Activation of a metal-halogen bond by halogen bonding

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Abstract: In recent years, the non-covalent interaction of halogen bonding (XB) has found increasing application in organocatalysis. However, reports of the activation of metal-ligand bonds by XB have so far been limited to a few reactions with elemental iodine or bromine. Herein, we present the activation of metal-halogen bonds by two classes of inert halogen bond donors and the use of the resulting activated complexes in homogeneous gold catalysis. The only recently explored class of iodo(III) derivatives were shown to be effective activators in two test reactions and their activity could be modulated by blocking of the Lewis acidic sites. Bis(benzimidazolium)-based halogen bonding activators provided even more rapid conversion, while the non-inodinated reference compound showed little activity. The role of halogen bonding in the activation of metal-halogen bonds was further investigated by NMR experiments and DFT calculations, which support the mode of activation occurring via halogen bonding.

Halogen bonding (XB) describes the non-covalent interaction between electrrophilic halogen substituents and Lewis bases. Its high directionality, tunability and complementarity to hydrogen bonding (HB) has led to frequent use of XB in the solid state, especially with numerous applications in crystal engineering. Increasingly, the use of halogen bonding has also expanded into solution chemistry, with a multitude of reports on anion recognition and the construction of supramolecular assemblies.

Previously: 

This work: 

enhanced reactivity 

enhanced reactivity

Figure 1. Schematic view of activation of C-X and M-X bonds by halogen bonding.

Figure 2. Overview of halogen bond donors and related reference compounds applied in this study.

In the last decade, halogen bonding has also been established in organocatalysis, with an ever increasing number of organic reactions reported which are promoted by XB donors. In many of these cases, halide leaving groups were abstracted from organohalogen compounds in order to facilitate nucleophilic substitution reactions (Figure 1, left). At this time, multiple classes of halogen bonding catalysts have been established and applied to different types of organic reactions, including monodentate or multidentate neutral as well as cationic iodo(III)-based XB donors, and also recently, iodo(III) derivatives. Lately, a first example has also been reported in which enantioselectivity in a Mukaiyama aldol reaction was induced by a chiral halogen bond donor devoid of any further coordinating groups.

The application of halogen bonding in transition metal chemistry has yet mostly been limited to halogen bonding ligands which induce organization of the ligand sphere. Halogen bonds to halide ligands as well as numerous other Lewis basic ligands in metal complexes have been observed for inorganic and organic halogen bond donors. Beyond coordination of these ligands by halogen bonding, only a handful of instances exist, in which ligand exchange is observed. In these cases, elemental iodine or bromine were used as halide exchange reagents: even though intermediary halogen bonding was postulated, in the progress of the reaction the I-I or Br-Br bonds were cleaved. The transfer of the concept of C-X activation to M-X bonds using inert XB donors has, to the best of our knowledge, not yet been realized (Figure 1, right).

Herein, we present the first example of such, in two gold-catalyzed reactions which are accelerated in the presence of two separate classes of halogen bond donors via Au-Cl bond activation. In this study, the scarcely explored class of halogen bonding catalysts based on an iodo(III) (cyclic diaryliodonium) motif, 1 and 2, are utilized (Figure 2). Additionally, the tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (BARF4) (4a), triflate (4b), and the newly synthesized hexafluorophosphate (4c) salts of the previously tested, highly preorganized bis(benzimidazolium) halogen bond donor 4b were investigated.
As first test reaction, the gold(I)-catalyzed cyclization of propargylic amide 6 to the oxazoline 7 was chosen (Scheme 1). This reaction has previously been used to benchmark catalyst activity and the effectiveness of added activators in homogenous gold catalysis.\textsuperscript{[29]-[32]} The reaction was performed with 2 mol% of chlorotriphenylphosphine gold and an equimolar amount of the halide abstracting agent in deuterated chloroform as solvent.

Table 1. Cyclization of 6 in the presence of activators and reference compounds.

| Entry | Activator\textsuperscript{a} | Conversion\% of 6 [%] | $k_{cat}$/[\textsuperscript{b}] |
|-------|-----------------------------|----------------------|-----------------------------|
| 1     | None                        | ≤5                    | /                           |
| 2     | 1a\textsuperscript{c}       | 60                    | 1100                        |
| 3     | 1b                          | ≤5                    | 10                          |
| 4     | 2a\textsuperscript{c}       | 38                    | 660                         |
| 5     | 2b                          | ≤5                    | 3                           |
| 6     | 3a                          | ≤5                    | 1                           |
| 7     | 3b                          | ≤5                    | /                           |
| 8     | 4a                          | 92                    | 3100                        |
| 9     | 4b                          | ≤5                    | 18                          |
| 10    | 4c                          | 25                    | 330                         |
| 11    | 5a                          | ≤5                    | 26                          |
| 12    | NaBAR\textsubscript{4}      | 95                    | 3500                        |
| 13    | TMABAr\textsubscript{4}     | ≤5                    | 15                          |
| 14    | AgOTf                       | 5                     | 100                         |
| 15    | AgBF\textsubscript{4}       | 14                    | 180                         |
| 16    | AgPF\textsubscript{6}       | 44                    | 740                         |
| 17    | I\textsubscript{3}\textsuperscript{c} | ≤5  | /                           |
| 18    | I\textsubscript{2}\textsuperscript{c} | ≤5  | /                           |

\[a\] Activators added in 2 mol% unless indicated otherwise. \[b\] Conversion determined by \textsuperscript{1}H NMR after 3 hours of reaction time, unless indicated otherwise. An error margin of -5% is assumed. All experiments were reproduced at least twice. \[c\] Relative initial rates after 70 minutes of reaction time, referenced to 3a (and rounded to two valid digits). \[d\] 30 hours reaction time. \[e\] The propargylic amide 6 was added to a preformed solution of the activator and the gold complex. \[f\] Added in 1 mol%. \[g\] Added in 1 mol%. 

Due to the subsequent slow aromatization of 7 to the corresponding oxazole\textsuperscript{[32]} (cf. Figure S1), for accuracy, only the conversion of the starting material is considered, the extent of which could be monitored by \textsuperscript{1}H NMR spectroscopy. Without the presence of any halide-abstracting agent, the reaction shows no background reactivity after more than 30 hours (Table 1, Entry 1). In contrast, addition of iodolium salt 1a results in 60% conversion after only 3 hours of reaction time (Table 1, Entry 2) and almost quantitative conversion is reached after 12 hours (Figure 3, yellow curve). Reference experiments showed no reaction when the activator was added with no gold complex present. Accordingly, doubly methylated halogen bond donor 2a showed the expected diminished activity, with only 38% conversion after 3 hours (Table 1, Entry 4; see also Figure 3, red curve). Gratifyingly, the doubly blocked iodolium salt 3a showed only little activity, with less than 5% conversion after 12 hours (Table 1, Entry 6). These results point to the mechanism of activation occurring via halogen bonding as the blockage of electrophilic axes results in markedly diminished activity. Initial rate accelerations for the iodolium salts revealed that 2a results in an acceleration of $k_{cat}$ = 657 relative to the fully blocked compound 3a; conversely, the completely unblocked XB donor 1a provides almost double the initial rate of 2a (Table 1, Entries 2, 4, and 6). The analogous triflate salts 1-3b all showed poor activity, with only slight conversion noticeable after 3 hours and comparatively poor rate accelerations (Table 1, Entries 3, 5, and 7). 

This counterion-rate dependence is likely due to the need for a weakly coordinating anion under these reaction conditions, as the addition of the strong halide abstracting agent silver triflate only results in 13% conversion after 12 hours. In comparison, the analogous silver tetrafluoroborate and hexafluorophosphate salts provided markedly increased conversions in the same time (87% and >95%, see SI; compare also Table 1, Entries 14-16). It is important to note, however, that rapid conversion was also reached by the addition of NaBAR\textsubscript{4}, likely due to the strong driving force of NaCl formation; almost complete (95%) conversion was obtained after only 3 hours of reaction time (Table 1, Entry 12). Therefore, possible activity of the BAR\textsubscript{4} anion itself was additionally tested by the addition of TMABAr\textsubscript{4}, which resulted only in trace amounts of conversion, even after 12 hours of reaction time. This result, combined with the inactivity of 3a, suggests that the observed activity in the cases of the iodolium compounds stems from the unblocked electrophilic axes on the iodine atom and thus, halogen bonding interactions.

With these promising results in hand, the highly preorganized bis(benzimidazolium)-based halogen bond donor 4a was tested

![Scheme 1. Au-catalyzed cyclization of amide 6 to oxazole 7.](image)

Figure 3. Kinetic plot for the reaction of amide 6 in the presence of various activators.
and showed exceptional activity, with 92% conversion after 3 hours and almost quantitative product formation after 8 hours of reaction time. The initial rate acceleration with 4a was almost triple that of iodolum salt 1a (Table 1, Entry 8; see also Figure 3, dark blue curve).

Scheme 2. Au-catalyzed cyclization of malonate ester 8.

This observation agrees with previous results,[11] in which iodolum salts were at times outperformed by a bidentate, dicationic XB donor; this highlights again the exceptional activity of this preorganized structural motif. The stability of 4a during the reaction could be followed by 19F NMR: no visible decomposition was observed after several hours of reaction time (see SI). To exclude the effect of possible undetected decomposition of the XB donors, molecular iodine was tested in the reaction as a possible decomposition product. Addition of 1 mol% of I2 yielded no conversion and even 1 mol% of I2, which would result from complete decomposition of the halogen bond donor, showed no activity. Unsurprisingly, the trflate salt 4b exhibited similar inactivity to the iodolum salts 1-2b. (Table 1, Entry 9).

Table 2. Cyclization of 8 in the presence of 1 mol% of activators and reference compounds.

| Entry | Activator[a] | Yield[bb] of 9a/b [%] | krel[c] |
|-------|--------------|----------------------|---------|
| 1     | None         | ≤5                   | /       |
| 2     | 1a           | 76                   | 740     |
| 3     | 1b           | ≤5                   | 14      |
| 4     | 2a           | ≤5                   | 10      |
| 5     | 2b           | ≤5                   | 1       |
| 6     | 3a           | ≤5                   | 10      |
| 7     | 3b           | ≤5                   | 10      |
| 8     | 4a           | 83                   | 830     |
| 9     | 4b           | ≤5                   | 3       |
| 10    | 5a           | ≤5                   | 41      |
| 11    | NaBARa4      | 84                   | 850     |
| 12    | TMABAr4      | ≤5                   | 5       |

[a] Activators added in 1 mol%. [b] 1H NMR yield of 9a/b after 40 minutes of reaction time, unless indicated otherwise. An error margin of ~5% is assumed. All experiments were reproduced at least twice. [c] Relative initial rates after 20 minutes of reaction time, referenced to 3a (and rounded to two valid digits). [d] 15 hours reaction time.

The hexafluorophosphate salt 4c however, which could be synthesized by simple anion exchange from 4b, showed markedly increased activity compared to the triflate salt, with 25% conversion after 3 hours of reaction time (Figure 3). This compound, however, suffers from poor solubility in chloroform, which limits the direct comparison with the analogous 4a and 4b. To probe the nature of the activation with 4a further, reference compound 5a was synthesized; the latter is structurally analogous to 4a, but incapable of halogen bonding (Figure 2). Expectedly, this salt showed drastically lower activity, with almost no conversion during the first 3 hours of reaction time (Table 1, Entry 11). It is interesting to note, however, that some activity is observed with longer reaction times; as much as 18% conversion is achieved after 12 hours of reaction time (Figure 3, orange curve). The mechanism behind this activation needs to be investigated further but is unlikely to be related to the XB activation observed for compound 4a, especially when considering the drastic differences in the initial rate accelerations (Table 1, cf. Entries 8 vs 11).

As a whole, the presented results constitute, to the best of our knowledge, the first application of cationic XB donors as inert activators in transition metal catalysis and show the compatibility of these compounds with complex reaction systems. We also tested the halogen bonding activators in the gold-catalyzed cycloisomerization of 1,6-ene 8 (Scheme 2). This reaction forms a mixture of the cyclic products 9a and 9b, which for all tested activators were obtained in a ratio of approximately 85:15 in favor of the 5-membered cyclic product 9a (see Figure S5). Since this rearrangement is believed to proceed through cyclopropyl gold carbene species, its efficacy underlines that halogen bonding activation is beyond generating simple Lewis acidity.[33-35] In this case, only negligible background reaction is observed in the absence of any halide abstracting agent, effecting less than 5% yield after 15 hours of reaction time (Table 2, Entry 1 and Figure 4).

Addition of 1 mol% of iodolum salt 1a resulted in 76% combined yield of products 9a/b after only 40 minutes of reaction time (Table 2, Entry 2). The partially hindered XB donor 2a again showed diminished activity, with only 43% yield in comparable reaction time (Table 2, Entry 4). The inactivity of the tetramethylated salt 3a was confirmed again; a negligible yield was observed after 5 hours of reaction time (Table 2, Entry 6). The relative rate acceleration of 1a proved to be almost double that of 2a, with both compounds being vastly more active than 3a (Table 2, Entries 2,
The parallel results obtained for two homogenous gold-catalyzed reactions and two separate classes of XB donors thus strongly indicate that the mode of activation occurs via halogen bonding. Further insight into the activation of the gold chloride complex was sought by NMR experiments. $^{31}$P NMR spectroscopy could be utilized to track the phosphorus shift of the triphenylphosphine ligand on the gold complex used in the catalysis experiments. For the addition of AgOTf to (PPh$_3$)$_2$AuCl, a shielding of the phosphine signal has been reported.\textsuperscript{[63]-[67]} When NaBAR$_2^{−}$ is added however, a significant deshielding occurs, with a signal at 45.2 ppm being observed (Figure 5, b). This signal has commonly been attributed to an (Au(PPh$_3$)$_2$)$^{+}$ species\textsuperscript{[34]-[38]} and indicates significant dissociation of the Au-Cl bond.\textsuperscript{[39]}

When a 1:1 mixture of XB donor 4a and (PPh$_3$)$_2$AuCl was prepared, the same shift could be observed (Figure 5, c). This result demonstrates again the observed activation of the Au-Cl bond, which could be applied in the reactions demonstrated. Finally, DFT calculations (M06-2X\textsuperscript{[45]}-D3\textsuperscript{[46]} def2-TZVP(D)\textsuperscript{[47]} with and without intrinsic solvation using SMD18\textsuperscript{[48]} with parameters for chloroform) were performed to obtain a first molecular picture of the interaction of the strongest XB donor 4a with the gold complex. In both cases, corresponding bidentate halogen bonded adducts were obtained as minima, the formation of which was predicted to be favorable by 27 kcal/mol (in the gas phase) or 5 kcal/mol (in chloroform). The Au-Cl bond length was elongated in both adducts compared to the isolated complex (2.42 Å vs. 2.32 Å in the gas phase and 2.41 Å vs. 2.37 Å in chloroform), in line with an activation of this bond by the XB donor. The further fate of the activated gold species will involve complex equilibria (leading to (Au(PPh$_3$)$_2$)$^{+}$, see above), the modelling of which is outside the scope of this paper.

In conclusion, two proof-of-principle reactions were presented, in which significant activation of a metal-halogen bond was effected by halogen bond donors. Two classes of XB donors were shown to be efficient activators in homogenous gold catalysis, including one of the first applications of iodolium-based XB donors. The activities of the tested activators agreed well with previously established trends. Different reference experiments were conducted for both classes of XB donors, which strongly suggest that halogen bonding is crucial to the activation observed.\textsuperscript{[31]}P NMR experiments strongly suggest activation of the Au-Cl bond, while computational results support the favorable interaction between the gold complex and halogen bond donors. These initial results for gold-catalyzed reactions show promise that the activation presented in this study can be expanded to more systems in transition metal catalysis. Halogen bond donors could present unique and desirable reactivity profiles for this type of activation.

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The activation of a gold-chloride complex by halogen-bonding-based Lewis acids is described as the first case of metal-ligand bond cleavage by inert halogen bond donors. Iodine(I) and iodine(III) derivatives provided excellent performance in two proof-of-principle reactions. Comparative experiments for both activators strongly suggest halogen bonding as the mode of activation.