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Halogen Bonds

Organocatalysis by Neutral Multidentate Halogen-Bond Donors[**]

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Over the last 15 years, hydrogen-bond donors, such as thiourea derivatives, have been used as noncovalent organocatalysts with ever-increasing sophistication.[1] Yet, despite the large structural variety of the currently known noncovalent organocatalysts, virtually all are based on the same interacting atom: positively polarized hydrogen.

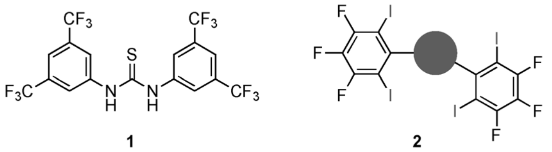
Although it has been known for a long time that compounds featuring electrophilic *halogen* substituents also form adducts with Lewis bases,[2] the corresponding interaction ("halogen bonding")[3,4] was mostly ignored until the 1990s.[5] An important difference between these two noncovalent interactions is the invariably high directionality of halogen bonds, with R−X−LB angles that are close to 180° ($X = Cl,Br,I$; $LB =$ Lewis base).[3] Most studies involving halogen bonds are related to the solid state and to crystal engineering,[6] but in recent years an increasing number of applications in solution-phase have been published,[7] including fundamental studies[8] and reports on anion receptors.[9]

In organocatalysis, the involvement of halogen bonds has only been postulated in two cases.[10,11] Bolm et al. reported that iodoperfluoroalkanes catalyze the reduction of quinoline derivatives.[10a] The participation of halogen bonds in this reaction was derived from experimental observations. In a second example, iodine trichloride was reported to catalyze the ring-opening polymerization of L-lactide.[10b] The elucidation of the exact mode of action of this highly reactive[12] interhalogen compound is not trivial, though, and in both reported cases the analysis is further complicated by the possible presence of traces of acid.[7b]

One particular application of hydrogen-bonding organocatalysts is based on the coordination to anions and/or the abstraction of the latter from organic substrates ("anion binding mechanism").[13] Recently, we could show that halogen-bond donors may also serve as activators in a halide-abstraction benchmark reaction.[14] To date, however, only dicationic compounds (based on either imidazolium,[14a] pyridinium,[14b] or 1,2,3-triazolium[14c] backbones) proved to be active, and stoichiometric amounts of the halogen-bond donor needed to be employed. As the use of cationic compounds comes along with several limitations (for example, concerning solubility, synthetic accessibility, and the presence of counteranions), our next goal was to design *neutral* halogen-bond donors for use as activators or, ideally, organocatalysts.

At present, our studies have primarily proof-of-principle character to demonstrate the feasibility of halogen-bond-based organocatalysis. In the long term, we envision that halogen-based organocatalysts and hydrogen-bond donors will complement each other. Halogen-bond donors might be especially suitable for Lewis basic substrates featuring heavier elements (such as sulfur, phosphorous, or the halogens) or for certain reaction conditions. Furthermore, neutral fluorinated halogen-bond donors will likely allow the use of very non-polar or fluorinated solvents in organocatalysis. Finally, the high directionality of halogen bonds might prove advantageous in future halogen-bond-catalyzed enantioselective transformations.

In analogy to thiourea organocatalyst **1**,[13a] we strove to develop multidentate halogen-based Lewis acids without further functional groups to study the isolated effect of halogen bonding. The 2,6-diiodo-3,4,5-trifluorophenyl group (Scheme 1) was chosen as building block for several reasons, namely: a) the electron-withdrawing fluorine substituents; b) the fact that high rigidity can be achieved by coupling to aryl moieties; and c) the fact that the formation of atropisomers can be avoided owing to the symmetry of this group. Orientating DFT studies to identify suitable backbones suggested that *p*- or *m*-substituted benzene should constitute ideal core structures (see the Supporting Information). Few neutral multidentate halogen-bond donors are known, and those either lack the desired rigidity[8f,9a,b] or do not point their electrophilic halogen substituents towards a single center.[15]



1 **2**

Scheme 1. Thiourea organocatalyst **1**, and the design principle for neutral multidentate halogen-bond donors (**2**).

The presence of several iodine substituents in compounds of type **2** severely restricts the use of cross-coupling strategies for their synthesis. Our first successful synthetic route (Scheme 2) consisted of a twofold nucleophilic aromatic

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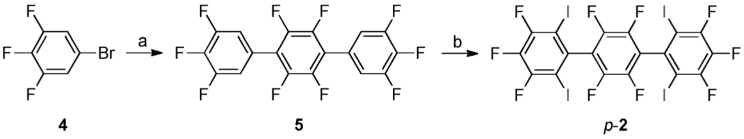


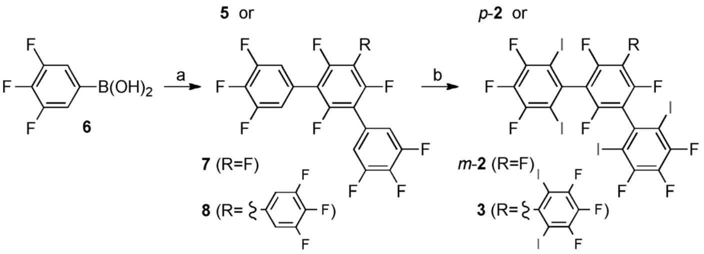
Scheme 2. Synthesis of neutral halogen-bond donor *p*-**2**; a) *n*BuLi, Et_2O, −78 °C, C_6F_6 (0.5 equiv); b) KI, $NaIO_4$, conc. H_2SO_4, RT; yields: 39% (**5**), 63% (*p*-**2**).

substitution of hexafluorobenzene[16] with lithiated **4**, followed by iodination of the very electron-poor intermediate **5** with $KI/NaIO_4$ in concentrated sulfuric acid.[17] However, the low yield in the initial aryl coupling to **5** and the fact that this route is limited to the synthesis of *para*-terphenyl derivatives necessitated the development of an alternative approach. Thus, Suzuki-type cross-coupling[18] followed by iodination of the intermediates with NIS/HOTf[19] allowed the preparation of terphenyls *m*-**2**, *p*-**2** and hexadentate analogue **3** in high yields (Scheme 3).

Compound *p*-**2** was co-crystallized with tris(dimethylamino)cyclopropenium chloride,[20] and a selected part of the crystal structure of this non-covalent adduct is shown in Figure 1.[21]

The crystallographic unit cell contains two molecules of *p*-**2** as well as three chloride salt ion pairs, and consequently multiple iodine–chloride contacts are found. Each halogen-bond donor exhibits bidentate binding to chloride on one side of the molecule. The accompanying slight distortion of the central benzene core leads to elongation of the iodine–iodine distance on the other side of the molecule (6.730 Å vs. 4.112 Å in the bidentate arrangement), allowing only monodentate binding to chloride on the second side. All of the iodine–chloride halogen bonds found are markedly shorter than the sum of the van-der-Waals radii (mean I−Cl distance:[21] 3.10 Å; sum of radii:[22] 3.73 Å)[23] and show high linearity (mean C<C-<I−Cl angle: 174°).

To probe the ability of halogen-bond donors *m*-**2**, *p*-**2**, and **3** to act as organocatalysts, we chose to investigate the reaction of 1-chloroisochroman (**9**) with ketene silyl acetal **10** (Table 1). Jacobsen et al. had previously used chiral thiourea organocatalysts to achieve high enantioselectivities in this anion-binding benchmark case.[24] We reasoned that the release of a silyl group during the reaction would quench the liberated chloride and prevent it from blocking the halogen-bond donor, thus enabling catalytic use of the latter. Accordingly, the test reaction was investigated in the presence of 10 mol% of various catalyst candidates in THF (Table 1). To maximize non-covalent binding and to suppress side reactions, a temperature of −78 °C was chosen and the reaction was quenched after 12 h by addition of NaOMe. Under these reaction conditions, no background reactivity was observed (Table 1, entry 1).



Scheme 3. Alternative synthesis of neutral halogen-bond donors; a) 1,4-$C_6F_4I_2$ (0.5 equiv) or 1,3-$C_6F_4I_2$ (0.5 equiv), XPhos (5 mol%), $[Pd_2(dba)_3]$ (1 mol%), Na_2CO_3 (**5**,**7**), 1,3,5-$C_6F_3I_3$ (0.11 equiv), XPhos (1 mol%), $Pd_2(dba)_3$ (0.1 mol%), Na_2CO_3 (0.33 equiv) (**8**), toluene/THF/H_2O, 95 °C; b) N-iodosuccinimide (NIS; 13 equiv) (*p*-**2**, *m*-**2**) or NIS (20 equiv) (**3**), HOTf, 0 °C to RT; yields: 87% (**5**), 86% (**7**), 90% (**8**) (all relative to polyiodopolyfluoroarenes), 80% (*p*-**2**), 80% (*m*-**2**), 69% (**3**). dba = dibenzylideneacetone, HOTf = trifluoromethanesulfonic acid, XPhos = 2-(2,4,6-*i*$Pr_3C_6H_2$)$C_6H_4PCy_2$.

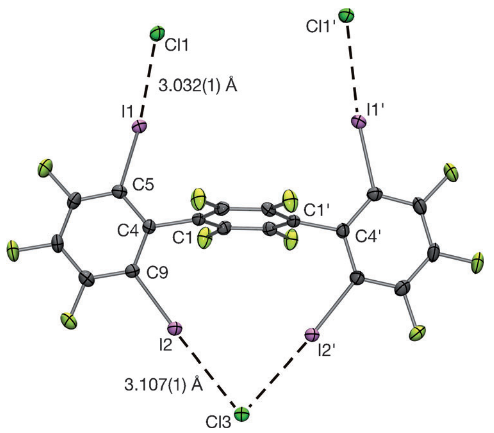
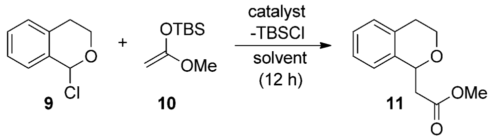


Figure 1. Part of the crystal structure of the adduct of *p*-**2** with tris(dimethylamino)cyclopropenium chloride (ellipsoids set at 50% probability). Cations have been omitted for clarity. Chloride anions Cl1 form additional halogen bonds with further molecules of *p*-**2**. Selected distances [Å] and angles [°]: C5–I1 2.110(3), C9–I2 2.112(3), I2–I2′ 4.1121(4), I1–I1′ 6.7302(5), C1′–C1-C4 170.54(2); C5-I1-Cl1 173.84(9), C9-I2-Cl3 172.19(9).

A representative strong but monodentate neutral halogen-bond donor, 1,3,5-triiodo-2,4,6-trifluorobenzene,[23] also did not lead to product formation (Table 1, entry 3). As (fluoro)aryl groups were postulated to engage in stabilizing interactions with the substrate or the nucleophile,[24] we tested the non-iodinated reference compounds **5** and **8** for catalytic activity, which was again not observed (entries 6 and 9). In contrast to the pure fluorinated backbones, however, formation of ester **11** *was* found for the analogous iodinated halogen-bond donors *p*-**2** and **3**: after 12 h at low temperature, the product was isolated in 37% yield for compound *p*-**2** and in 91% yield for the tridentate variant **3** (entries 13 and 17). As the halogen-bond donors were only added in 10 mol%, these yields of ester **11** clearly indicate a catalytic process. Interestingly, the bidentate halogen-bond donor *m*-**2** lead to only 14% product formation (entry 11). The fact that the catalytic activity crucially depends on the number (and relative orientation) of the iodine substituents, while the non-iodinated backbones themselves are not active, is strong evidence for the involvement of halogen bonding in this reaction. When 20 mol% of compound **3** were used as catalyst,

Table 1: Reaction of 1-chloroisochroman (**9**) with ketene silyl acetal **10** in the presence of various catalysts.



No.	Catalyst	Equiv.[a]	Solvent[b]	T[c]	Yield [%][d]
1	–	–	THF	−78	≤5
2	–	–	MTBE	−78	≤5
3	$C_6F_3I_3$[e]	0.1	THF	−78	≤5
4	HOTf	0.01	THF	−78	14
5	HOTf	0.1	THF	−78	27
6	**5**	0.1	THF	−78	≤5
7	**5**	0.1	THF	−40	≤5
8	**5**	0.1	MTBE	−78	≤5
9	**8**	0.1	THF	−78	≤5
10	**8**	0.1	MTBE	−78	≤5
11	*m*-**2**	0.1	THF	−78	14
12	*m*-**2**	0.1	MTBE	−78	17
13	*p*-**2**	0.1	THF	−78	37
14	*p*-**2**	0.1	THF	−40	52
15	*p*-**2**	0.1	MTBE	−78	27
16	*p*-**2**	0.1	MTBE	−40	48
17	**3**	0.1	THF	−78	91
18	**3**	0.1	MTBE	−78	88
19	**1**	0.1	THF	−78	12
20	**1**	0.1	MTBE	−78	17

[a] Equivalents of catalyst (relative to **9**). [b] THF = tetrahydrofuran, MTBE = methyl *tert*-butyl ether. [c] Temperature [°C]. [d] Yields of isolated product. [e] 1,3,5-Triiodo-2,4,6-trifluorobenzene.

quantitative product formation was already observed in less than six hours. No product was formed, however, when 10 mol% of halogen-bond donor **3** as well as 20 mol% of NBu_4Cl were employed in the same reaction, confirming that the mode of action of the catalyst is based on anion binding.[24]

In these benchmark reactions, it is often very difficult to rigorously exclude traces of acids, which might also be formed by imperceptible decomposition of the halogen-bond donors. To rule out hidden acid catalysis[25] in the present case, we conducted the reaction in the presence of either 1 or 10 mol% of HOTf (Table 1, entries 4 and 5). However, the product was only obtained in 14 and 27% yield, respectively, which is markedly below that for catalyst **3** under the same conditions. In this respect, it should be noted that the halogen-bond donors are purified by column chromatography with pentane as eluent. Furthermore, more than 95% of pure catalyst **3** could be re-isolated from the test reactions by column chromatography, and a solution of compound **3** in [D_8]THF showed no measurable signs of decomposition after 10 days at room temperature. Thus, even the presence of 1 mol% of acid, either as impurity or by decomposition of the halogen-bond donor, seems highly unlikely in the reported benchmark reactions. This is further evidence that halogen bonds are crucially involved in the catalytic process.

Although the tridentate halogen-bond donor **3** shows higher catalytic activity than the bidentate variants *m*/*p*-**2** (Figure 2), the latter should constitute a better basis for the future design of chiral halogen-bond donors. Thus, the test reaction was also performed with 10 mol% of *p*-**2** at higher temperatures (−40 °C) to increase the reaction rate, and a yield of 52% was obtained for ester **11**. No side products were observed, and in the absence of catalyst (or with 10 mol% of **5**), again no background reaction took place.

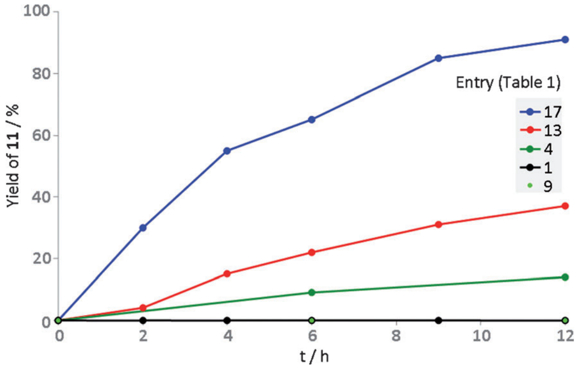
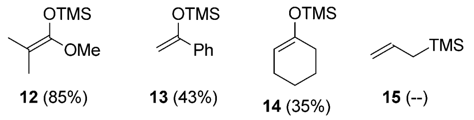


Figure 2. Yield versus time profile of selected reactions from Table 1.

For the sake of comparison with a prototypical hydrogen-bond donor, we also performed the reaction with 10 mol% of thiourea **1** (Scheme 1), but we could only isolate the product in 12% yield (Table 1, entry 19). As methyl *tert*-butyl ether (MTBE) was used as solvent in the reported thiourea catalysis,[24] we ran all previously discussed experiments in this ether to exclude solvent effects, but found very similar trends as for THF (see Table 1).[26] This seems to indicate that the catalytic effect of halogen bonding is at least comparable to that of (more or less) purely hydrogen bonding based compounds in the present benchmark reaction.

In further orientating experiments, nucleophile **10** was substituted by ketene silyl acetal **12**, silyl enol ethers **13** and **14**, and allyl trimethylsilane **15** in the reaction with 1-chloroisochroman (in the presence of 10 mol% of **3** as catalyst). The yields of the corresponding isolated products (see Scheme 4) are in qualitative agreement with the Mayr nucleophilicity indexes N[27] of compounds **12** (9.00), **13** (6.22), and **14** (5.21).[28] No product was formed in the reaction with allyl silane **15** (1.68).[29] Although further mechanistic studies on the halogen-bond catalysis are necessary, we note that the addition of the nucleophile to the intermediately formed oxocarbenium–chloride–thiourea complex was postulated as rate-determining step in the hydrogen-bond based catalysis.[24]



Scheme 4. Additional nucleophiles for the reaction with 1-chloroisochroman (**9**) as well as yields of the respective products in the presence of 10 mol% of **3** (after 12 h in THF at −78 °C). TMS = trimethylsilyl.

Finally, quantification of the halide binding strength of the neutral multidentate halogen-bond donors was aspired by isothermal calorimetric titrations.[8e,f] While the results of the titration of compound **3** with tetrabutylammonium chloride and bromide could not yet be interpreted owing to a nontrivial shape of the corresponding isotherms, Lewis acids *m*-**2** and *p*-**2** were found to form 1:1 adducts with both anions (see stoichiometry coefficients N in Table 2).

Table 2: Thermodynamic data for the binding of two halogen-bond-based (*m*-**2**, *p*-**2**) and one hydrogen-bond-based (**1**) Lewis acid(s) to halides, determined by isothermal calorimetric titrations at 30 °C in THF.

LA[a]	LB[b]	K[c] [mol^{-1}]	ΔG^{0}[d] [$kJ\,mol^{-1}$]	ΔH^{0} [$kJ\,mol^{-1}$]	$T\Delta S^{0}$ [$kJ\,mol^{-1}$]	N[e]
m-**2**	Cl^{-}	1.8×10^{4}	−24.7	−22.4	2.4	1.3
m-**2**	Br^{-}	1.3×10^{4}	−23.9	−27.7	−3.8	1.2
p-**2**	Cl^{-}	7.5×10^{4}	−28.3	−27.6	0.7	1.2
p-**2**	Br^{-}	6.2×10^{4}	−27.8	−33.0	−5.1	1.0
1	Cl^{-}	2.9×10^{5}	−31.7	−18.4	13.3	1.2
1	Br^{-}	2.9×10^{5}	−31.7	−19.2	12.5	0.8

[a] Lewis acid (catalyst). [b] Lewis base (anion as tetrabutylammonium salt). [c] Equilibrium constant. [d] In some cases, ΔG^{0} deviates slightly from $\Delta H^{0}-T\Delta S^{0}$ owing to rounding effects. [e] Stoichiometry coefficient.

Both Lewis acids seem to bind slightly more strongly to chloride compared to bromide, and the complexes of compound *p*-**2** are a slightly more stable than those of *m*-**2** for both anions. Unlike our dicationic imidazolium-based halogen-bond donors,[8e] the entropy term $T\Delta S^{0}$ represents only a minor contribution to the overall binding free energy ΔG^{0} in the case of the neutral halogen-based Lewis acids. At the measurement temperature of 30 °C, thiourea **1** binds somewhat stronger to both anions than *m*-**2** and *p*-**2**.[30] Compared to the latter, the enthalpy of binding ΔH^{0} is markedly lower for the hydrogen-bond donor **1**, whereas the entropy term is decidedly more relevant.

In summary, we could show that neutral multidentate halogen-bond donors *m*/*p*-**2** and **3** catalyze the reaction of 1-chloroisochroman with ketene silyl acetals and silyl enol ethers. To the best of our knowledge, this is the first case in which organocatalytic activity can be linked to the presence (and number as well as relative orientation) of iodine substituents. As the occurrence of hidden acid catalysis can be ruled out with high probability, this case constitutes strong evidence for halogen-bond-based organocatalysis. Finally, the benchmark reaction presented here is also the first example of halogen-bond-induced carbon–carbon bond formation.

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[21] Crystal data: formula: $3[(C_{18}F_{10}I_4)]$, $5[(C_9H_{18}N_3)^+]$, $5[(Cl)^-]$; $M_r = 3759.91$, colorless fragment, $0.05 \times 0.15 \times 0.51$ mm^3, monoclinic, space group $C2/c$ (no. 15); $a = 7.7361(2)$, $b = 52.0535(16)$, $c = 30.3246(9)$ Å, $\beta = 96.9665(12)°$; $V = 12121.3(6)$ Å^3, $Z = 4$, $\mu(\mathrm{Mo_{K\alpha}}) = 3.273$ mm^{-1}, $\rho_{\mathrm{calcd}} = 2.060$ g cm^{-3}; θ-range = 0.78–25.45°, data collected: 89343, independent data $[I_o > 2\sigma(I_o)$/all data/$R_{\mathrm{int}}]$: 10962/11219/0.038; data/restraints/parameter: 11219/0/742; R1 $[I_o > 2\sigma(I_o)$/all data]: 0.0244/0.0252; wR2 $[I_o > 2\sigma(I_o)$/all data]: 0.0541/0.0546; GOF = 1.205; $\Delta\rho_{\mathrm{max/min}}$: 1.32/−0.80 e Å^{-3}. See the Supporting Information; CCDC 924128 (*p*-**2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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