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Activation of Michael Acceptors by Halogen-Bond Donors

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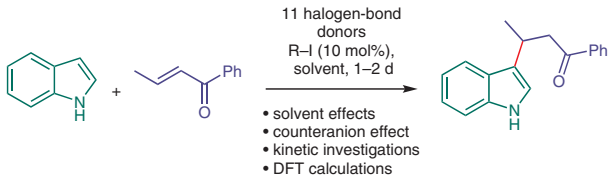
In memoriam Professor J. Peter Guthrie



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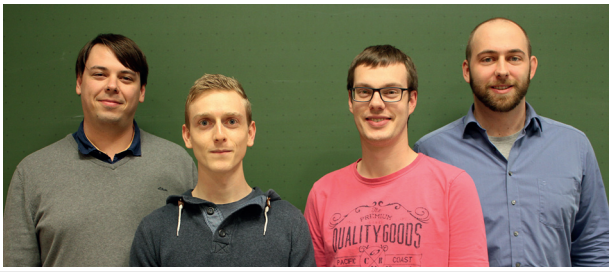
Abstract Extending earlier studies on iodine catalysis, experimental investigations show that various halogen-bond donors can also be employed to accelerate the Michael addition between *trans*-crotonophenone and indole. Solvent as well as counteranion effects have been analyzed, and kinetic and computational investigations provide additional insights into the mode of activation.

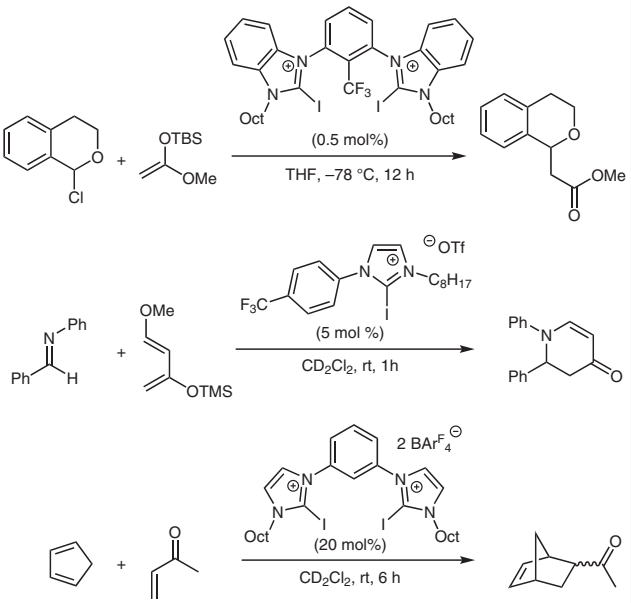
Key words catalysis, DFT calculations, halogen bonding, kinetics, solvent effects

Halogen bonding – the noncovalent interaction between an electrophilic region of a halogen atom and a Lewis base – has enjoyed a tremendous success over the last decade in various fields of chemistry.[1] Within the framework of organocatalysis, Bolm and coworkers were the first to employ 1-iodoperfluoroalkanes as catalysts for the reduction of 2-substituted quinolines with a Hantzsch ester in 2008.[2] Systematic investigations by Huber and coworkers revealed a few years later that halogen-bond-based catalysts (typically polydentate iodinated azolium ions or perfluorinated iodobenzene derivatives) can be employed for the activation of carbon–halogen bonds (Scheme 1).[3] Similar catalyst systems have subsequently also been used for the activation of imines[4] and carbonyl dienophiles (Scheme 1).[5] Recently, Takemoto and coworkers reported on a halogen-bond-catalyzed cross-enolate coupling reaction that yields 1,4-dicarbonyls in high yields.[6] Building on previous investigations on the halogen-bond properties of iodoalkynes,[7] Matsuzawa, Takeuchi, and Sugita relied on electron-deficient iodoalkynes as effective catalysts for the activation of thioamides.[8]

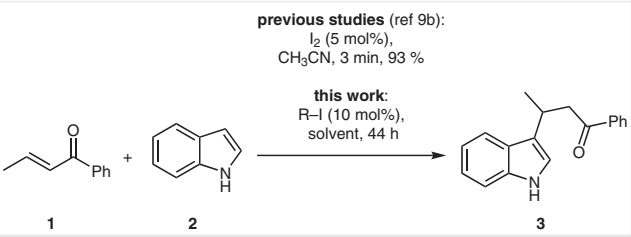


Martin Breugst (left) studied chemistry at the Ludwig-Maximilians-Universität (LMU) in Munich (Germany). He received his Ph.D. in physical-organic chemistry from the LMU Munich under the supervision of Prof. Dr. Herbert Mayr in 2010. Afterwards, Martin moved to the University of California, Los Angeles as a Feodor-Lynen postdoctoral fellow where he worked with Prof. Dr. Kendall N. Houk on different aspects of computational organic chemistry. Since 2013, he has worked at the Department of Chemistry at the University of Cologne as an independent researcher supported by a Liebig scholarship of the Fonds der Chemischen Industrie and completed his habilitation in October 2017. His research interests include noncovalent interactions and the elucidation of reaction mechanisms. **Daniel von der Heiden** (right, M.Sc. from the Westfälische Wilhelms-Universität in Münster) is currently pursuing his Ph.D. with Martin Breugst and is funded through a scholarship of the Fonds der Chemischen Industrie. **Robert Kuchta** (middle left, B.Sc. from the University of Cologne) and **Eric Detmar** (middle right, B.Sc. from the University of Cologne) are working as M.Sc. students in the research

In the light of the success of various halogen-bond donors in catalysis, we have recently analyzed different iodine-catalyzed Michael additions (e.g., Scheme 2) both experimentally and computationally.[9] Based on our investigations, we were able to show that iodine acts as a halogen-bond donor in these reactions and significantly lowers the activation free energies of these transformations. A hidden Brønsted acid catalysis,[10] which is often used as an explanation,[11] could be ruled out experimentally.[9b]



Scheme 1 Selected examples for halogen-bond-catalyzed reactions (BAr^F_4 = $B[3,5\text{-}(CF_3)_2C_6H_3]_4^-$).



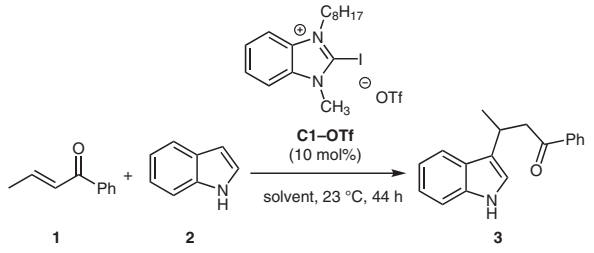
Scheme 2 Michael addition between *trans*-crotonophenone (**1**) and indole (**2**) catalyzed by molecular iodine[9b] and different halogen-bond donors

Building on these findings, we wondered whether iodine can be replaced by other halogen-bond donors in these reactions. Therefore, we have analyzed the catalytic potential of different monodentate halogen-bond donors for the Michael reaction of Scheme 2 between *trans*-crotonophenone (**1**) and indole (**2**). We now report on the results of these investigations and compare their catalytic activities to that of molecular iodine.

We started our experimental investigation with the iodinated benzimidazolium triflate **C1–OTf** in acetonitrile,[12] a solvent that worked best for iodine catalysis.[9b] We employed 10 mol% of the halogen-bond catalyst and monitored the reaction progress by ^{1}H NMR spectroscopy with respect to the internal standard $SiEt_4$ (see the Supporting Information for details).[13]

For all cases discussed below, the yields of the isolated product at the end of the experiments (typically after 44 h) were in very good agreement with those determined from in situ NMR spectroscopy and no alternate reaction products (e.g., double alkylation) could be detected under the reaction conditions. As initially anticipated, the halogen-bond donor **C1–OTf** is also catalytically active and affords **3** in 36 % yield after 44 h (Table 1). However, in comparison to molecular iodine (Scheme 2, 93 % after 3 min), the halogen-bond donor **C1–OTf** is significantly less reactive. Intrigued by this unexpected low reactivity, we next tested the same catalyst in various solvents (Table 1). Generally, almost no background reaction (< 5 % conversion after 44 h) could be observed in the absence of any catalyst.[14] A catalytic effect could be observed in most aprotic solvents, when 10 mol% **C1–OTf** were used. However, almost no product formation could be detected in DMSO and DMF. This effect might be attributed to their higher Lewis basicities compared to the other solvents.[15] A similar effect had already been observed for iodine catalysis[9b] and can be explained by a competing, strong halogen bond between the catalyst and the solvent, deactivating the catalyst. Surprisingly, methanol, a solvent that resulted in a poor yield in the iodine-catalyzed reaction, performs very well for **C1–OTf** (92 % yield). However, all reactions are significantly slower than molecular iodine[9b] indicating that **C1–OTf** is a much weaker catalyst for this transformation.

Table 1 Solvent Dependency of the Reaction between *trans*-Crotonophenone (**1**) and Indole (**2**) Catalyzed by the Iodobenzimidazolium Triflate **C1–OTf**[a]



Entry	Solvent	Yield (%)
1	Ph_2O	97
2	dioxane	97
3	EtOAc	95
4	CD_3OD	93
5	C_6D_6	87
6	DCE	80
7	$CDCl_3$	75
8	CD_2Cl_2	75
9	THF	67
10	CD_3CN	36
11	d_6-DMSO	7[a]
12	DMF	0[a]

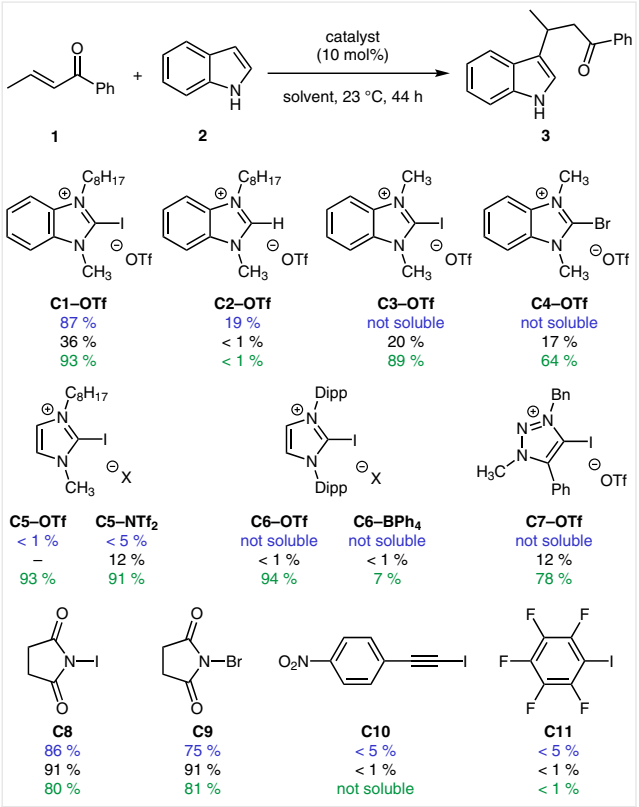
[a] Yield determined by ^{1}H NMR spectroscopy with respect to the standard $SiEt_4$.

In our investigations on iodine catalysis, we were able to experimentally rule out catalysis by traces of Brønsted acids formed by decomposition of molecular iodine.[9b] Similar experiments failed in this investigation, as weak bases such as Na_2CO_3 are ineffective to deactivate acid traces and nonnucleophilic bases lead to catalyst decomposition.[5] However, NMR-spectroscopic investigations reveal that the catalysts are stable in the presence of the reactants (see the Supporting Information) and cause a considerable shift in the ^1H NMR and ^{13}C NMR spectra. At this point, we cannot completely rule out the formation of very small amounts of iodine by partial decomposition of the employed catalysts. However, no change in color of the reaction mixture has been observed which renders iodine formation unlikely.

As iodinated benzimidazolium salts are catalytically active in the Michael addition between **1** and **2**, we subsequently tested other halogenated structures for their activities in this reaction. Due to different solubilities of charged species, we employed three different solvents (C_6D_6, CD_3CN, and CD_3OD) for these experiments. The results are summarized in Scheme 3 and Figure 1. In a control experiment, the noniodinated benzimidazolium salt **C2–OTf** turned out to be significantly less reactive and a slow product formation could only be observed in C_6D_6. Furthermore, the employed counteranions (tested as NaOTf, NBu_4OTf, and NBu_4NTf_2 salts) were completely inactive in both benzene and methanol. The replacement of the octyl substituent to the smaller methyl group (**C3–OTf**) only slightly affects the catalytic activity while the solubility in less polar solvents (e.g., benzene) significantly decreases. As observed before,[2,3g,16] the brominated analogue **C4–OTf** is also catalytically active, but the reaction is significantly slower (Figure 1). However, there are also cases known in which the brominated structures are more reactive than their iodinated counterparts.[3a]

Surprisingly, the iodinated imidazolium ions **C5** and **C6** turned out to be almost unreactive in benzene and acetonitrile (< 12 % yield). Interestingly, these structures remain catalytically active in methanol as also indicated in the kinetic experiments (**C5–NTf$_2$**, Figure 1). When the heterocyclic structure is changed to a triazole system (e.g., in **C7–OTf**), the reaction also takes place but is slightly slower.

Among neutral halogen-bond donors, electron-poor iodoalkynes like **C10** – excellent catalysts for the activation of thioamides[8] – are catalytically inactive in the Michael addition studied here. Similarly, the addition of perfluoroiodobenzene **C11** only results in a very slow product formation. In contrast, *N*-halogenated succinimides **C8** and **C9** are highly active in this transformation and high conversions are already obtained after several minutes (see the Supporting Information for details). However, NMR spectroscopic investigations indicate in these cases that a significant decomposition of the catalysts has taken place until the end of that reaction and the dehalogenated succinimide



Scheme 3 Catalytic activities of different halogen-bond donors in the reaction of *trans*-crotonophenone (**1**) and indole (**2**) in C_6D_6 (blue), CD_3CN (black), and CD_3OD (green); Dipp = 2,6-diisopropylphenyl

might have formed. As a consequence, other pathways have to be discussed for these species in addition to a halogen-bond mechanism (see also below).

To get a better understanding of the underlying reaction mechanism and mode of activation, we monitored the kinetics of the Michael addition in more detail by ^1H NMR spectroscopy and determined the reaction order in the halogen-bond catalyst. Therefore, a series of kinetic experiments with variable catalyst concentrations in both C_6D_6 and CD_3OD under otherwise identical conditions were studied in these solvents. Plotting the logarithm of the initial rate against the logarithm of the catalyst concentration resulted in linear correlations with a slope around 0.5. While this deviation from unity could indicate the formation of dimeric species,[17] another explanation might be more likely. An unfavorable pre-equilibrium, which results from the dissociation of the ion pair to yield the 'free' halogen-bond donor, results in a slope of 0.5.[18] When ion pairing is not possible (e.g., for NIS (**C8**)), a reaction order close to unity can be determined for the halogen-bond catalyst. Therefore, the kinetic investigations indicate that one halogen-bond donor is involved in the rate-limiting transition state and support the initial assumption of a halogen-bond activation.

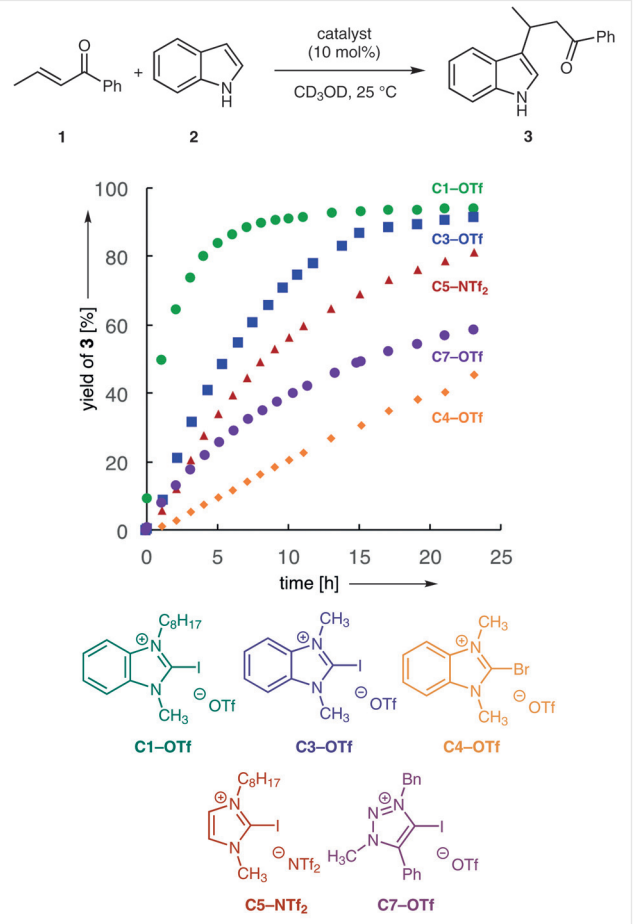
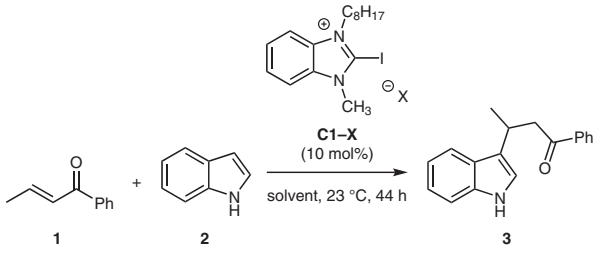


Figure 1 Conversion vs. time profiles for the halogen-bond-catalyzed reaction between *trans*-crotonophenone (**1**) and indole (**2**) in CD_3OD (25 °C)

Based on the results of the kinetic analysis and as different counterions had been used in the preparation of the azolium salts of Scheme 3, we decided to closer analyze how the counteranion affects the catalytic properties of the iodobenzimidazolium catalyst **C1** as a model system. Besides the initially employed trifluoromethylsulfonate (OTf^-), we also relied on other weakly coordinating anions like bis(trifluoromethylsulfonyl)amide (NTf_2^-) and the borates BF_4^-, BPh_4^-, and $BAr^F{}_4^-$ ($B[3,5\text{-}(CF_3)_2C_6H_3]_4^-$). The corresponding salts were either synthesized from the corresponding benzimidazole and Meerwein's salt (Me_3OBF_4) or by anion metathesis from **C1–OTf**. Three solvents with different polarities (C_6D_6, CD_3CN, and CD_3OD, Table 2) were chosen for this analysis, and the results are summarized in Table 2. While the reactivities of the different salts are almost comparable in benzene and methanol, no reactions have been observed in acetonitrile with any anions other than OTf^-. In benzene and methanol, the NTf_2^- and BF_4^- counterions resulted in comparable yields, while the BPh_4^- salt turned out to be unreactive or significantly less reactive in all solvents. Interestingly, the addition of BPh_4 salts significantly reduced the catalytic activity of **C1–OTf** in both benzene and methanol solution. This finding is also in line with the results of the kinetic analysis and indicates the formation of ion pairs under the reaction conditions. This indicates that the interaction between **C1** and the BPh_4^- ion could be stronger than that to the triflate ion.[19]

Table 2 Counteranion Effects of the Reaction between *trans*-Crotonophenone (**1**) and Indole (**2**) Catalyzed by Iodobenzimidazolium Salts **C1–X**



Entry		d_6-Benzene (%)	d_3-CH_3CN (%)	d_4-MeOH (%)
1	**C1–OTf**	87	37	93
2	**C1–NTf_2**	81	< 1	90
3	**C1–BPh_4**	< 1[a]	< 1	17
4	**C1–BF_4**	63	< 1	89
5	**C1–$BAr^F{}_4$**	67	< 1	88

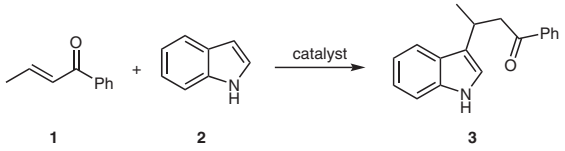
[a] No product formation observed in ^1H NMR spectroscopy after 44 h.

Counterion effects have been observed before for other reactions, but it seems that no general trends can be observed: While the BF_4^- salt is only slightly more effective than the OTf^- salt in the activation of benzhydryl bromide,[3c] the $BAr^F{}_4^-$ salt is significantly more active than the OTf^- analogue in a Diels–Alder reaction.[5] In contrast, for the activation of 1-chloroisochromane, the OTf^- salt is superior to $BAr^F{}_4^-$ and BPh_4^- salts.[3g]

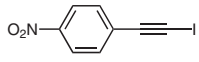
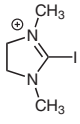
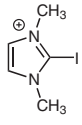
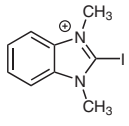
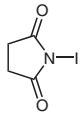
In addition to the experimental investigations described above, we also calculated the influence of selected halogen-bond donors on the activation free energies for this transformation.[20] For the computational investigation, we have analyzed this reaction in the gas phase as well as in benzene and methanol (using the IEFPCM continuum model). In general, the calculated catalytic effects follow the same trend in the gas phase and in solution. As expected from experimental studies on solvent effects of halogen bonds,[17c,21] the calculated catalytic effects were typically largest in the gas phase compared with their values in solution. This again indicates that the solvent has an important influence on the halogen bond, and the results obtained from gas-phase calculations might overestimate the strength of this noncovalent interaction. In addition, specific solvent–solute interactions are not taken into account in continuum models. While all results are summarized in the Supporting In-

formation, for the sake of clarity, we will only discuss the values obtained for benzene solution in the following. These results are summarized in Table 3.

Table 3 Activation Free Energies ($\Delta G^{\ddagger}$) for the Michael Reaction between *trans*-Crotonophenone (**1**) and Indole (**2**) in the Presence of Different Catalysts[a]



1 **2** **3**

Entry	Catalyst	$\Delta G^{\ddagger}$
1	 **C10**	+41.1
2	 **C11**	+41.0
3	 **C12**	+40.7
4	uncatalyzed	+37.9
5	 **C13**	+33.0
6	 **C14**	+32.5
7	 **C3**	31.5
8	 **C8**	+30.3

[a] In kcal mol^{-1}; M06-2X-D3/aug-cc-pVTZ/IEFPCM(benzene)//M06-2X-D3/6-311+G(d,p)/IEFPCM(benzene); aug-cc-PVTZ-PP was used for iodine.

In all cases, very high activation free energies have been calculated. The uncatalyzed reaction proceeds with an activation free energy of +37.9 kcal mol^{-1} in line with no background reaction being observed after prolonged reaction times. Among the computationally employed halogen-bond donors, F_3C–I (**C12**), F_5C_6–I (**C11**), and the iodoalkyne **C10** resulted in higher activation free energies compared to the uncatalyzed reactions (+2.8 < $\Delta\Delta G^{\ddagger}$ < +3.2 kcal mol^{-1}). Despite the stabilizing nature of the halogen bond, the unfavorable entropy term ($-T\Delta S$) compensates this favorable interaction resulting in an overall unfavorable process. In line with these findings, these compounds were also found to be inactive in the experimental studies described above (Scheme 3 and the Supporting Information).

In contrast, the iodinated azolium ions **C3**, **C13**, and **C14** all resulted in a substantial reduction of the activation free energies (–6.4 < $\Delta\Delta G^{\ddagger}$ < –4.9 kcal mol^{-1}). However, the calculated activation free energies are still substantially large indicating that the calculations might underestimate the strength of the halogen bond.[8] Qualitatively, the computed results are in line with the long reaction times. Furthermore, the benzimidazole catalyst is also calculated to be the most active iodinated azolium ion. By far, the most active halogen-bond donor in the computational investigation is *N*-iodosuccinimide which lowers the activation free energy by 7.6 kcal mol^{-1}. NIS (**C8**) is also the most active catalyst in the experimental investigations. This value is also close to the previously calculated catalytic activity of molecular iodine ($\Delta\Delta G^{\ddagger}$ = 7.6 kcal mol^{-1}) using a slightly different computational method.[9b] However, in the case of NIS, a significant decomposition to the nonhalogenated succinimide was also observed at the end of the reaction. Therefore, we additionally examined whether the transfer of an I^+ atom to the Michael acceptor **1** could be an alternate explanation (Scheme 4). However, the dissociation of the corresponding C–I (in the azolium salts) or N–I bond (in NIS) resulted in highly endergonic intermediates (ΔG > 50 kcal mol^{-1}, Scheme 4). As a consequence, this alternative seems to be less likely.

1 **C3**, **C13**, or **C14**

C3: ΔG = +63.7 kcal mol^{-1}
C13: ΔG = +67.8 kcal mol^{-1}
C14: ΔG = +66.7 kcal mol^{-1}

Scheme 4 Calculated free energies for the transfer of an iodine atom to the Michael acceptor **1** in benzene solution

In summary, we were able to show that molecular iodine can be replaced by other halogen-bond donors as catalyst in the Michael reaction between *trans*-crotonophenone and indole. These results show that neutral electrophiles

can be activated for a subsequent nucleophilic attack by halogen-bond donors. Therefore, these findings will turn out useful in the development of more active (and ideally chiral) catalysts in the field of halogen bonding.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591841.

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(12) **C1–OTf** was synthesized from 2-iodo-1-octylbenzimidazole (1.0 equiv) and methyl triflate (1.2 equiv) as described in the Supporting Information. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.86 (t, $^3J_{HH}$ = 6.3 Hz, 3 H), 1.26–1.43 (m, 10 H), 1.90 (quint, $^3J_{HH}$ = 7.5 Hz, 2 H), 4.16 (s, 3 H), 4.49 (t, $^3J_{HH}$ = 7.6 Hz, 2 H), 7.56–7.63(m, 2 H), 7.70–7.75 (m, 1 H), 7.82–7.87 (m, 1 H). ^{13}C{apt} NMR ($CDCl_3$, 75 MHz): δ = 14.1 (s), 22.6 (s), 26.7 (s), 29.1 (s), 29.2 (s), 29.3 (s), 31.7 (s), 36.9 (s), 50.6 (s), 112.0 (s), 112.7 (s), 13.4 (s), 120.6 (d, $^1J_{CF}$ = 320.4 Hz), 127.3 (s), 127.4 (s), 133.2 (s), 134.2 (s). IR (neat, ATR): $\tilde{\nu}$ = 2928 (w), 2857 (w), 1479 (w), 1028 (s), 747 (m), 637 (s) cm^{-1}. ESI-HRMS: *m/z* [M]$^+$ calcd for $C_{16}H_{24}N_2I^+$: 371.0979; found: 371.0976. Anal. Calcd for $C_{17}H_{24}F_3IN2O_3S$: C, 39.24; H, 4.65; N, 5.38. Found: C, 39.31; H, 4.91; N, 5.16.

C5–OTf was obtained from 2-iodo-3-methyl-1-octylimidazolium bromide (1.0 equiv) by anion metathesis with NaOTf (1.5 equiv) in CH_2Cl_2/H_2O. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88 (t, $^3J_{HH}$ = 6.8 Hz, 3 H), 1.23–1.39 (m, 10 H), 1.84 (quint, $^3J_{HH}$ = 7.2 Hz), 3.95 (s, 3 H), 4.17 (t, $^3J_{HH}$ = 7.5 Hz, 2 H), 7.57 (d, $^3J_{HH}$ = 2.0 Hz, 1 H), 7.73 (d, $^3J_{HH}$ = 2.0 Hz, 1 H). ^{13}C{apt} NMR ($CDCl_3$, 125 MHz): δ = 14.2 (s), 22.7 (s), 26.4 (s), 29.1 (s), 29.1 (s), 31.8 (s), 30.5 (s), 39.9 (s), 53.1 (s), 103.1 (s), 120.8 (q, $^1J_{CF}$ = 320 Hz), 124.9 (s), 126.7 (s). ^{19}F{^{1}H} NMR ($CDCl_3$, 376 MHz) δ = –78.2 (s), –78.4 (d, $^1J_{F13C}$ = 320 MHz). IR (neat, ATR): $\tilde{\nu}$ = 3107 (w), 2926 (w), 2857 (w), 1568 (w), 1497 (w), 1456 (w), 1246 (s), 1223 (m), 1153 (s), 1028 (s), 756 (w), 665 (w), 637 (s) cm^{-1}. ESI-LRMS: *m/z* (%) = 321.0 (100) [**C5**]$^+$ 320.8 (20) [Na(OTf)$_2$]$^-$, 148.9 (100) [OTf]$^-$. ESI-HRMS [**C5**]$^+$: *m/z* calcd for $C_{12}H_{22}N_2I^+$: 321.0822; found: 321.0821.

(13) **Typical Experimental Procedure**

A stock solution (1.00 mL) containing the reactants **1** and **2** as well as the internal standard $SiEt_4$ was added to the pure catalyst in an NMR tube. This resulted in approximate concentration of 50 mM in the catalyst, 500 mM in the reactants, and 125 mM in the standard. The course of the reaction was followed by ^{1}H NMR spectroscopy. If a reasonable amount of product was observed in the final NMR spectrum, the reaction was deactivated with 100 µL DMSO. Within 2 h, all volatile residues were removed under reduced pressure, and the product was isolated by column chromatography (SiO_2, cyclohexane/EtOAc = 9:1 (v/v), R_f = 0.11) as an off-white solid.

Analytical Data for Compound 3

103–104 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz): δ = 1.42 (d, ^3J = 6.9 Hz), 3.23 (dd, ^3J = 8.5 Hz, ^2J = 16.5 Hz, 1 H), 3.44 (dd, ^3J = 5.4 Hz, ^2J = 16.4 Hz, 1 H), 3.73–3.84 (m, 1 H), 6.97 (d, ^3J = 2.2 Hz, 1 H), 7.04–7.16 (m, 2 H), 7.31 (d, ^3J = 8.0 Hz, 1 H), 7.41 (t, ^3J = 7.5 Hz, 2 H), 7.52 (t, ^3J = 7.4 Hz 1 H), 7.63 (d, ^3J = 7.8 Hz, 1 H), 7.91–7.93 (m, 2 H), 8.12 (br s, 1 H). ^{13}C{^{1}H} NMR (CD_2Cl_2, 75.5 MHz): δ = 21.4 (s), 27.5 (s), 46.8 (s), 111.7 (s), 119.5 (s), 119.5 (s), 120.7 (s), 121.7 (s), 122.2 (s), 126.8 (s), 128.4 (s), 128.9 (s), 133.3 (s), 137.0 (s), 137.8 (s), 200.0 (s). IR (neat, ATR): $\tilde{\nu}$ = 3352 (m), 3057 (w), 2982 (w), 2961 (w), 2872 (w), 1667 (s), 1618 (w), 1593 (w), 1489 (w), 1445 (m), 1339 (m) 1215 (s), 999 (m), 745 (s), 60 (m) cm^{-1}. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{18}H_{18}NO^+$: 264.1383; found: 264.1384.

(14) Slightly higher values (up to 10 %) could be detected for $CDCl_3$ and CH_2Cl_2.

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