JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

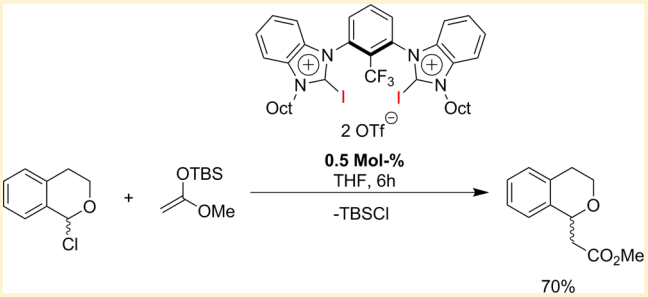
Cationic Multidentate Halogen-Bond Donors in Halide Abstraction Organocatalysis: Catalyst Optimization by Preorganization

Stefan H. Jungbauer and Stefan M. Huber*

Fakultät für Chemie und Biochemie, Organische Chemie I, Ruhr-Universität Bochum, Universitätsstrasse 150, 44801 Bochum, Germany

Supporting Information

ABSTRACT: In contrast to hydrogen bonding, which is firmly established in organocatalysis, there are still very few applications of halogen bonding in this field. Herein, we present the first catalytic application of cationic halogen-bond donors in a halide abstraction reaction. First, halopyridinium-, haloimidazolium-, and halo-1,2,3-triazolium-based catalysts were systematically tested. In contrast to the pyridinium compounds, both the imidazolium and the triazolium salts showed promising potency. For the haloimidazolium-based organocatalysts, we could show that the catalytic activity is based on halogen bonding using, e.g., the chlorinated derivatives as reference compounds. On the basis of these studies, halobenzimidazolium organocatalysts were then investigated. Monodentate compounds featured the same trends as the corresponding imidazolium analogues but showed a stronger catalytic activity. In order to prepare bidentate versions which are preorganized for anion binding, a new class of rigid bis(halobenzimidazolium) compounds was synthesized and structurally characterized. The corresponding syn isomer showed unprecedented catalytic potency and could be used in as low as 0.5 mol % in the benchmark reaction of 1-chloroisochroman with a silyl enol ether. Calculations confirmed that the syn isomer may bind in a bidentate fashion to chloride. The respective anti isomer is less active and binds halides in a monodentate fashion. Kinetic investigations confirmed that the syn isomer led to a 20-fold rate acceleration compared to a neutral tridentate halogen-bond donor. The strength of the preorganized halogen-bond donor seems to approach the limit under the reaction conditions, as decomposition is observed in the presence of chloride in the same solvent at higher temperatures. Calorimetric titrations of the syn isomer with bromide confirmed the strong halogen-bond donor strength of the former ($K \approx 4 \times 10^6$ M^{-1}, $\Delta G \approx 38$ kJ/mol).



INTRODUCTION

Organocatalysis mediated by hydrogen bonding has attracted much interest over the past two decades.[1] A closely related noncovalent interaction which is based on polarizable halogen substituents is halogen bonding.[2] Although the latter shares several similarities with hydrogen bonding, a major difference is the high directionality of halogen-bond adduct formation: halogen substituents may only act as Lewis acids in the elongation of their covalent bond, forming an interaction angle of approximately 180°.[2c,e,4] The formation of strong halogen bonds with Lewis bases requires the halogen-bearing moiety to feature an electronegative backbone. This can be achieved by either polyfluorinated[2b−f] or cationic[5] core structures.

Since the mid-1990s, halogen bonding has gained renewed and strongly increased attention, mostly with regard to gas-phase studies,[6] computational modeling,[7] and applications in crystal engineering.[8] More recently, a growing number of solution-phase studies[9] have appeared, dealing, for example, with anion recognition,[10] anion transport,[11] and fundamental investigations.[12]

Examples of halogen bonding in organocatalysis are still quite rare, however.[13] One such approach is the activation of neutral compounds like carbonyl groups and imines by halogen-bond donors (halogen-based Lewis acids). Thus far, two types of reactions have been catalyzed in this fashion: Bolm et al. reported the Hantzsch ester-based reduction of quinoline derivatives using perfluorinated iodoalkanes as catalysts.[13a] Tan et al. subsequently showed that this reaction may also be catalyzed by bis(iodoimidazolinium) compounds.[13d] In addition, two reports on Diels−Alder-type reactions have appeared. Takeda, Minkata, et al. activated a hetero Diels−Alder reaction by iodo(benz)imidazolium catalysts,[13f] while our group described the catalysis of a classical Diels−Alder reaction by bis(iodoimidazolium) compounds.[13c] A conceptually slightly different approach is the use of halogen-bond donors in reactions in which a carbon−halogen bond is cleaved by coordination of the Lewis acid to the halogen substituent of the substrate or to the released halide. In one such example, polyfluorinated and -iodinated terphenyls and quaterphenyls were used for the catalytic activation of a carbon−chlorine bond.[13b] In a related case, Takemoto et al. employed *N*-

Received: July 27, 2015
Published: September 2, 2015

DOI: 10.1021/jacs.5b07863
J. Am. Chem. Soc. 2015, 137, 12110−12120

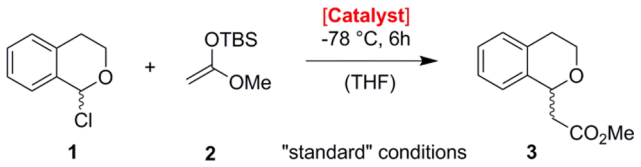
iodosuccinimide for the cleavage of a carbon−halogen bond.[13e] Yet, to date, no halide abstraction reaction catalyzed by cationic halogen-bond donors has been published.[14]

In our previous studies, we showed that cationic halogen-bond donors based on imidazolium,[15a] pyridinium,[15b] and triazolium[15c] backbones can act as *stoichiometric* activators for the cleavage of a carbon−bromine bond. Furthermore, a competitive study comparing the activating effect of a neutral polyfluorinated and iodinated azobenzene derivative with that of a geometrically very similar cationic analogue revealed that the cationic halogen-bond donor was much superior to its neutral counterpart in the corresponding test reaction.[16]

Consequently, we were interested to see whether cationic halogen-based Lewis acids may also be used in halide abstraction reactions. The analysis of catalysis studies using weak interactions like halogen bonding is complicated by the fact that other effects may also contribute to the observed activity. Often it is not trivial to identify and/or quantify the influence of halogen bonding, especially in the presence of other Lewis acidic groups on the catalyst backbone. Most of the previous studies have shown that the interpretation of reaction data was nontrivial and that parameters like the backbone structure, the counterions, or the solvent might lead to trends which are hard to rationalize.

Thus, a simple test reaction was necessary in order to isolate, as best as possible, the effect of halogen bonding on any observed catalytic activity. The previously reported[17] reaction of 1-chloroisochroman with a ketene silyl acetal (Scheme 1) was chosen as benchmark as it had already proven to be suitable in a proof-of-principle reaction with neutral halogen-bond donors.[13b]

Scheme 1. Benchmark Reaction[a]



[a]TBS = *tert*-butyldimethylsilyl.

Also, much more data on the effects of various parameters on catalytic activity was needed in order to rationally design powerful halogen-based organocatalysts given the difficulties described above. Therefore, a second aim of this study was to compare halogen-bond donors based on various heterocyclic cationic backbones featuring differently coordinating counterions in their catalytic performance.

Finally, we will herein describe how these results led to a new kind of cationic, conformationally locked halogen-bond organocatalyst. Due to its preorganized syn conformation, this halogen-bond donor is much more active in halide binding catalysis than the corresponding first generation of Lewis acids.

RESULTS AND DISCUSSION

In the first part, we will focus on the use of those halogen-bond donors in the catalysis benchmark reaction (Scheme 1) that we could already successfully use as stoichiometric activators.[15] The catalyst candidates will be based on iodopyridinium, iodoimidazolium, and iodo-1,2,3-triazolium backbones, in that order. In the second part, we will extend these studies toward benzimidazolium core structures, which have proven to be more active than our previous catalyst systems.

Initial Experiments. Before the actual catalysis studies, several initial test experiments needed to be performed in order to rule out effects by impurities or possible decomposition products. For all following experiments, the benchmark reaction of Scheme 1 was run at −78 °C to maximize noncovalent interactions and to suppress side reactions. Tetrahydrofuran (THF) was chosen as solvent due to solubility reasons, and in each case the reaction was quenched after 6 h by the addition of sodium methanolate (NaOMe). Under these conditions, in the absence of any additive, no background reaction was observed (Table 1, entry 1).

Table 1. Initial Experiments[a]

no.	catalyst	mol %	yield of **3** [%][b]
1			≤5
2	I_2	10	≤5[c]
3	$NaBAr^F_4$	10	6[c]
4	$TMA-BAr^F_4$	10	*c*
5	$TMA-B[C_6F_5]_4$	10	≤5[c]
6	$NaBPh_4$	10	17[c]
7	4a/OTf	10	≤5[c]
8	4b/OTf	10	14[c,d]

[a]Yields are the average of at least two experiments. [b]On the basis of NMR unless otherwise noted. [c]In the presence of 4 Å molecular sieve (MS) (see ref 18). [d]Isolated yield.

Hidden acid catalysis had already been ruled out for this reaction in our previously reported study.[13b] Another conceivable catalytically active decomposition product of the halogen-bond donors is elemental iodine. However, the use of 10 mol % of I_2 led only to negligible product formation of compound **3** (Table 1, entry 2).

The halogen-bond donors were typically prepared as triflate salts (trifluoromethylsulfonate, OTf^-). In order to investigate the influence of the counterion, triflate was subsequently exchanged with borate-based noncoordinating counterions by treatment with the corresponding sodium or tetramethylammonium (TMA) salt of the borate. Thus, to avoid false-positive results by traces of these exchange reagents, any catalytic effect of these salts needed to be excluded. For that purpose, 10 mol % of the corresponding metal and/or TMA salt was used in the reaction. Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate ("$NaBAr^F_4$") yielded 6% of product **3** (Table 1, entry 3), while the TMA salts of $BAr^F_4{}^-$ and tetrakis-(pentafluorophenyl)borate did not form any product at all (Table 1, entries 4 and 5). In contrast, sodium tetraphenylborate resulted in a yield of 17% (Table 1, entry 6).

Pyridinium-Based Catalysts. In our first test reaction for halide abstraction—the solvolysis of benzhydryl bromide with *stoichiometric* amounts of activator—pyridinium-based halogen-bond donor **4b** (Figure 1) had proven to be superior[15b] to imidazolium-[15a] or triazolium-based[15c] variants. Consequently, this class of catalyst candidates was tested first. To verify that the mode of activation is solely based on halogen bonding, noniodinated compound **4a/OTf** was used as reference, resulting in negligible product formation (Table 1, entry 7). With this promising result in hand, we employed halogen-bond donor **4b/OTf** in the reaction. Yet, only 14% of product was isolated (Table 1, entry 8).

DOI: 10.1021/jacs.5b07863
J. Am. Chem. Soc. 2015, 137, 12110−12120

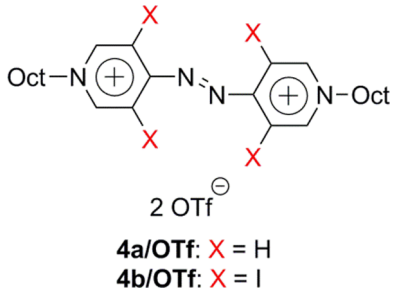


Figure 1. Pyridinium-based catalysts.

While the difference between the iodinated and the noniodinated compound was a clear indication for halogen-bonding catalysis, the overall level of activation was relatively disappointing. It is likely that the azopyridinium backbone, which has to distort to bind to bromide in a bidentate fashion,[15b] is ill suited for the monodentate binding of the smaller chloride anion.

Imidazolium-Based Catalysts. As a consequence of the poor performance of the pyridinium compounds, we turned our focus toward imidazolium-based halogen-bond donors. First, monodentate Lewis acids were tested, starting with 10 mol % of **I-Im^{Me,Oct}/OTf** (Figure 2), which led to a yield of 25% of **3** (Table 2, entry 3). Increasing the catalyst load to 20 mol % led to 67% of **3** (Table 2, entry 4).

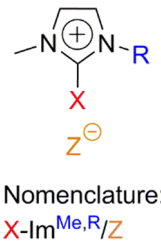


Figure 2. Monodentate 2-haloimidazolium halogen-bond donors.

Table 2. Yield of 3 in the Presence of Monodentate 2-Haloimidazolium Halogen-Bond Donors[a]

no.	catalyst	mol %	yield of **3** [%][b]
1	Cl-Im^{Me,Me}/OTf	20	≤5[c,d]
2	Br-Im^{Me,Oct}/OTf	20	≤5[c]
3	I-Im^{Me,Oct}/OTf	10	25
4	I-Im^{Me,Oct}/OTf	20	67
5	Cl-Im^{Me,Me}/BAr$^{F}_{4}$	20	≤5[c]
6	Br-Im^{Me,Me}/BAr$^{F}_{4}$	20	≤5[c,d]
7	I-Im^{Me,Oct}/BAr$^{F}_{4}$	20	34

[a]Yields are the average of at least two experiments. [b]Isolated yield unless otherwise noted. [c]On the basis of NMR. [d]In the presence of 4 Å MS (see ref 18).

To check if the catalytic activity is based on halogen bonding, 20 mol % of the corresponding chlorinated and brominated analogues **Cl-Im^{Me,Me}/OTf** and **Br-Im^{Me,Oct}/OTf** were also used (Table 2, entries 1 and 2). Negligible product formation was observed in both cases, which indicates that the catalysis depends on the presence of the iodine substituent. As it is well established that the halogen-bonding strength of compounds R–X increases in the order X = Cl < Br < I,[2] the observed difference between the halogenated variants is also a strong indication that halogen bonding is at the heart of the observed reactivity.

The influence of the counterion was studied by exchange of triflate with the noncoordinating BAr$^{F}_{4}$$^{-}$ anion, realized by metathesis with TMA–BAr$^{F}_{4}$. As for the triflate salts, 20 mol % of the corresponding chlorinated and brominated compounds **Cl-Im^{Me,Me}/BAr$^{F}_{4}$** and **Br-Im^{Me,Me}/BAr$^{F}_{4}$** resulted in only negligible yields of **3** (Table 2, entries 5 and 6). The iodinated version (**I-Im^{Me,Oct}/BAr$^{F}_{4}$**) induced 34% product formation under comparable conditions, which is again in line with the more polarizable iodine substituent forming stronger halogen bonds. However, the BAr$^{F}_{4}$ salt is markedly less active than the corresponding triflate analogue (Table 2, entry 4 vs 7). This is somewhat unexpected and in stark contrast to the behavior of these compounds in a Diels–Alder model reaction, which was catalyzed by the BAr$^{F}_{4}$ salt but not the triflate one.[13c] At the moment, we lack a plausible explanation for this difference. It clearly indicates, however, that counterion effects in halogen-bonding catalysis are complicated and that increasing the catalytic activity is not always simply an issue of using the less coordinating counterion.

In our previous studies, we had repeatedly shown that bis(haloimidazolium) compounds featuring a suitable iodine–iodine distance are markedly more active than comparable monoimidazolium derivatives, likely due to a bidentate complexation of Lewis bases.[12g,13c,15a] Thus, with the promising results of iodoimidazolium salts in hand, we studied the catalytic capabilities of meta- and para-substituted bis-imidazolium compounds (Figure 3). Focusing first on meta-

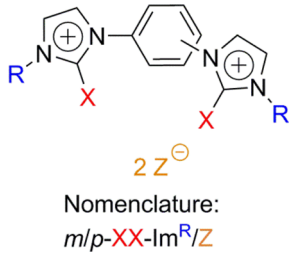


Figure 3. Bis(imidazolium) compounds.

substituted derivatives, we found that neither the non-halogenated triflate salt ***m*-HH-Im^{Oct}/OTf** nor the chlorinated analogue ***m*-ClCl-Im^{Oct}/OTf** (both in 10 mol %) led to any product formation (Table 3, entries 1 and 2). These compounds again serve as reference to demonstrate that substituents at positions C2 of the imidazolium rings are crucial for product formation. Accordingly, under the same conditions, the brominated and iodinated halogen-bond donors ***m*-BrBr-Im^{Oct}/OTf** and ***m*-II-Im^{Oct}/OTf** formed 29% and 67% of product, respectively (Table 3, entries 3 and 4). Once again, this trend is as expected from the polarizability of the halogen substituent and hence the halogen-bonding strength.

Changing the bite angle of the potential bidentate Lewis bases by moving the iodine substituent a bit further apart in the para-substituted compound ***p*-II-Im^{Oct}/OTf** resulted in a decrease of product formation (52%, Table 3, entry 7). This dependency of the catalytic activity on the relative orientation of the iodine centers seems to indicate that at a least a partial bidentate coordination of chloride is involved in the activation process.

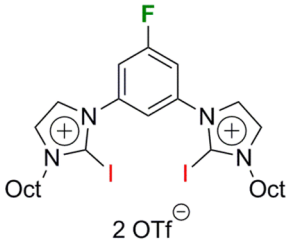
DOI: 10.1021/jacs.5b07863
J. Am. Chem. Soc. 2015, 137, 12110–12120

Table 3. Yield of 3 in the Presence of Various Halogen-Bond Donors and Reference Compounds[a]

no.	catalyst	mol %	yield of 3 [%][b]
1	*m*-HH-Im^{Oct}/OTf	10	≤5[c]
2	*m*-ClCl-Im^{Oct}/OTf	10	≤5[c,d]
3	*m*-BrBr-Im^{Oct}/OTf	10	29
4	*m*-II-Im^{Oct}/OTf	10	67
5	*m*-II-Im^{Oct}/OTf	20	90
6	8/OTf	10	62
7	*p*-II-Im^{Oct}/OTf	10	52
8	*p*-II-Im^{Oct}/OTf	20	83
9	*m*-HH-Im^{Oct}/BAr$^{F}_4$	10	35
10	*m*-ClCl-Im^{Oct}/BAr$^{F}_4$	10	≤5[c]
11	*m*-II-Im^{Oct}/BAr$^{F}_4$	10	56
12	*m*-II-Im^{Oct}/BAr$^{F}_4$	20	78
13	*p*-II-Im^{Oct}/BAr$^{F}_4$	10	36
14	*m*-II-Im^{Oct}/BPh$_4$	10	55
15	*m*-II-Im^{Oct}/[B(C$_6$F$_5$)$_4$]	10	61
16	9a/OTf	10	10[c,d]
17	9b/OTf	10	61

[a]Yields are the average of at least two experiments. [b]Isolated yield unless otherwise noted. [c]On the basis of NMR. [d]In the presence of 4 Å MS (see ref 18).

The benchmark reaction is usually quenched with sodium methanolate before workup to ensure the exact reaction time at low temperature. As this strongly basic reagent will likely decompose our catalysts, it is difficult to assess whether they are stable under the reaction conditions. To facilitate this, a derivative of the most active catalyst ***m*-II-Im^{Oct}/OTf** was synthesized, in which an additional fluorine substituent was introduced on the central benzene ring (**8/OTf**, Figure 4). Fluorine serves as a sensible marker, as any decomposition of the catalyst would induce additional resonances in ^{19}F NMR spectroscopy.



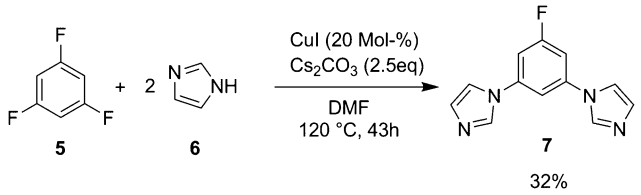
8/OTf

Figure 4. Fluorine-tagged bis(imidazolium) halogen-bond donor **8/OTf**.

The crucial step in this synthesis comprised the 2-fold coupling of imidazole **6** with 1,3,5-trifluorobenzene **5** in the presence of copper iodide and Cs_2CO_3 to yield 32% of product **7** (Scheme 2).[19] The remaining iodination and alkylation steps were performed analogously to our previously reported procedure.[15a]

To study the stability of catalyst **8/OTf** under reaction conditions, the latter was used in comparable amounts to our previous experiments (10 mol %). Instead of quenching the reaction, the solvent was removed in vacuo, the residue was redisolved in CD_3CN, and a ^{19}F NMR spectrum was recorded. Only the resonance peak of the pure catalyst was obtained,

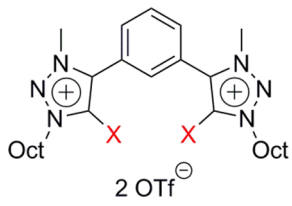
Scheme 2. *N*-Arylation of 1,3,5-Trifluorobenzene



demonstrating the stability of this compound during the benchmark reaction.

We then turned our focus toward the analogous BAr$^{F}_4$ salts of the bis-imidazolium compounds. The intended reference compounds ***m*-HH-Im^{Oct}/BAr$^{F}_4$** and ***m*-ClCl-Im^{Oct}/BAr$^{F}_4$** gave either 35% or a negligible amount of product **3** (Table 3, entries 9 and 10). The observed activity of nonhalogenated ***m*-HH-Im^{Oct}/BAr$^{F}_4$** after anion exchange from triflate to BAr$^{F}_4$ may be rationalized by the hydrogen-bond-donating ability of the imidazolium moieties. The strong influence of the anions (Table 3, entry 1 vs 9) is presumably due to better accessible hydrogen substituents with the less coordinating counterion. In contrast to the chlorinated compound, the iodinated BAr$^{F}_4$ salts ***m*-II-Im^{Oct}/BAr$^{F}_4$** and ***p*-II-Im^{Oct}/BAr$^{F}_4$** did induce product formation of 56% and 36%, respectively (Table 3, entry 11 and 13). Thus, just like for the triflate salts, the para-substituted compound was markedly less active. Overall, the BAr$^{F}_4$ salts were not as active as their triflate analogues, which resembles the situation with the monodentate imidazolium compounds. To test whether this is a peculiar effect of the BAr$^{F}_4$ counterion, triflate was also exchanged with tetraphenylborate (***m*-II-Im^{Oct}/BPh$_4$**) and its perfluorinated version (***m*-II-Im^{Oct}/[B(C$_6$F$_5$)$_4$]**). Both resulting salts gave similar yields as the BAr$^{F}_4$ compound, however (Table 3, entries 14 and 15), indicating that the catalytic performance is mostly independent of the exact nature of this class of anions.

Triazolium-Based Catalysts. Previously, 1,2,3-triazolium-based halogen-bond donors had shown almost identical Lewis acidic behavior as related imidazolium derivatives.[15a,c,16] For the present reaction, we focused on the meta-substituted compounds, since they are geometrically very similar to the more active *meta*-bis(imidazolium) catalysts. In the present benchmark reaction, halogen-bond donor **9b/OTf** (Figure 5)



9a/OTf: X = H
9b/OTf: X = I

Figure 5. 1,2,3-Triazolium-based halogen-bond donor and reference compound.

indeed resulted in a very comparable yield of product **3** (61%; Table 3, entry 17) compared with the analogous bis-imidazolium compound ***m*-II-Im^{Oct}/OTf** (67%). The non-iodinated derivative **9a/OTf** showed some slight activation (10%; Table 3, entry 16) but was again much less active than the halogenated version. Since it seemed that, overall, the triazolium catalysts once again behaved almost identical as the

DOI: 10.1021/jacs.5b07863
J. Am. Chem. Soc. 2015, 137, 12110−12120

imidazolium ones, we decided not to further investigate this class of halogen-bond donors in the present study.

Summary and Discussion of the Catalysis Studies with Known Halogen-Bond Donors. While pyridinium-based halogen-bond donors showed little activity in the benchmark reaction of 1-chloroisochroman with a silyl enol ether, imidazolium- and triazolium-based donors resulted in promising catalytic activity. For mono- and bis-imidazolium derivatives, a series of systematic experiments was performed, which revealed some general trends. In both cases, the potency of the catalyst candidates R−X (X = Cl, Br, I) followed the trend expected from halogen-bonding theory, with iodine being the most favorable substituent and bromine being somewhat less suitable. No product formation was observed for any chlorinated compound. This observation allows us to rule out with high certainty that the catalytic activity is due to anion−π interactions between the imidazolium moieties and the anion or due to hydrogen bonding between the acidic backbone protons of the heterocycles and chloride. Both effects would be at least as strong, likely stronger, for the chlorinated analogues. The only decisive difference between the differently halogenated compounds is the fact that chlorine is much less polarizable and so the chlorinated products are much weaker halogen-bond donors. The nonhalogenated derivatives were less suitable reference compounds to demonstrate the crucial importance of halogen bonding, as at least in one case (***m*-HH-Im^{Oct}/BAr$^{F}_4$**) a similar activity was observed, very likely due to hydrogen bonding.

Triflate and BAr$^{F}_4$ salts were compared in their catalytic activity for several systems, namely, monoimidazolium compounds as well as meta- and para-substituted bis-imidazolium halogen-bond donors. In all cases, the triflate salts showed higher potency despite them being the more strongly coordinating anions. This result is somewhat puzzling and cannot be satisfactorily explained at the moment. One possible explanation is that, in the current solvent system, ion pairs are formed for both types of counterions (triflate and tetraphenyl borate derivatives) and that the latter are shielding the iodine substituent to a stronger extent due to their steric bulk. In any case, the strong difference in activity (67% vs 34% product formation for **I-Im^{Me,Oct}/OTf** vs **I-Im^{Me,Oct}/BAr$^{F}_4$**) clearly demands further in-depth investigations.

Irrespective of the counterion, the meta-substituted bis-(iodoimidazolium) catalysts were consistently more active than the para-substituted versions. This dependency on the bite angle of the catalyst seems to indicate a bidentate coordination of the latter to chloride. Such a 2-fold binding mode of the bis(haloimidazolium) derivatives is also corroborated by the fact that the bis(bromoimidazolium) catalyst ***m*-BrBr-Im^{Oct}/OTf** is markedly more active than its corresponding monodentate version. For the iodinated compounds, however, a similar comparison does not seem to support multidentate binding: 20 mol % of monodentate halogen-bond donor **I-Im^{Me,Oct}/OTf** yielded nearly the same amount of product as 10 mol % of the potentially bidentate catalyst ***m*-II-Im^{Oct}/OTf**. Since the amount of iodine substituents in solution is the same for both experiments, at first glance this seems to indicate that ***m*-II-Im^{Oct}/OTf** is binding chloride in a monodentate fashion.

Such a coordination is also seen in a cocrystal structure of ***m*-II-Im^{Me}/OTf** with tris(dimethylamino)cyclopropenium chloride (Figure 6).[20] Each iodine center binds to a different chloride anion, with bond lengths (2.855 and 2.902 Å) that are shorter than the sum of the van der Waals radii[21] and show high linearity (C−I1−Cl1 = 176°, C1′−I2−Cl2 = 178°). In addition to halogen bonding, hydrogen bonds are also found in the crystal structure. The backbone protons closest to the core (bound to C3/C3′ in Figure 6) coordinate to the same chloride atom, which is located above the central benzene moiety. The protons on C2/C2′ (Figure 6) also each form a hydrogen bond with the counterion (see SI for details).

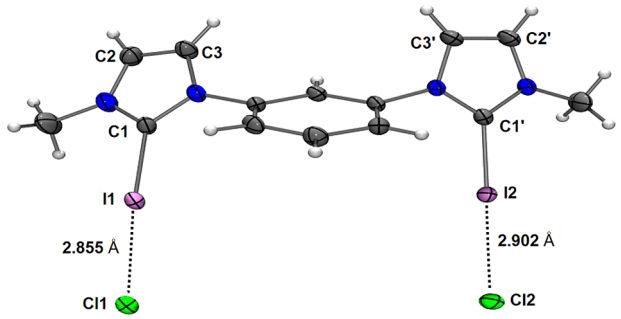


Figure 6. X-ray structural analysis of halogen-bond donor ***m*-II-Im^{Me}/OTf** and tris(dimethylamino)cyclopropenium chloride (ellipsoids set at 50% probability). Single crystals were obtained from acetonitrile. Selected distances [Angstroms] and angles [degrees]: I1−Cl1 2.855, I_2−Cl2 2.902, C1−I1 2.115, C1′−I2 2.090, C1−I1−Cl1 175.74, C1′−I2−Cl2 177.62.

Still, the situation in the solid state is likely somewhat different to the binding pattern in solution, as several other parameters, including the solvent, come into play. Also, the yield of product **3** after a set amount of time is only an approximate measure of the catalyst strength of the halogen-bond donors, and other minor effects might also exert some influence. This is indicated by the yield of the para-substituted analogue ***p*-II-Im^{Oct}/OTf**, which induces less product formation than the monodentate variant **I-Im^{Me,Oct}/OTf** in twice the amount. Overall, the binding pattern in solution is hard to deduce. It is conceivable that several alternative modes exist in equilibrium, which are shifted by subtle influences. In a previous calorimetric binding study in a different solvent (acetonitrile), we found that the meta-substituted compounds bind to chloride in a 1:1 (bidentate) fashion, while the para-substituted ones prefer a 2:1 coordination.[12g]

Benzimidazolium-Based Catalysts: Monodentate Variants. As the above X-ray structural analysis has shown, the acidic backbone protons of the imidazolium groups may also act as Lewis acids and may thus complicate the analysis of halogen-bonding organocatalysis. For all previously mentioned halogen-bond donors, we can rule out with high certainty that this has any major influence, as the corresponding chlorinated compounds (e.g., ***m*-ClCl-Im^{Oct}/OTf**) did not show any activity, even though they also feature these acidic protons. Still, there could be a cancellation of opposing trends, and so to further demonstrate the crucial role of halogen bonds, we decided to also employ halobenzimidazolium catalysts in the test reaction (Figure 7).[13d,f] These compounds do not possess comparably acidic hydrogen substituents, and so if the latter were involved in the activation, the catalytic potential should be somewhat reduced.

Once again, the chlorinated version (**Cl-BIm^{Me,Oct}/OTf**) was used as reference, and 10 mol % of this catalyst candidate did not induce any product formation in the test reaction (Table 4, entry 1).

In contrast to the monodentate bromoimidazolium compound, the corresponding brominated *benzimidazolium* catalyst

DOI: 10.1021/jacs.5b07863
J. Am. Chem. Soc. 2015, 137, 12110−12120

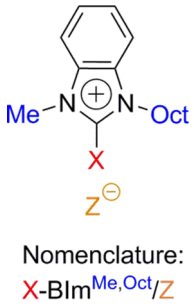


Figure 7. Monodentate 2-halobenzimidazolium halogen-bond donors.

Table 4. Yield of 3 in the Presence of 2-Halobenzimidazolium Halogen-Bond Donors[a]

no.	catalyst	mol %	yield of 3 [%][b]
1	Cl-BIm^{Me,Oct}/OTf	10	≤5[c,d]
2	Br-BIm^{Me,Oct}/OTf	10	9[c]
3	Br-BIm^{Me,Oct}/OTf	20	20
4	I-BIm^{Me,Oct}/OTf	10	49
5	I-BIm^{Me,Oct}/OTf	20	71
6	Cl-Im^{Me,Oct}/BAr$^{F}_{4}$	20	≤5[c]
7	Br-Im^{Me,Oct}/BAr$^{F}_{4}$	20	14
8	I-BIm^{Me,Oct}/BAr$^{F}_{4}$	10	25
9	I-BIm^{Me,Oct}/BAr$^{F}_{4}$	20	57
10	I-BIm^{Me,Oct}/[B(C$_6$F$_5$)$_4$]	20	44

[a]Yields are the average of at least two experiments. [b]Isolated yield unless otherwise noted. [c]On the basis of NMR. [d]In the presence of 4 Å MS (see ref 18).

Br-BIm^{Me,Oct}/OTf did show some activity, inducing a product yield of 20% when used in 20 mol % (Table 4, entry 3). As expected, the iodinated catalyst was even more active. The use of 10 mol % of **I-BIm^{Me,Oct}/OTf** led to 49% product formation, while 71% was obtained with a catalyst loading of 20 mol % (Table 4, entries 4 and 5). In comparison to the imidazolium compound **I-Im^{Me,Oct}/OTf**, which gave yields of 25% and 67% under comparable conditions, the benzimidazolium variant is clearly superior (see Table 2, entries 4 and 5).

Exchanging the counterion from triflate to BAr$^{F}_{4}$ confirmed the above trends, even though the yield was always less for the BAr$^{F}_{4}$ salts compared to their triflate counterparts. The latter is in agreement with the previous findings described in earlier sections. More specifically, 20 mol % of **Cl-Im^{Me,Oct}/BAr$^{F}_{4}$** did not induce any product formation (Table 4, entry 6), while 20 mol % of **Br-Im^{Me,Oct}/BAr$^{F}_{4}$** gave 14% and 20 mol % of **I-BIm^{Me,Oct}/BAr$^{F}_{4}$** gave 57% of product **3** (Table 4, entries 7 and 9). The analogous salt with a perfluorinated tetraphenylborate anion was even less active (Table 4, entry 10). Still, the general trend that benzimidazolium catalysts are more active than imidazolium ones also holds true in a comparison of the respective BAr$^{F}_{4}$ salts. For example, **I-Im^{Me,Oct}/BAr$^{F}_{4}$** gave only a yield of 34% (Table 2, entry 7) compared to the 57% mentioned above for **I-BIm^{Me,Oct}/BAr$^{F}_{4}$** under the same reaction conditions.

Benzimidazolium-Based Catalysts: Bidentate Variants. Having established that halobenzimidazolium moieties form stronger catalysts, we focused our attention on the synthesis of bis(halobenzimidazolium) derivatives, which could potentially act as bidentate Lewis acids. Initial findings suggested that in these compounds, a rotation of the benzimidazolium groups around the C–N axis which connects these groups to the benzene core is still possible. However, from a supramolecular perspective, the host should be as preorganized[22] as possible to ensure strong binding to the guest. Certainly, losing two rotational degrees of freedom upon anion binding will be detrimental to the free energy of adduct formation between a bis-benzimidazolium halogen-bond donor and chloride. In this context of preorganized Lewis acids, highly rigid *neutral* multidentate halogen-bond donors had proven to be very powerful in the recognition of anions[23a] and neutral Lewis bases[23b] as well as in catalysis.[13b] In contrast, there was no literature precedence for rigid *cationic* multidentate halogen-bond donors. Consequently, our aim was to rigidify the aspired bis(halobenzimidazolium) catalysts in a way that at least no rotational degrees of freedom would be lost upon chloride binding. First and foremost, we decided to stick to a 1,3-disubstituted benzene ring as core motif, which had proven successful in the construction of strong bidentate halogen-bond donors (see above). To inhibit rotation of the halobenzimidazolium moieties, a sterically demanding substituent was placed in the 2-position of this core (group R in Figure 8).

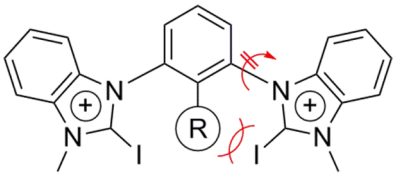


Figure 8. General design principle of a rigid (preorganized) multidentate halogen-bond donor.

As a suitable substituent R, we chose the trifluoromethyl group for several reasons, namely, (a) its steric demand which prevents rotation around the C–N axis, (b) its traceability via ^{19}F NMR (on the one hand, this allows one to determine the stability of the halogen-bond donor under reaction conditions (analogously to **8/OTf**); on the other hand, the ^{19}F NMR signal may be used for NMR titrations), and (c) its chemical inertness.

The synthesis of the corresponding atropisomers **15a/OTf** and **15b/OTf** is depicted in Scheme 3. First, two equivalents of benzimidazole were coupled with 1,3-difluoro-2-(trifluoromethyl)benzene[24] to yield 82% of a 0.8:1 mixture of isomers **12a** and **12b**. Halogenation in the 2-position of the coupled benzimidazoles was performed via lithiation, followed by the addition of elemental iodine or CBr_4.

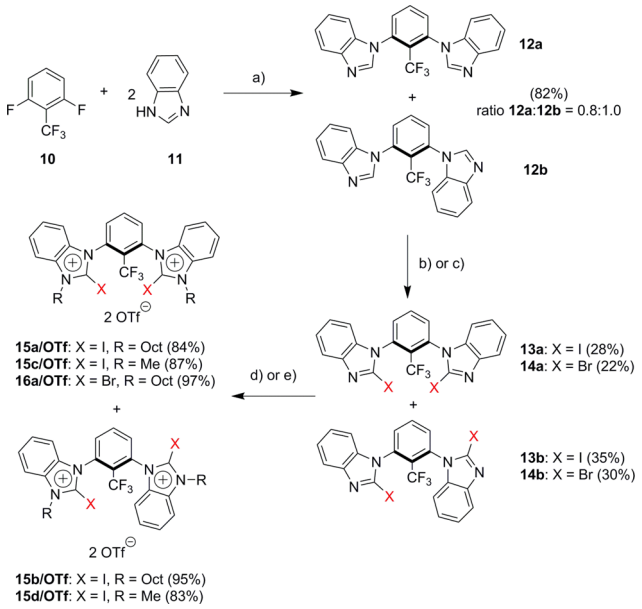
While the use of *n*-butyllithium or *tert*-butyllithium led to some byproducts which were hard to separate from the aspired products, lithium diisopropylamide (LDA) turned out to be a more suitable lithiating reagent, which produced the desired iodinated or brominated isomers without inseparable byproducts. Despite various optimization attempts, the yields of the halogenation step were still quite moderate (52–63%, see Scheme 2). Final alkylation was perfomed with either octyl or methyl triflate in CH_2Cl_2 at room temperature. Simple recrystallization yielded the desired cationic halogen-bond donors in good to excellent yield (83–97%).

In order to unambiguously identify the syn- and the anti-atropisomer of the product, the corresponding methylated compounds **15c** and **15d** were crystallized (Figures 9 and 10).

This X-ray structural analysis of **15d** (Figure 9) clearly shows the opposing orientation of the two iodinated centers. Both iodine atoms form a halogen bond with an oxygen atom of the

DOI: 10.1021/jacs.5b07863
J. Am. Chem. Soc. 2015, 137, 12110–12120

Scheme 3. Synthesis of the Rigid, Cationic, and Mulitdentate XB Donors[a]



[a]Reagents and conditions: (a) Benzimidazole (2.5 equiv), K_3PO_4 (10 equiv), DMF, 43 h, 155 °C. (b) Diisopropylamine (2.6 equiv), *n*-butyllithium (2.4 equiv), 0 to −78 °C, 12a/b, 1 h, I_2 (2.4 equiv), 1 h, −78 °C to rt. (c) Diisopropylamine (2.6 equiv), *n*-butyllithium (2.4 equiv), 0 to −78 °C, 12a/b, 1 h, CBr_4 (2.4 equiv); 1 h, −78 °C to rt. (d) Octyl triflate (3.0 equiv), CH_2Cl_2, 3 days, rt. (e) Methyl triflate (4.0 equiv), CH_2Cl_2, rt.

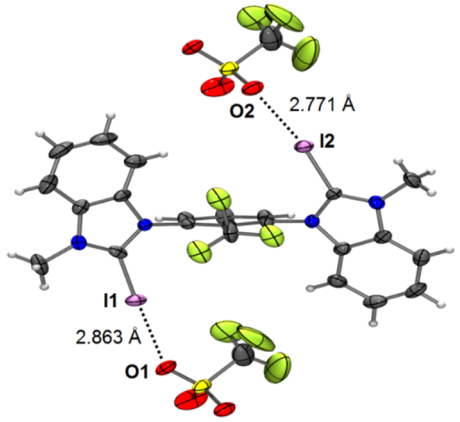


Figure 9. X-ray structural analysis of halogen-bond donor **15d** (ellipsoids set at 50% probability). Selected distances [Angstroms] and angles [degrees]: I1−O1 2.863, I_2−O2 2.776, C−I1 2.055, C−I2 2.063, C−I1−O1 171.5, C−I2−O2 168.5.

triflate counterion, indicated by the I−O binding lengths, which are shorter than the sum of the van der Waals radii.[21] One I−O distance (I2−O2 = 2.771 Å) is a bit shorter than the other one (I1−O1 = 2.863 Å), but both show relatively high directionality (C−I1−O1 = 172°, C−I2−O2 = 169°), in accord with halogen-bonding theory.

Correspondingly, crystallization of **15c** revealed the syn isomer (Figure 10). Again, both iodine substituents are engaged in a halogen bond with the counterion, but since two oxygen atoms of the same anion are involved, an overall bidentate coordination to the anion is realized. The I−O distances are similar to the shorter halogen bond in **15d** (2.777 and 2.783 Å).

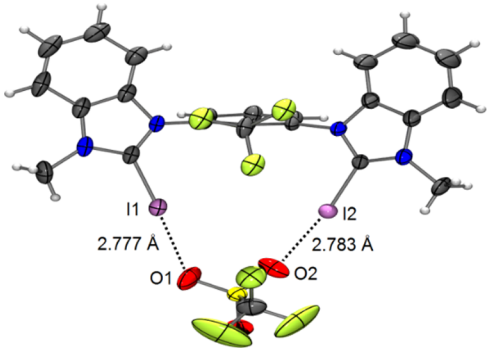


Figure 10. X-ray structural analysis of halogen-bond donor **15c** (ellipsoids set at 50% probability). The second triflate counterion was omitted for clarity. Selected distances [Angstroms] and angles [degrees]: I1−O1 2.777, I_2−O2 2.783, C−I1 2.069, C−I2 2.056, C−I1−O1 177.2, C−I2−O2 169.5.

The mean I−O distance of 2.780 Å in **15c** is a tad (0.06 Å) shorter than the one in the corresponding imidazolium derivative ***m*-II-Im^{Me}/OTf**.[15a] This could indicate higher Lewis acidity of the benzimidazolium catalyst, which would be in agreement with the experimental comparison of monodentate imidazolium and benzimidazolium catalysts (see above).

To verify whether this difference in catalytic activity is also true for the bidentate versions, we applied both *N*-octylated compounds **15a** and **15b** in the benchmark reaction (Table 5).

Table 5. Yield of 3 in the Presence of Bis(2-halobenzimidazolium) Halogen-Bond Donors[a]

no.	catalyst	mol %[b]	yield of **3** [%][c]
1	15a	2.5	85
2	15a	0.5	70
3	16a	2.5	8
4	15b	10	73
5	15b	0.5	51

[a]Yields are the average of at least two experiments. [b]Mol % of catalyst. [c]Isolated yield.

When the syn-isomer **15a** was used in the same amount as previous catalysts (10 mol %), the reaction had already reached completion before the usual reaction time of 6 h. This clearly demonstrates the superiority of the rigid bis-benzimidazolium catalyst against the flexible bis-imidazolium analogue (10 mol % of ***m*-II-Im^{Oct}/OTf** had resulted in 67% yield).

To be able to compare the syn and anti isomers of **15**, the catalyst loading was subsequently markedly lowered. When 2.5 mol % of **15a** was used, a yield of product **3** of 85% was obtained (Table 5, entry 1), and even a catalyst loading of 0.5 mol % resulted in 70% product formation (Table 5, entry 2).

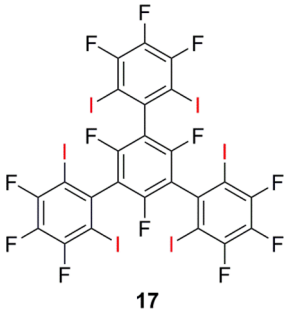
To verify that compound **15a** is stable under the reaction conditions, the same procedure as mentioned above for **8/OTf** was performed, revealing one set of signals in the ^{19}F NMR spectrum after 6 h and thus demonstrating the stability of the catalyst. When used in 2.5 mol %, the brominated compound **16a** yielded only 8% of **3** (entry 3), which is probably due to the low solubility of **16a** in THF.

The use of 10 mol % of the iodinated anti-isomer **15b** in the test reaction led to the isolation of 73% of **3** (Table 5, entry 4), a yield that is similar to the use of 20 mol % of the corresponding monodentate iodobenzimidazolium compound

DOI: 10.1021/jacs.5b07863
J. Am. Chem. Soc. 2015, 137, 12110−12120

I-BIm^{Me,Oct}/OTf (71%). This is easily explained by the fact that the rotation of the halogen-bonding groups around the C−N bond to the core is hindered in **15b**, and so it can only function as a monodentate catalyst. A respectable yield of 51% of product **3** was isolated when 0.5 mol % of anti-isomer **15b** was used. (Table 5, entry 5). Although the syn isomer is definitely more active, the difference to the anti isomer is less pronounced than expected. This seems to indicate that a bidentate binding of **15a** to the comparably small chloride, although likely present, is not ideal from a geometric point of view (compare the DFT calculations presented below).

Kinetic Investigation. Thus far, the yield of product **3** in the test reaction under standard conditions had been interpreted as an indication of the catalytic performance of the various compounds that had been screened. Given the broad variety of catalyst candidates, this was the only feasible way to conduct the screening in a justifiable amount of time. Still, a somewhat better measure of catalyst activity is the comparison of relative rate constants. This kind of kinetic study was performed for the best catalysts identified by the investigations described above using 0.5 mol % of halogen-bond donors **15a** and **15b**. As a reference point, the already reported[13b] neutral tridentate halogen-bond donor **17** was chosen (Figure 11).



17

Figure 11. Neutral multidentate halogen-bond donor **17**.

Using the initial inclination of the yield versus time profile as a rough orientation, relative rate constants k_{rel} were obtained (Figure 12). The relative rate constant k_{rel} of the reaction catalyzed by **15b** versus the one catalyzed by the neutral compound **17** is approximately 4.

As already seen above, the syn-isomer **15a** is markedly more active, and its relative rate constant compared to the one of **15b** is about 5. Thus, overall, our best cationic catalysts are more than 20-fold more active than the most powerful neutral halogen-bond donor. This difference is even more impressive given that the neutral halogen-bond donor is tridentate, whereas the cationic ones are, at best, bidentate. Yet, the strong halogen-bond-donating strength of the cationic compounds comes along with a potential drawback, which is the reduced stability against certain Lewis bases, as will be described below.

Calorimetric Titrations. In our previous organocatalysis studies, we found that the catalytic activities of halogen-bond donors in halide abstraction reactions correlate with the binding strength of the respective compounds to halides, as is to be expected. To determine the binding strength of the most potent catalyst, **15a**, with chloride, an isothermal calorimetric titration was performed in THF at 25 °C using tetra-*n*-octylammonium chloride (TOA-Cl) as halide source. The

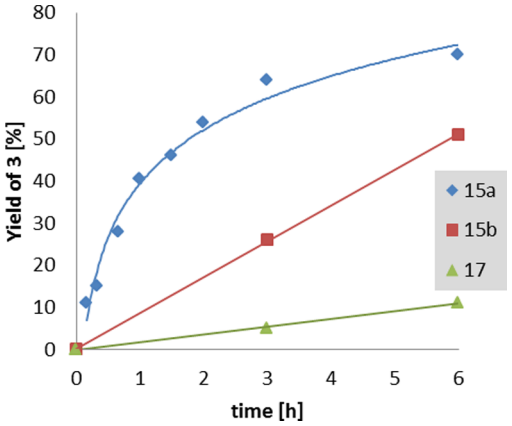


Figure 12. Yield versus time profile of three different halogen-bond donors (**15a**, **15b**, and **17**) with a catalyst load of 0.5 mol %. Isolated yields are shown for **15a** and **15b**. When **17** was used, NMR yields in the presence of 4 Å molecular sieves are given.[18]

obtained isotherm seemed to indicate that a chemical reaction had occurred, likely the decomposition of the halogen-bond donor. This was then further investigated by an NMR study in THF-d_8, which confirmed that compound **15a** was not stable in the presence of chloride at room temperature. The observed lability of **15a** constitutes an inherent risk in the design and synthesis of strong halogen-bond donors: just as a hydrogen bond may be described as a frozen deprotonation, a halogen bond may be depicted as a frozen deiodination reaction. As the halogen bond gets stronger and stronger, the point of actual iodonium transfer is approached or crossed, leading to the observed decomposition. Alternatively, the chloride may also react with the halogen-bond donor via a nucleophilic substitution reaction, but since the decomposition led to a variety of unidentified products, iodonium abstraction and subsequent carbene reactions appear more likely.

In an earlier study,[12g] we determined the binding data of imidazolium-based halogen-bond donors with halides (mostly bromide) in acetonitrile. Accordingly, we also tested the stability of **15a** against bromide in CD_3CN at room temperature, and no decomposition was observed in the NMR spectrum. This allowed us to obtain the corresponding thermodynamic parameters by calorimetry (Table 6). Isothermal calorimetric titrations of halogen-bond donor **15a** with tetra-*n*-butylammonium bromide in CH_3CN revealed that the corresponding binding constant is about 1 order of magnitude higher than that of ***m*-II-Im^{Me}/OTf** under the same conditions (3.5×10^6 vs 4.5×10^5 M^{-1}, respectively, see Table 6).

Table 6. Results of Isothermal Calorimetric Titrations of Three Cationic Halogen-Bond Donors in CH_3CN with Tetra-*n*-butylammonium Bromide at 30 °C

halogen-bond donor	K [M^{-1}]	$\Delta G°$ [kJ/mol]	$\Delta H°$ [kJ/mol]	$-T\Delta S°$ [kJ/mol]	n^b
15a	3.5×10^6	−37.9	−20.3	−17.6	0.9
15b	4.4×10^4	−27.0	−13.3	−13.7	2.0
m-II-Im^{Me}/OTf[a]	4.5×10^5	−32.8	−16.2	−16.6	0.9

[a]Taken from ref 12g. [b]Correction factor for cell concentrations ("stoichiometry").

Interestingly, although the entropic part $-T\Delta S$ is also somewhat more favorable, this difference is mainly due to

DOI: 10.1021/jacs.5b07863
J. Am. Chem. Soc. 2015, 137, 12110−12120

enthalpic effects. The titration data also showed that at least in acetonitrile the *syn*-isomer **15a** binds in a bidentate fashion to bromide (stoichiometry coefficient = 0.9).

As the anti-isomer **15b** may only act as a monodentate Lewis acid, a markedly lower binding constant with chloride was expected. Indeed, a K value of 4.4×10^4 M^{-1} was obtained, 2 orders of magnitude lower compared to **15a** and 1 order of magnitude lower compared to ***m*-II-Im^{Me}/OTf**. The monodentate binding of **15b** to bromide is also obvious from the stoichiometry factor of 2. The overall difference between atropisomers **15a** and **15b** has enthalpic and entropic origins, with the former being more relevant than the latter.

The correlation between binding strength and catalytic performance is not as straightforward as with earlier studies: while the strongest Lewis acid, syn-isomer **15a**, also clearly showed the best organocatalytic activity, the anti-isomer **15b** induced slightly more product formation (73%) than ***m*-II-Im^{Oct}/OTf** (67%) under the same reaction conditions, even though the latter binds 1 order of magnitude stronger to bromide. There are two likely reasons for this observation: first, while the titrations were performed with bromide, the actual halide liberated in the reaction is chloride. The different size and Lewis basicity of these anions alone might suffice to explain the seemingly contradictory results. Second, the reaction is performed at much lower temperature than the calorimetric titration. As the entropic contribution to the overall binding energy is higher for ***m*-II-Im^{Oct}/OTf** (−16.6 kJ/mol) compared to **15b** (−13.7 kJ/mol), the former will also experience a stronger reduction of the entropic part ($-T\Delta S$) of the overall binding strength at lower temperatures. This will likely lead to more similar halogen-bond-donating strengths of ***m*-II-Im^{Oct}/OTf** and **15b** at −78 °C.

Density Functional Theory (DFT) Calculations. Finally, the binding of the most potent halogen-bond donor **15a** to chloride was also investigated quantum chemically by DFT calculations. To this end, the M06-2X density functional[25] was employed with the Gaussian09 suite of programs[26] using a triple-ζ TZVPP[27] basis set and the corresponding pseudopotential for iodine.[28] We were most interested in the binding mode of **15a** and the structural changes which occur upon coordination of the anion. The structures of the isolated cation of the halogen-bond donor and of its complex with chloride are shown in Figures 13 and 14.

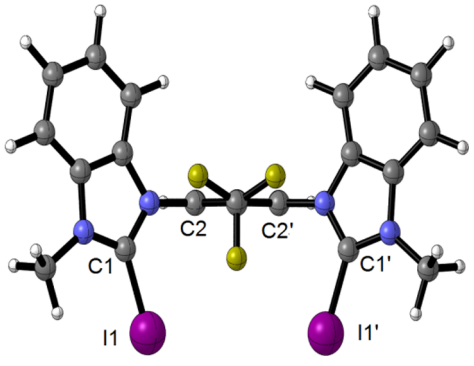


Figure 13. DFT calculation (M06-2X TZVPP) of the cation of halogen-bond donor **15a**. Graphical representation by CYLview.[29] Selected distances [Angstroms] and angles [degrees]: C1−I1/C1′−I1′ 2.048, C1−N−C2/C1′−N−C2′ 127.1.

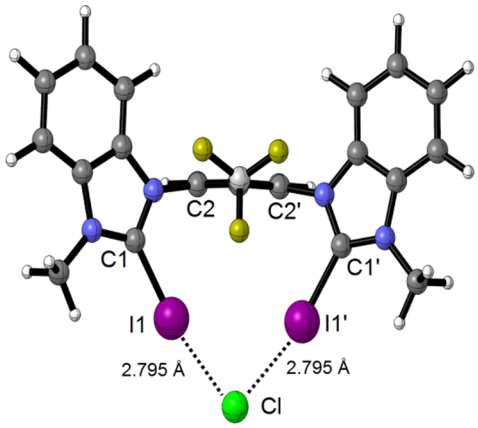


Figure 14. DFT calculation (M06-2X TZVPP) of the complex of the cation of halogen-bond donor **15a** with chloride. Graphical representation by CYLview.[28] Selected distances [Angstroms] and angles [degrees]: C1−I1/C1′−I1′ 2.128, C1−N−C2/C1′−N−C2′ 124.4.

A stable minimum for a bidentate complex of the cation of **15a** with chloride was obtained (Figure 14). The corresponding I−Cl distances are very short (2.795 Å), and the C−I bonds are markedly elongated compared to the noncoordinated cation (Figure 13) (2.128 vs 2.048 Å). This data is indicative for strong halogen bonding and thus in agreement with the calorimetric study, while it may also partly explain the observed lability of **15a** against chloride in THF at room temperature.

The view of the halogen-bonded adduct in Figure 14 also suggests that the bis-benzimidazolium dication has to undergo a slight distortion in order to realize the bidentate coordination to chloride. This is apparent from the slight bending of the central benzene core and the different C1−N−C2 angles in the isolated cation and the coordinated one (127° vs 124°). It seems that chloride is a bit too small to be ideally suited for a bidentate complex, which might help to explain why the difference in catalytic activity between the isomers **15a** and **15b** is not more pronounced (see above).

Summary and Discussion of the Catalysis Studies with Benzimidazolium-Based Halogen-Bond Donors. In order to rule out any activating effect of the acidic backbone protons of our bis-imidazolium compounds, the previously most active catalysts, we decided to also systematically study benzimidazolium-based halogen-bond donors. Direct comparisons with the corresponding monoimidazolium compounds revealed that the analogous benzimidazolium variants are the more potent organocatalysts. The activity could again be linked to the iodine centers and thus to halogen bonding. All in all, similar trends were observed as for the imidazolium species, namely, an increasing activity of compounds R−X in the order Cl < Br < I and the fact that the triflate salts were always more active than the halogen-bond donors featuring noncoordinating BAr^F_4 counterions.

The wish to design a bidentate catalyst that is as preorganized as possible for anion binding led to the synthesis of a new class of rigid bis-benzimidazolium halogen-bond donors. Both the syn and the anti isomers **15a** and **15b** were characterized by solid-state structures, which featured strong halogen bonds with the counterion. In particular, the syn-isomer **15a** showed very strong organocatalytic activity and could be used in as low as 0.5 mol %. The anti isomer, which may only bind halides in monodentate fashion, was less active,

DOI: 10.1021/jacs.5b07863
J. Am. Chem. Soc. 2015, 137, 12110−12120

although the difference was not as pronounced as could have been expected. Presumably, the structure of the syn isomer is not perfectly set up for complexation of the comparably small chloride anion, so that the effect of the bidentate coordination in **15a** compared to **15b** is somewhat reduced. Density functional theory calculations confirmed the possibility of a bidentate coordination for **15a** but also suggested a slight distortion of the dication upon complexation, which might be seen as a further indication for the point just mentioned.

We had already shown in a halide abstraction reaction which needed stoichiometric amounts of a halogen-bond-based activator that cationic compounds were much more active than neutral ones.[16] In the present study, this fact has now been confirmed for organocatalytic uses of halogen-bond donors: the most potent dicationic catalyst (**15a**) featured a rate constant which was more than 20 times higher than that of the strongest neutral halogen-bond donor (**17**), even though the latter has more Lewis acidic sites.

Finally, the stability of halogen-bond donor **15a** under reaction conditions was proven via ^{19}F NMR spectroscopy. Still, this halogen-based Lewis acid seems to be close to the limit between strong halogen-bonding ability and overall stability, as it decomposes in the presence of chloride at room temperature. This observation is a strong indication that great care has to be invested in the design and use of stronger and stronger halogen-bond-based organocatalysts. The stability of the catalyst under reaction conditions has to be closely monitored in these cases, and it might become necessary to actually tone down the strength of the halogen-bond donor by various means in order to avoid a too strong coordination of some Lewis bases, which will lead to iodonium transfer and subsequent decomposition. Catalyst **15a** was less sensitive to bromide in acetonitrile, and the calorimetric data that was obtained for this adduct indicated that **15a** binds about 1 order of magnitude stronger to the halide than a bis-(iodoimidazolium) compound.

CONCLUSION

Although halogen bonding shares many similarities with hydrogen bonding, its use in organocatalysis is still very rare, and the exact mode of action of halogen-bond donors is often difficult to elucidate. In this study, we presented the first case of a halide-abstraction-type reaction which was catalyzed by cationic halogen-bond donors. Although all our previously reported halogen-based Lewis acids (halopyridinium, -imidazolium, and -triazolium derivatives) showed catalytic activity that could be assigned to halogen bonding, a new type of preorganized halobenzimidazolium-based organocatalyst was by far the most potent compound. Unprecedentedly low catalyst loadings of 0.5 mol % could be used in the common benchmark reaction of 1-chloroisochroman with a silyl enol ether.[13b] Accordingly, this new representative of a rigid dicationic halogen-bond donor seems to be superior in activity to thiourea[17] or electron-deficient pyridinium organocatalysts[30] used earlier.

While they certainly are the most promising catalyst structures moving forward, compounds like the syn-isomer **15a** also remind us that for every reaction environment, there is a limit to the strength of halogen bonding, the transgression of which will lead to iodonium transfer. Our findings seem to indicate that atropisomer **15a** is already reasonably close to this limit for the present reaction. This subtle balance makes future investigations more challenging but also more interesting. Studies toward further applications of this new class of halogen-bond donors as well as toward enantioselective halogen-bond-induced organocatalysis are currently underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07863.

Full experimental details, characterization data, ITC spectra, computational data, and X-ray structural analysis (PDF)
(CIF)
(CIF)
(CIF)

AUTHOR INFORMATION

Corresponding Author

*stefan.m.huber@rub.de

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

S.H.J. and S.M.H. thank the Deutsche Forschungsgemeinschaft (DFG) for financial support (Cluster of Excellence RESOLV, EXC 1069), Dr. Florian Kniep for preliminary experiments, and Dr. Bert Mallick for X-ray measurments.

REFERENCES

(1) See, for example: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.

(2) (a) In *Halogen Bonding: Fundamentals and Applications*; Metrangolo, P., Resnati, G., Eds.; Springer: Berlin, 2008. Selected recent reviews: (b) Metrangolo, P.; Neukirch, H.; Pilati, T.; Resnati, G. *Acc. Chem. Res.* **2005**, *38*, 386. (c) Metrangolo, P.; Meyer, F.; Pilati, T.; Resnati, G.; Terraneo, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6114. (d) Fourmigué, M. *Curr. Opin. Solid State Mater. Sci.* **2009**, *13*, 36. (e) Legon, A. C. *Phys. Chem. Chem. Phys.* **2010**, *12*, 7736. (f) Cavallo, G.; Metrangolo, P.; Pilati, T.; Resnati, G.; Sansotera, M.; Terraneo, G. *Chem. Soc. Rev.* **2010**, *39*, 3772.

(3) (a) Hassel, O.; Rømming, C. *Q. Rev., Chem. Soc.* **1962**, *16*, 1. (b) Bent, H. A. *Chem. Rev.* **1968**, *68*, 587. (c) Weiss, R.; Miess, G.-E.; Haller, A.; Reinhardt, W. *Angew. Chem.* **1986**, *98*, 102; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 103.

(4) Lu, Y.; Wang, Y.; Zhu, W. *Phys. Chem. Chem. Phys.* **2010**, *12*, 4543.

(5) (a) Jungbauer, S. H.; Schindler, S.; Kniep, F.; Walter, S. M.; Rout, L.; Huber, S. M. *Synlett* **2013**, *24*, 2624. (b) Schindler, S.; Huber, S. M. *Top. Curr. Chem.* **2014**, *359*, 167.

(6) Legon, A. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2686.

(7) Selected reviews: (a) Karpfen, A. *Struct. Bonding (Berlin)* **2008**, *126*, 1. (b) Wolters, L. P.; Schyman, P.; Pavan, M. J.; Jorgensen, W. L.; Bickelhaupt, F. M.; Kozuch, S. *WIREs Comput. Mol. Sci.* **2014**, *4*, 523. Selected publications: (c) Politzer, P.; Murray, J. S.; Concha, M. C. *J. Mol. Model.* **2007**, *13*, 643. (d) Chudzinski, M. G.; Taylor, M. S. *J. Org. Chem.* **2012**, *77*, 3483. (e) Huber, S. M.; Jiminez-Izal, E.; Ugalde, J. M.; Infante, I. *Chem. Commun.* **2012**, *48*, 7708. (f) Huber, S. M.; Scanlon, J. D.; Jiminez-Izal, E.; Ugalde, J. M.; Infante, I. *Phys. Chem. Chem. Phys.* **2013**, *15*, 10350. For computational studies on the role of halogen bonding in the activity of *iodothyronine deiodinases*, see e.g.: (g) Bayse, C. A.; Rafferty, E. R. *Inorg. Chem.* **2010**, *49*, 5365. (h) Fortino, M.; Marino, T.; Russo, N.; Sicilia, E. *Chem. - Eur. J.* **2015**, *21*, 8554.

DOI: 10.1021/jacs.5b07863
J. Am. Chem. Soc. 2015, 137, 12110−12120

(8) Selected reviews: (a) Fourmigué, M.; Batail, P. *Chem. Rev.* **2004**, *104*, 5379. (b) Rissanen, K. *CrystEngComm* **2008**, *10*, 1107. (c) Brammer, L.; Espallargas, G. M.; Libri, S. *CrystEngComm* **2008**, *10*, 1712. (d) Bertani, R.; Sgarbossa, P.; Venzo, A.; Lelj, F.; Amati, M.; Resnati, G.; Pilati, T.; Metrangolo, P.; Terraneo, G. *Coord. Chem. Rev.* **2010**, *254*, 677. (e) Cavallo, G.; Metrangolo, P.; Pilati, T.; Resnati, G.; Sansotera, M.; Terraneo, G. *Chem. Soc. Rev.* **2010**, *39*, 3772. (f) Mukherjee, A.; Tothadi, S.; Desiraju, G. R. *Acc. Chem. Res.* **2014**, *47*, 2514. Selected publications: (g) Yamamoto, H. M.; Yamaura, J.-I.; Kato, R. *J. Am. Chem. Soc.* **1998**, *120*, 5905. (h) Nguyen, H. L.; Horton, P. N.; Hursthouse, M. B.; Legon, A. C.; Bruce, D. W. *J. Am. Chem. Soc.* **2004**, *126*, 16. (i) Bruce, D. W.; Metrangolo, P.; Meyer, F.; Pilati, T.; Praesang, C.; Resnati, G.; Terraneo, G.; Wainright, S. G.; Whitwood, A. C. *Chem. - Eur. J.* **2010**, *16*, 9511. (j) Troff, R. W.; Mäkelä, T.; Topić, F.; Valkonen, A.; Raatikainen, K.; Rissanen, K. *Eur. J. Org. Chem.* **2013**, *2013*, 1617.

(9) For recent reviews, see: (a) Erdelyi, M. *Chem. Soc. Rev.* **2012**, *41*, 3547. (b) Beale, T. M.; Chudzinski, M. G.; Sarwar, M. G.; Taylor, M. S. *Chem. Soc. Rev.* **2013**, *42*, 1667.

(10) (a) Mele, A.; Metrangolo, P.; Neukirch, H.; Pilati, T.; Resnati, G. *J. Am. Chem. Soc.* **2005**, *127*, 14972. (b) Serpell, C. J.; Kilah, N. L.; Costa, P. J.; Félix, V.; Beer, P. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 5322. (c) Kilah, N. L.; Wise, M. D.; Serpell, C. J.; Thompson, A. L.; White, N. G.; Christensen, K. E.; Beer, P. D. *J. Am. Chem. Soc.* **2010**, *132*, 11893. (d) Sarwar, M. G.; Dragisić, B.; Sagoo, S.; Taylor, M. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1674. (e) Dimitrijević, E.; Kvak, P.; Taylor, M. S. *Chem. Commun.* **2010**, *46*, 9025. (f) Caballero, A.; White, N. G.; Beer, P. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1845. (g) Caballero, A.; Zapata, F.; White, N. G.; Costa, P. J.; Félix, V.; Beer, P. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 1876. (h) Zapata, F.; Caballero, A.; White, N. G.; Claridge, T. D. W.; Costa, P. J.; Félix, V.; Beer, P. D. *J. Am. Chem. Soc.* **2012**, *134*, 11533. (i) Gillis, E. A. L.; Demireva, M.; Sarwar, M. G.; Chudzinsky, M. G.; Taylor, M. S.; Williams, E. R.; Fridgen, T. D. *Phys. Chem. Chem. Phys.* **2013**, *15*, 7638. (j) Raatikainen, K.; Cavallo, G.; Metrangolo, P.; Resnati, G.; Rissanen, K.; Terraneo, G. *Cryst. Growth Des.* **2013**, *13*, 871. (k) Gilday, L. C.; Beer, P. D. *Chem. - Eur. J.* **2014**, *20*, 8379. (l) Mullaney, B. R.; Thompson, A. L.; Beer, P. D. *Angew. Chem.* **2014**, *126*, 11642. (m) Caballero, A.; Swan, L.; Zapata, F.; Beer, P. D. *Angew. Chem.* **2014**, *126*, 12048. (n) Langton, M. J.; Robinson, S. W.; Marques, I.; Félix, V.; Beer, P. D. *Nat. Chem.* **2014**, *6*, 1039. (o) Karim, A.; Reitti, M.; Carlsson, A.-C. C.; Graefenstein, J.; Erdelyi, M. *Chem. Sci.* **2014**, *5*, 3226. (p) Robinson, S. W.; Mustoe, C. L.; White, N. G.; Brown, A.; Thompson, A. L.; Kennepohl, P.; Beer, P. D. *J. Am. Chem. Soc.* **2015**, *137*, 499.

(11) (a) Jentzsch, A. V.; Emery, D.; Mareda, J.; Metrangolo, P.; Resnati, G.; Matile, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11675. (b) Jentzsch, A. V.; Emery, D.; Mareda, J.; Nayak, S. K.; Metrangolo, P.; Resnati, G.; Sakai, N.; Matile, S. *Nat. Commun.* **2012**, *3*, 905. (c) Jentzsch, A. V.; Matile, S. *J. Am. Chem. Soc.* **2013**, *135*, 5302. (d) Jentzsch, A. V.; Henning, A.; Mareda, J.; Matile, S. *Acc. Chem. Res.* **2013**, *46*, 2791. (e) Jentzsch, A. V.; Matile, S. *Top. Curr. Chem.* **2014**, *358*, 205.

(12) (a) Metrangolo, P.; Panzeri, W.; Recupero, F.; Resnati, G. *J. Fluorine Chem.* **2002**, *114*, 27. (b) Libri, S.; Jasim, N. A.; Perutz, R. N.; Brammer, L. *J. Am. Chem. Soc.* **2008**, *130*, 7842. (c) Sarwar, M. G.; Dragisić, B.; Salsberg, L. J.; Gouliaras, C.; Taylor, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 1646. (d) Laurence, C.; Graton, J.; Berthelot, M.; El Ghomari, M. J. *Chem. - Eur. J.* **2011**, *17*, 10431. (e) Hardegger, L. A.; Kuhn, B.; Spinnler, B.; Anselm, L.; Ecabert, R.; Stihle, M.; Gsell, B.; Thoma, R.; Diez, J.; Benz, J.; Plancher, J.-M.; Hartmann, G.; Banner, D. W.; Haap, W.; Diederich, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 314. (f) Cametti, M.; Raatikainen, K.; Metrangolo, P.; Pilati, T.; Terraneo, G.; Resnati, G. *Org. Biomol. Chem.* **2012**, *10*, 1329. (g) Walter, S. M.; Kniep, F.; Rout, L.; Schmidtchen, F. P.; Herdtweck, E.; Huber, S. M. *J. Am. Chem. Soc.* **2012**, *134*, 8507. (h) Carlsson, A.-C. C.; Gräfenstein, J.; Budnjo, A.; Laurila, J. L.; Bergquist, J.; Karim, A.; Kleinmeier, R.; Brath, U.; Erdelyi, M. *J. Am. Chem. Soc.* **2012**, *134*, 5706. (i) Sarwar, M. G.; Dragisić, B.; Dimitrijević, E.; Taylor, M. S. *Chem. - Eur. J.* **2013**, *19*, 2050. (j) Carlsson, A.-C. C.; Uhrbom, A.; Karim, A.; Brath, U.; Gräfenstein, J.; Erdelyi, M. *CrystEngComm* **2013**, *15*, 3087. (k) Dumele, O.; Wu, D.; Trapp, N.; Goroff, N.; Diederich, F. *Org. Lett.* **2014**, *16*, 4722. (l) Bedin, M.; Karim, A.; Reitti, M.; Carlsson, A.-C. C.; Topic, F.; Cetina, M.; Pan, F.; Havel, V.; Al-Ameri, F.; Sindelar, V.; Rissanen, K.; Gräfenstein, J.; Erdelyi, M. *Chem. Sci.* **2015**, *6*, 3746.

(13) (a) Bruckmann, A.; Pena, M. A.; Bolm, C. *Synlett* **2008**, *2008*, 900. (b) Kniep, F.; Jungbauer, S. H.; Zhang, Q.; Walter, S. M.; Schindler, S.; Schnapperelle, I.; Herdtweck, E.; Huber, S. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7028. (c) Jungbauer, S. H.; Walter, S. M.; Schindler, S.; Rout, L.; Kniep, F.; Huber, S. M. *Chem. Commun.* **2014**, *50*, 6281. (d) He, W.; Ge, Y.-C.; Tan, C.-H. *Org. Lett.* **2014**, *16*, 3244. (e) Tsuji, N.; Kobayashi, Y.; Takemoto, Y. *Chem. Commun.* **2014**, *50*, 13691. (f) Takeda, Y.; Hisakuni, D.; Lin, C.-H.; Minakata, S. *Org. Lett.* **2015**, *17*, 318.

(14) During the preparation of this manuscript, Takemoto et al. reported the activation of a silicon−halogen bond by a catalyst system comprised of molecular iodine and an iodoimidazolium compound: Saito, M.; Tsuji, N.; Kobayashi, Y.; Takemoto, Y. *Org. Lett.* **2015**, *17*, 3000.

(15) (a) Walter, S. M.; Kniep, F.; Herdtweck, E.; Huber, S. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7187. (b) Kniep, F.; Walter, S. M.; Herdtweck, E.; Huber, S. M. *Chem. - Eur. J.* **2012**, *18*, 1306. (c) Kniep, F.; Rout, L.; Walter, S. M.; Bensch, H. K. V.; Jungbauer, S. H.; Herdtweck, E.; Huber, S. M. *Chem. Commun.* **2012**, *48*, 9299.

(16) Walter, S. M.; Jungbauer, S. H.; Kniep, F.; Schindler, S.; Herdtweck, E.; Huber, S. M. *J. Fluorine Chem.* **2013**, *150*, 14.

(17) Reisman, S. A.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198.

(18) Some catalyst candidates induced the formation of an ether-bridged bis(isochroman) derivative, which resulted from hydrolysis of 1-chloroisochroman, likely due to traces of water in hygroscopic compounds. This side reaction could be almost completely suppressed by the addition of 4 Å molecular sieves. Several comparison experiments were performed, which indicated that the formation of the side product was unrelated to the catalytic activity of the halogen-bond donors and that the respective yield in product **3** was identical (within the experimental errors) regardless of whether molecular sieve was present or not.

(19) Zhu, L.; Guo, P.; Li, G.; Lan, J.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 8535.

(20) Yoshida, Z.; Tawara, Y. *J. Am. Chem. Soc.* **1971**, *93*, 2573. (b) Weiss, R.; Brenner, T.; Hampel, F.; Wolski, A. *Angew. Chem.* **1995**, *107*, 481.

(21) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

(22) (a) Cram, D. J. *Science* **1988**, *240*, 760. Selected recent studies on preorganized hydrogen-bond donors: (b) Beletskiy, E. V.; Schmidt, J.; Wang, X.-B.; Kass, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 18534. (c) Samet, M.; Kass, S. R. *J. Org. Chem.* **2015**, *80*, 7727.

(23) (a) Jungbauer, S. H.; Bulfield, D.; Kniep, F.; Lehmann, C. W.; Herdtweck, E.; Huber, S. M. *J. Am. Chem. Soc.* **2014**, *136*, 16740. (b) Jungbauer, S. H.; Schindler, S.; Herdtweck, E.; Keller, S.; Huber, S. M. *Chem. - Eur. J.* **2015**, 13625.

(24) Diness, F.; Fairlie, D. P. *Angew. Chem.* **2012**, *124*, 8136.

(25) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.

(26) Frisch, M. J.; et al. *Gaussian 09*, Revision D.01l Gaussian, Inc.: Wallingford CT, 2009 (see also SI).

(27) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.

(28) Peterson, K. A.; Figgen, D.; Goll, E.; Stoll, H.; Dolg, M. *J. Chem. Phys.* **2003**, *119*, 11113.

(29) Legault, C. Y. *CYLview*, 1.0b; Université de Sherbrooke: Sherbrooke, 2009, http://www.cylview.org.

(30) Berkessel, A.; Das, S.; Pekel, D.; Neudörfl, J.-M. *Angew. Chem., Int. Ed.* **2014**, *53*, 11660.

DOI: 10.1021/jacs.5b07863
J. Am. Chem. Soc. 2015, 137, 12110−12120