTf}$	17
3	$\mathbf{9}^{Im\text{-}OTf}$	17
4	$\mathbf{9}^{BIm\text{-}OTf}$	25
5	$\mathbf{9}^{BIm\text{-}CF3\text{-}OTf}$	55

[a] 0.5 mol-% of the respective catalyst was used. [b] The reaction time was 6 h. [c] Isolated yields.

Table 5. Overview of the ^{1}H NMR conversion and the relative rate constants for the Diels Alder reaction of cyclopentadiene (**17**) with methyl vinyl ketone (**18**) in presence of selected halogen bond activators.

Entry	XB donor[a]	Conversion to **19** [%][b,c,d]	k_{rel}[e]
1	/	10	1
2	$\mathbf{9}^{Im\text{-}CF3\text{-}BArF4}$	22 (4)	2
3	$\mathbf{9}^{Im\text{-}BArF4}$	25 (4)	2
4	$\mathbf{9}^{BIm\text{-}BArF4}$	92 (11)	6
5	$\mathbf{9}^{BIm\text{-}CF3\text{-}BArF4}$	94 (21)	10

[a] 0.5 mol-% halogen bond catalysts were used. [b] The reaction time was 1 h. [c] Determined via integration of selected signals of the starting material vs. the product in the ^{1}H NMR spectrum. [d] Conversion of the reaction after 5 min for entries 4 and 5 and conversion of the reaction after 20 min for entries 2 and 3. [e] Referenced values to the background reactivity after approximately 20–30 min reaction time.

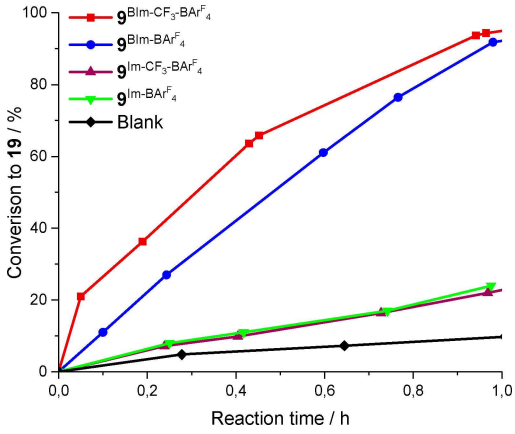


Figure 9. Conversion vs. time profile for the Diels-Alder reaction of cyclopentadiene (**17**) and methyl vinyl ketone (**18**) in presence of different halogen bond activators. The conversion was determined by integration of selected signals of the ^{1}H NMR spectrum after defined periods.

As the relative rate constants (Table 5) show, the use of $9^{Blm\text{-}CF3\text{-}BArF4}$ allowed a 10 times faster reaction compared to background reactivity, while with imidazolium catalysts $9^{Im\text{-}BArF4}$ and $9^{Im\text{-}CF3\text{-}BArF4}$, only a reaction acceleration by a factor of two was observed (Table 5). Again, the preorganized catalyst $9^{Blm\text{-}CF3\text{-}BArF4}$ was the strongest activator and the CF_3-marked imidazolium catalyst $9^{Im\text{-}CF3\text{-}BArF4}$ was equally active as its non-subststituted analogue $9^{Im\text{-}BArF4}$, which corroborates the findings of the halide abstraction benchmark reactions discussed above.

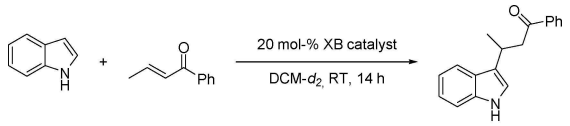
Overall, though, there are some drawbacks to this reaction (comparably strong background reactivity, sensitivity to water and acids, high toxicity of reactants), and hence we focused on a more robust carbonyl activation reaction. In 2017, Breugst et al.[27c] and our group[31] independently published the activation α,β-unsaturated ketones in a Michael addition reaction by halogen bonding (Scheme 6). Earlier case studies of Breugst et al. showed that molecular iodine can accelerate the reaction through halogen bonding and that a participation and activation by Brønsted acids can be ruled out.[39]

Most of our catalysts **9** (except for $9^{Im\text{-}CF3\text{-}BArF4}$) were already tested in this reaction, and a conversion of only 70% was previously found when $9^{Blm\text{-}CF3\text{-}BArF4}$ was used as catalyst.[31] This result was not reproduced this time but instead, almost full conversion to compound **22** was observed (Figure 10). Again, the most plausible explanation is a too high water content in the earlier experiments, which resulted in partial toxification of catalysts **9**. This phenomenon was confirmed for catalyst $9^{Im\text{-}BArF4}$, which showed initially no activity, but after removal of water (via addition of molecular sieves), the reaction was catalyzed smoothly. Reference experiments with molecular sieves as only additives showed no conversion to product **22**, which excludes the possibility of it being a catalyst.

Somewhat surprisingly, the CF_3-marked imidazolium compound $9^{Im\text{-}CF3\text{-}BArF4}$ was more active than its non-substituted analogue $9^{Im\text{-}BArF4}$ and virtually as active as bisbenzimidazolium catalyst $9^{Blm\text{-}BArF4}$ (Figure 10). The reason for this unexpectedly strong performance are currently unclear. As Table 6 shows, the final conversions achieved with $9^{Im\text{-}CF3\text{-}BArF4}$ and $9^{Blm\text{-}BArF4}$ are almost identical (55% vs. 54%, Entries 2 and 4). With catalyst $9^{Blm\text{-}CF3\text{-}BArF4}$, 90% conversion to compound **22** was obtained, whereas in presence of $9^{Im\text{-}BArF4}$ only 35% conversion was achieved, which is comparable to previous results. Relative rate accelerations displayed a 1200-fold higher activation for $9^{Blm\text{-}CF3\text{-}BArF4}$ with respect to the background reactivity and a 3.5–8 fold faster reaction in comparison to the remaining catalysts. The imidazolium catalyst accelerated the reaction by about 300 times and with the non-preorganized benzimidazolium catalyst $9^{Blm\text{-}BArF4}$ a 240 times faster reaction was observed.

Finally, we were interested in the activation of nitro groups in a Michael type addition reaction (Scheme 7) which was recently published by our group in the context of chalcogen bonding organocatalysis.[33b] To the best of our knowledge, this constituted the first example of a nitro group activation by halogen bonding, albeit elemental iodine is reported to accelerate this type of reaction by an unknown mode of action.[39–40] Conveniently, nearly no background reactivity is observed in the conversion of indole **23** to product **25**, while in presence of Brønsted acids, several Lewis acids or selected thiourea-based hydrogen bond donors, also only minor amounts of **25** are formed.

The strongest halogen bond donor $9^{Blm\text{-}CF3\text{-}BArF4}$ converted only 39% of indole **23** to compound **25** (Table 7, Entry 5 and Figure 11). In comparison, a triazolium-based organotellurium



20 **21** **22**

Scheme 6. Schematic reaction of indole (**20**) with trans-β-crotonophenone (**21**) in presence of different halogen bond donors.

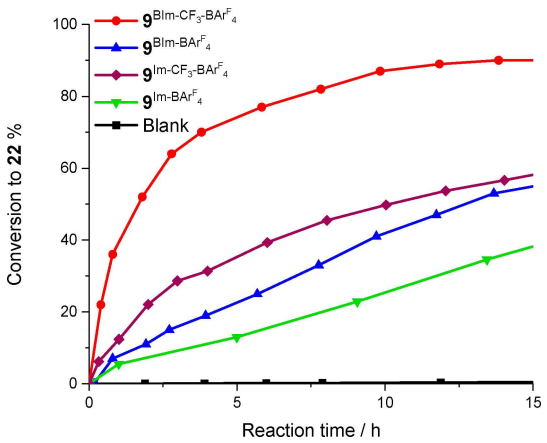


Figure 10. Conversion vs. time profile for the Michael addition reaction of indole (**20**) and trans-β-crotonophenone (**21**) in presence of different halogen bond activators. The conversion was determined by integration of selected signals of the ^{1}H NMR spectrum after defined periods.

Table 6. Overview of the ^{1}H NMR conversion and the relative rate constants for the Michael addition reaction of indole (**20**) with *trans*-β-crotonophenone (**21**) in presence of selected halogen bond activators.

Entry	XB donor[a]	Yield of **22** [%][b,c]	k_{rel}[d]
1	/	<5	1
2	$9^{Im\text{-}CF3\text{-}BArF4}$	55	325
3	$9^{Im\text{-}BArF4}$	35	150
4	$9^{Blm\text{-}BArF4}$	54	240
5	$9^{Blm\text{-}CF3\text{-}BArF4}$	90	1200

[a] 20 mol-% halogen bond catalysts were used. [b] The reaction time was 14 h. [c] Determined via integration of selected signals of the starting material vs. the product in the ^{1}H NMR spectrum. [d] Values referenced to the background reactivity after approximately 1 h reaction time.

23 **24** **25**

Scheme 7. Reaction of 5-methoxyindole (**23**) with *trans*-β-nitrostyrene (**24**) in presence of different halogen bond donors.

Table 7. Overview of the ^{1}H NMR conversion and the relative rate constants for the nitro Michael addition reaction of 5-methoxyindole (**23**) with trans-β-nitrostyrene (**24**) in presence of selected halogen bond activators.

Entry	XB donor[a]	Yields to **25** [%][b,c]	k_{rel}[d]
1	/	< 5	1
2	**9**$^{Im\text{-}CF3\text{-}BArF}$	7	20
3	**9**$^{Im\text{-}BArF}$	4	12
4	**9**$^{BIm\text{-}BArF}$	16	55
5	**9**$^{BIm\text{-}CF3\text{-}BArF}$	39	100

[a] 20 mol-% halogen bond catalysts were used. [b] The reaction time was 48 h. [c] Determined via integration of selected signals of the TES standard vs. the product in the ^{1}H NMR spectrum. [d] Referenced values to the background reactivity after approximately 6 h reaction time.

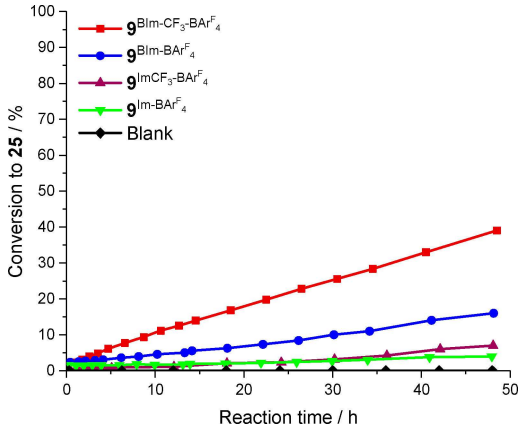


Figure 11. Conversion vs. time profile for the nitro Michael addition reaction of 5-methoxyindole (**23**) and *trans*-β-nitrostyrene (**24**) in presence of different halogen bond activators. The conversion was determined by integration of selected signals of the ^{1}H NMR spectrum after defined periods.

catalyst (10 mol-%) resulted in 81% conversion to compound **25** after the same period.[33b] One possible explanation for this observation is a better fit of the tellurium moieties to the nitro group than is possible for iodine, which is in accordance with findings that an iodinated triazolium catalyst was almost inactive. Next, the remaining halogen bond catalysts were tested in the reaction. With catalyst **9**$^{BIm\text{-}BArF4}$ only 16% conversion to compound **25** was noted and with **9**$^{Im\text{-}BArF4}$ and **9**$^{Im\text{-}CF3\text{-}BArF4}$ nearly no reaction was observed (4–7%, Table 7, Entries 2/3). These observations are fully in line with the trends established earlier.

Both catalysts only led to a 12–20 times faster reaction with respect to the background reaction. For catalyst **9**$^{BIm\text{-}BArF4}$ a 55-fold rate acceleration was observed and for the strongest catalyst **9**$^{BIm\text{-}CF3\text{-}BArF4}$, this figure reached two orders of magnitude (Table 7, Entry 5).

Regardless of the low catalytic activity of all tested XB catalysts in this reaction, both the superiority of the preorganized system and the lack of any electron withdrawing effect of the CF_3 moiety towards the XB-donating moieties was demonstrated again.

3. Conclusions

In this study, four structurally very related halogen bond donors were investigated via ITC titrations and in catalysis benchmark reactions. In all cases, it could be clearly demonstrated that a preorganized bis(benzimidazolium)-based XB donor features the strongest Lewis acidity and catalytic activity. Its performance was clearly superior to the one of its unsubstituted analogues lacking a central CF_3 group (which is pivotal for preorganization via hindered rotation). As the corresponding imidazolium-based pair of CF_3-substituted and -unsubstitued XB donors were similar active in nearly every reaction, any electronic effect of this group can be ruled out. The comparable performance of these two catalysts also indicates that the CF_3 group does not exert any negative steric influence on substrate binding. Future work will deal with the application of our strongest catalyst in further catalytic reactions and with the continued optimization of other preorganized halogen bonding motifs.

Experimental Section

ITC experiments: Extra dry acetonitrile was purchased from *Acros Organics* (< 10 ppm H_2O). Chloroform was dried over 3 Å molecular sieves and filtered over activated, basic aluminium oxide 90 (63–200 μm) to remove adventitious traces of hydrogen chloride. Methylene chloride was distilled, stored over 3 Å molecular sieves and finally dried on an alox column using a *MBRAUN MB SPS-800* solvent purification system. Synthesized compounds used in measurements were dried under high vacuum prior to use, weighed out and then dissolved in the respective amount of solvent to prepare either 0.5 mM or 1.0 mM solutions, which were titrated against 5.0 mM or 10.0 mM solutions of tetralkylammonium halides, respectively. Commercially available tetraalkylammonium halides were used without further purification.

ITC measurements were performed on a MicroCal VP-ITC system from GE Healthcare using a reference power of 34.7 μcal/s, a filter period of 2 s, a stirrer speed of 329 rpm, an injection volume of 8.0 μL for guest solutions (ammonium salt) and a time spacing of 160 s between injections. All titrations were performed at a jacket temperature of either 30 °C (303.25 K) when using acetonitrile or chloroform as solvent or 20 °C (293.25 K) when using methylene chloride as solvent. Evaluation of the data sets was performed using Origin 7 with manual integral correction and, if necessary, a subtraction of straight lines.

Part A: General information for catalysis experiments: For all reactions freshly prepared stock solutions of the respective compounds were used. All solvents were previously dried with 4 Å molecular sieves. Unless specified differently, deuterated solvents were used. ^{1}H NMR spectra were recorded on a *Bruker AVIII 300* at 298.5 K. Evaluation of the ^{1}H NMR data was performed with *MestReNova* 9.0.1-13254. The exact acquisition time was extracted from the *MestReNova*-fid. file.

Part B: Catalysis Experiments

Activation of benzhydryl bromide (10): The reaction was performed in acetonitrile. In each case, 200 μl of the respective stock solution of the halogen bond activator (9.99 mmol, 0.05 M, 1 eq.), benzhydryl bromide (**10**) (2.47 mg, 9.99 μmol, 0.05 M, 1 eq.)

and wet acetonitrile (0.36 mg, 19,99 μmol, 0.1 M, 2 eq.) were added to an NMR tube, sealed and vigorously shaken for one minute. Finally, periodic ^{1}H NMR spectra were recorded with a total duration of 10 h. The conversion was determined by the ratio of starting material **10** and the product **11**. Hereto, the relative integral of a significant singlet of benzhydryl bromide (6.45 ppm) was set to 1. The conversion is equal to 100%, divided through the sum of starting material **10** and product **11** (significant doublet at 6.30 ppm) and multiplied with the integral of the product signal.

Activation of benzhydryl bromide (10) in a Friedel-Crafts alkylation reaction with 1,3,5-trimethoxy benzene (12): The reaction was performed in chloroform. For the reaction, Cs_2CO_3 (3.26 mg, 9.99 μmol, 1 eq.) and in each case 200 μl of the respective stock solution of the halogen bond activator (9.99 μmol, 0.05 M, 1 eq.), benzhydryl bromide (**10**; 2.47 mg, 9.99 μmol, 0.05 M, 1 eq.) and 1,3,5-trimethoxy benzene (**12**; 1.68 mg, 9.99 μmol, 0.05 M, 2 eq.) were added to an NMR tube, sealed, shaken and sonicated for 2 minutes. Finally, periodic ^{1}H NMR spectra were recorded with a total duration of 8 h. The conversion was determined by the ratio of starting material **12** and the product **13**. Hereto the relative integral of methoxy groups of 1,3,5-trimethoxy benzene (**12**) (s, 3.77 ppm) was set as 1. The conversion is equal 100%, divided through the sum of starting material **12** and product **13** (signals for the two methoxy groups at 3.80 ppm (s) and 3.58 ppm (s)) and multiplied with the integral of the product signals.

Catalytic activation of 1-chloroisochroman (14): The reaction was performed in non-deuterated THF. To an oven dried Schlenk finger, equipped with a stirring bar and rubber septum under argon atmosphere were added the respective halogen bond catalyst (0.5 μmol, 0.005 eq.) and 900 μl dry THF. The mixture was cooled to −78 °C and subsequently, 100 μl of a freshly prepared 1 M stock solution of 1-chloroisochroman (**14**) in THF were added. The mixture was stirred for 20 min and ketene silyl acetal **15** (28.26 mg, 150 μmol, 32.9 μl, 1.5 eq.) was added and the mixture was stirred at −78 °C for 6 h. Next, the reaction mixture was quenched through addition of 200 μl of a 0.5 M methanolate solution in methanol (100 μmol, 1 eq.), filtered through a plug of silica with diethyl ether and was finally purified via column chromatography (pentane:diethyl ether 9:1). Product compound **16** was obtained as colourless oily compound. The purity of the isolated compound was proven by TLC and ^{1}H NMR measurements.

Catalytic Diels-Alder reaction of cyclopentadiene (17) and methyl vinyl ketone (18): The reaction was performed in methylene chloride. Cyclopentadiene (**17**) was freshly prepared from dicyclopentadiene through thermal cracking at 250 °C. In each case, 200 μl of the respective stock solution of the halogen bond catalyst (0.03 μmol, 0.015 M, 0.005 eq.), cyclopentadiene (**17**; 10.24 mg, 155 μmol, 0.78 M, 10 eq.) and methyl vinyl ketone (**18**; 1.09 mg, 15.5 mmol, 0.078 M, 1 eq.) were added to an NMR tube, sealed and shaken for 1 min. Finally, periodic ^{1}H NMR spectra were recorded with a total duration of 1 h. The conversion was determined by the ratio of starting material **18** and the product **19**. Hereto the relative integral of methyl group of methyl vinyl ketone (**18**; s, 2.25 ppm) was set as 1. The conversion is equal 100%, divided through the sum of starting material **18** and product **19** (signal of the methyl group of the *endo*- and *exo*- product at 2.09 ppm (s) and at 2.18 ppm (s) with a ratio of approximately 10:1) and multiplied by the sum of integrals of the product signals.

Catalytic Michael addition reaction of indole (20) and *trans*-β-crotonophenone (21): The reaction was performed in methylene chloride. In each case, 200 μl of the respective stock solution of the halogen bond catalyst (12 μmol, 0.06 M, 0.2 eq.), indole (**20**; 7.03 mg, 60 μmol, 0.3 M, 1 eq.) and *trans*-β-crotonophenone (**21**; 8.77 mg, 60 μmol, 0.3 M, 1 eq.) were added to an NMR tube, sealed and shaken for 1 min. Finally, periodic ^{1}H NMR spectra were recorded with a total duration of 14 h. The conversion was determined by the ratio of starting material **21** and the product **22**. Hereto the relative integral of the methyl group of *trans*-β-crotonophenone (**21**, dd, 1.99 ppm) was set to 1. The conversion is equal 100%, divided through the sum of starting material **21** and product **22** (signal of the methyl group at 1.46 ppm (d) and multiplied by the integral of the product signal. Alternatively, the signal of the CH bond (s, 3.78 ppm) in the product **22** was compared with the hydrogen in β-position (m, 6.55 ppm) of the indole (**20**).

Catalytic nitro-Michael addition reaction of 5-methoxyindole (23) and trans-β-nitrostyrene (24): The reaction was performed in methylene chloride. In each case, 200 μl of the respective stock solution of the halogen bond catalyst (3.74 μmol, 0.04 M, 0.2 eq., 88.0 μl), 5-methoxyindole (**23**; 8.25 mg, 56.1 μmol, 0.28 M, 3 eq.) and *trans*-β-nitrostyrene (**24**; 2.79 mg, 18.7 μmol, 0.09 M, 1 eq.) were added to an NMR tube, sealed and shaken for 1 minute. Finally, periodic ^{1}H NMR spectra were recorded with a total duration of 48 h. The conversion was determined by the ratio of the product **25** against a tetraethyl silyl (TES) standard. Hereto the relative integral of C_2 group of TES (0.38 eq., q, 0.55 ppm) was set as 1. Integration of the newly formed CH_2- and C*H*-bond (m, 5.04 ppm) of product **25** and multiplication with 100% directly gave the conversion.

Conflict of Interest

The authors declare no conflict of interest.

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