Highly Enantioselective Organocatalysis with Bidentate Halogen Bond Donors

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Abstract: As the employment of ”non-classical” non-covalent interactions like halogen bonding (XB) in asymmetric catalysis is still at a very early stage, there are significant challenges to overcome. In some reported cases, the relevance of halogen bonding to the catalytic action is unclear, while in others, catalyst activity is limited. Herein, we present the second generation of a bidentate iodine(I)-based halogen bond donor as a modifiable and highly active chiral halogen bonding catalyst. With these modified derivatives, high stereocontrol of up to 98% *ee* could be achieved in a model Mukaiyama aldol reaction for a range of different substrates. Importantly, the crucial role of halogen bonding in this catalytic process was demonstrated by the low performance of the non-iodinated variants.

Over the course of the last few decades, the non-covalent interaction of halogen bonding (XB)[1,2] has risen from being somewhat of an obscurity to an almost routine concept in many applications, e.g. in crystal engineering,[3] biomolecular and medicinal chemistry,[4] as well as in the supramolecular recognition of Lewis bases (LB) in solution.[5] Further research has also demonstrated the potential of halogen bond donors to facilitate organic reactions, providing intriguing alternatives to established organocatalysts.[6]

While a large variety of reactions[7] have by now been catalyzed or activated by XB donors, achieving asymmetric induction with this interaction remains difficult. The intrinsic characteristics of halogen bonding, namely the high directionality of the R-X--LB interaction as well as a large distance of the substrate to the (chiral) catalyst backbone, present significant challenges for the development of effective enantiocontrol. Consequently, successes in this area have only started to emerge in the last five years.

In 2020, our group introduced a chiral bis(imidazolium) based catalyst (**1**$^{\mathbf{BArF}}$), which achieved only moderate enantioselectivity in a Mukaiyama aldol reaction (Figure 1).[8] Later in the same year, Garcia-Mancheño and coworkers disclosed the application of a neutral, tetradentate iodotriazole-based system for anion binding catalysis, with similarly limited selectivity.[9] However, in 2023, they could achieve enantiomeric excesses of up to 90% *ee*, albeit only with particular substrates that featured additional electrophilic sites.[10]

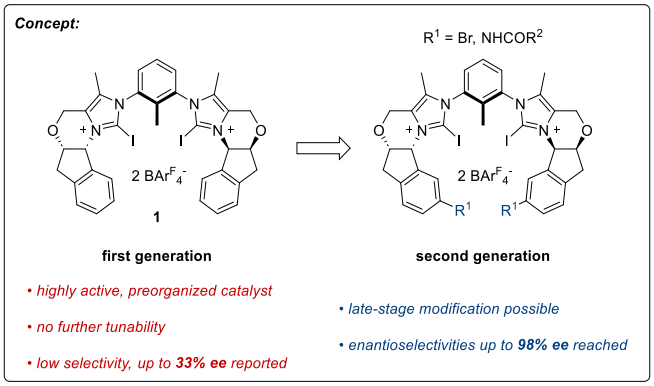
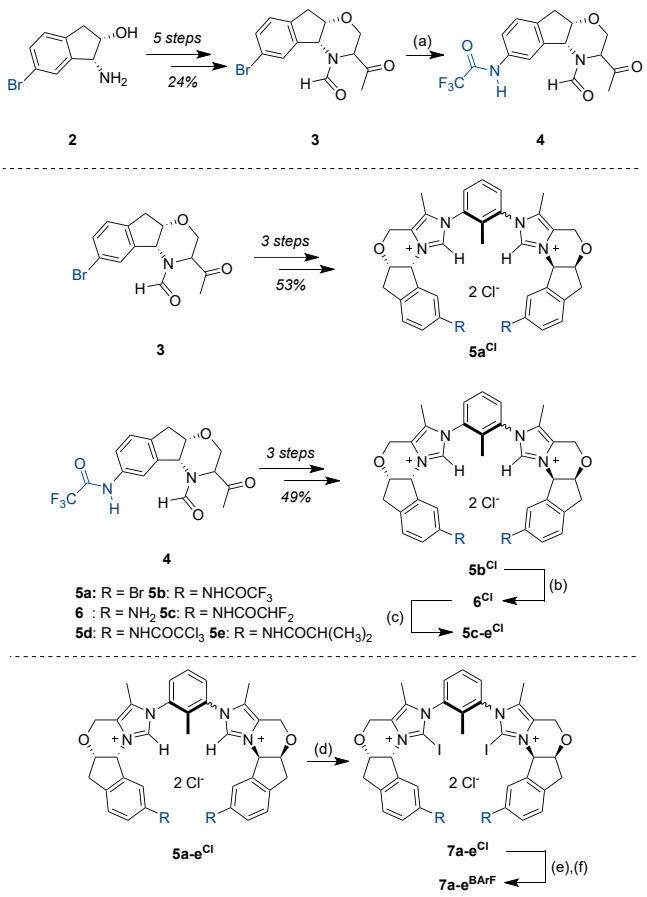


Figure 1. Previously reported (left) and modifiable second-generation (right) chiral halogen bonding catalysts for effective enantioinduction.

In addition, Yoshida and coworkers have reported several examples, in which bifunctional halonium(III) salts act as potent and enantioselective catalysts in the reaction of isatin derivatives with various nucleophiles. Halogen bonding, however, seems to play a more complementary role in these cases.[11] High enantiomeric excesses in the same reaction have very recently been presented by Nachtsheim in a preliminary report,[12] using a monodentate iodine(III) derivative.

Thus, there is currently still no precedence on the highly enantioselective activation of unbiased substrates by iodine(I)-based catalysts, or bidentate ones in general, in which halogen bonding acts as the key driving force (“engine”). Herein, we present a first such example, in which a more potent modifiable variant of our previous catalyst motif **1**$^{\mathbf{BArF}}$ induces enantioselectivities of more than 90%.

To this end, we reasoned that in the synthesis of a modifiable catalyst system, the derivatization of a common precursor should occur as late as possible. Due to the tolerance to different reaction conditions and a plethora of possibilities for later derivatization, the easily accessible[13] (1*R*,2*S*)-1-Amino-6-bromo-indan-2-ol (**2**) was thus chosen as starting point (Scheme 1).



Scheme 1. Synthesis of chiral halogen bond donors. Reaction conditions: a): F_3CCONH_2, K_2CO_3, CuI (cat.), DMEDA (cat.), 1,4-dioxane, 80°C, 45 h, 75%. b): K_2CO_3, MeOH/H_2O (1:1), r.t., 14 h, 85%. c): $Acyl_2O$, EtOAc, r.t., 18 h, 65-93%. d): NIS, MeCN 50°C to 40°C, 2 h. e): NaOTf, MeCN/MeOH (4:1), r.t., 16 h, 70-81% over two steps. (f): $NaBAr^F{}_4$, acetone, 42°C, 2.5 h, 86-98%.

From here, the transformation in 5 steps to the *N*-formyl methyl ketone **3** was achieved in 24% yield, based on established procedures (see SI).[14] This ketone was then used to form the corresponding bis(imidazolium) species **5a^{Cl}** (Scheme 1) in 53% yield in a one-pot process over three steps, analogously to the methods developed for the synthesis of **1^{BArF}**.

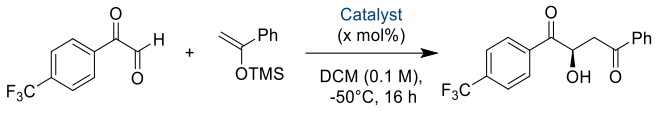
As derivatization of this imidazolium intermediate proved difficult in orientating studies, further modification was already undertaken at the stage of the more robust ketone **3**. Here, an Ullmann-type coupling[15] introduced a trifluoroacetamide moiety as an anchor point, which allows for later modifications under mild conditions. With the resulting intermediate **4** in hand, the transformation into bis(imidazolium) derivative **5b^{Cl}** was possible with 49% yield over 3 steps. After cleavage of the trifluoroacetamide, the widely functionalizable aniline **6^{Cl}** was obtained in 85% yield, which should allow late-stage modification. As an initial set of derivatives, amides like **5c-e^{Cl}** were targeted: they provide a stable linkage of the new substituents and offer a direct comparison to the original structure **5b^{Cl}**. All these compounds were then smoothly transformed into halogen bond donors using *N*-iodosuccinimide (NIS). Stepwise anion exchange and (partial) separation of atropisomers resulted in strong, functionalized halogen bond donors **7b-e^{Cl}**. Separation of atropisomers initially proved difficult and a mixture was typically obtained. All screening experiments reported in the following were consequently conducted with these mixtures, in which very likely only the *syn*-atropisomer will be the active species. A comparison of the enantiomeric excesses of the different catalysts should still be valid, as was later confirmed for **7b^{BArF}** once the clean "*syn*"-isomer could be obtained (see below). The obtained yields, however, can only be considered an estimate of catalyst performance, as the active *syn*-atropisomer is "diluted" to different degrees with the corresponding *anti*-isomer. Similar procedures for iodination and anion exchange were also applied for bromide species **5a^{Cl}**, resulting in XB catalyst structure **7a^{BArF}**. In order to determine the relevance of halogen bonding in relation to possible additional hydrogen bonding from the catalyst backbone, the hydrogen-bearing analogues **5a^{BArF}** and **5b^{BArF}** were also prepared (see SI).

With this starting batch of modified, bidentate halogen bond donors in hand, we tested their performance in the asymmetric Mukaiyama aldol reaction of aryl glyoxals, for which we had previously attained only moderate enantioselectivity. As model substrate we chose the little-explored[16] trifluoromethyl-bearing variant **8** (Table 1, top), which allows for facile reaction monitoring *via* ^{19}F NMR. During orientating studies, the use of water-free aryl glyoxals proved crucial for high selectivity and conversion, however the monomeric aryl glyoxals are prone to oligomerization, resulting in lowered yields. Nevertheless, after some optimization for this substrate, the product could be obtained in well reproducible enantioselectivities and acceptable yields.

With 5% catalyst loading, after 16 hours at -50°C, non-substituted catalyst **1^{BArF}** provided product **10a** in acceptable enantioselectivity of 67% *ee*, while the bromide substituted catalyst **7a^{BArF}** already yielded a higher selectivity of 77% *ee* (Table 1, entries 1 and 2). Another marked jump in stereocontrol was observed with the trifluoroacetamide moiety of **7b^{BArF}**, resulting in excellent 94% *ee* (Table 1, entry 3). To the best of our knowledge, this represents the first organocatalytic approach to achieve 90%+ *ee* in such aldol reactions.[17] The comparably low difference in enantiomeric excess between bromine- and amide-substituted donors **7a^{BArF}** and **7b^{BArF}** indicates that the key enantioinduction is exerted by the catalyst backbone, while the hydrogen-bonding amide plays more of an assisting role. Fortuitously, from these experiments the aldol product crystallized in enantiomerically pure form, and its configuration could be determined as (*R*)-**10a** (see SI).[18]

The structurally similar, but marginally less sterically demanding catalyst **7c^{BArF}** showed similar activity, with a yield of 46% after 16 h, and a slightly reduced selectivity of 91% *ee* (Table 1, entry 4). Derivative **7d^{BArF}**, which offers more steric bulk compared to **7b^{BArF}**, also provided lower enantioselectivity (81% *ee*, Table 1, entry 5), indicating a good steric match for the parent derivative **7b^{BArF}**. Interestingly, XB donor **7e^{BArF}** with its more electron-rich isobutyramide moieties performed poorly, with only 9% of aldol product obtained after 16 h (Table 1, entry 6). Comparison with the results obtained for the non-amide substituted catalysts **1^{BArF}** and **7a^{BArF}** indicates that the electron-rich isobutyramide moieties appear to be detrimental to catalytic activity, resulting in drastically lower yields and selectivity for **7e^{BArF}**.

Table 1. Examination of XB catalysts, related reference compounds and reaction conditions in a Mukaiyama aldol reaction.[a]



8 **9** **10a**

Entry	Catalyst	Catalyst loading [mol%]	Yield [%][b]	*ee* [%][c]
1	**1**^{BArF}	5	51	67
2	**7a**^{BArF}	5	51	77
3	**7b**^{BArF}	5	45	94
4	**7c**^{BArF}	5	46	91
5	**7d**^{BArF}	5	29	81
6	**7e**^{BArF}	5	9	11
7	**5a**^{BArF}	5	6	13
8	**5b**^{BArF}	5	12	< 2
9	**7b**^{BArF}	2.5	25	94
10	**7b**^{BArF}	10	50	94
11[d]	**"*syn*"-7b**^{BArF}	5	63	94
12[d]	**"*syn*"-7b**^{BArF}	1.7	50	94
13[d]	**"*syn*"-7b**^{BArF}	0.8	43	93

[a] All reactions were conducted on a 0.09 mmol scale, using dry CH_2Cl_2 under argon atmosphere, employing 2 eq. of silyl enol ether **9**. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] A single catalyst atropisomer was used.

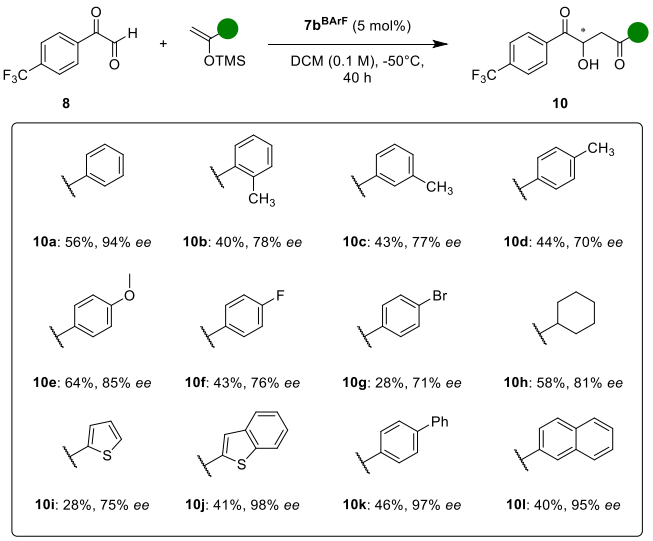
The role of halogen bonding in both the activity as well as the selectivity of the catalyst was then further probed by the application of the non-iodinated reference compounds **5a**^{BArF} and **5b**^{BArF}. The bromine-substituted hydrogen bond donor **5a**^{BArF} yielded 6% of product with an enantiomeric excess of only 13%, and the trifluoroacetamide derivative **5b**^{BArF} generated 12% of racemic product (Table 1, entries 7 and 8).

All these findings clearly indicate that halogen bonding is the key interaction in this catalysis, not only in the activation of the substrate but also as essential driving force for strong asymmetric induction. The low yields observed for **5a**^{BArF} and **5b**^{BArF} are possibly the result of hydrogen bonding activation.

Further variation of the reaction conditions for the best catalyst **7b**^{BArF} did not yield noticeable improvements: while a catalyst loading of 10% resulted in an only marginally improved amount of product, a considerably reduced yield was obtained with 2.5 mol%. In both cases, the same excellent stereoselectivity was still observed (Table 1, entries 9 and 10). As stated above, all experiments described so far were conducted with mixtures of *syn*/*anti*-atropisomers. For **7b**^{BArF}, the pure "*syn*"-atropisomer[19] could eventually be obtained in small amounts, which allowed a comparison of its performance with the one of the mixture. While the enantioselectivities remained unaltered (Table 1, entries 11-13), the yield noticeably improved for the same overall catalyst loading (entry 11 vs. entry 3). The yield could be approximated, however, by using the equivalent amount of pure *syn*-isomer (1.7 mol%) that would be present in the 5 mol% loading of the mixture (entry 12).[20] Even when the loading of the pure catalyst is lowered below 1%, decent yields are still achieved.

Following this, our interest shifted to a screening of the silyl enol ethers used in the reaction. As we are currently mainly interested in the elucidation of the mode of enantioinduction by the halogen bond donors, the behavior of different substrates could allow to draw conclusions on the structure of the key transition state.

Surprisingly, even slight modifications, such as the addition of methyl groups towards products **10b**-**10d**, led to noticeable drops in enantioselectivity (Scheme 2). While the 2-Me (**10b)** and 3-Me (**10c**) substituted products were obtained in similar yield and selectivity, the enantiomeric excess of the 4-Me substituted aldol product **10d** was even lower, at only 70% *ee*. Nevertheless, for methoxy-substituted product **10e**, still 85% *ee* could be achieved, while the fluoride and bromide derivatives were obtained in considerably reduced selectivities (Scheme 2, **10f** and **10g**).

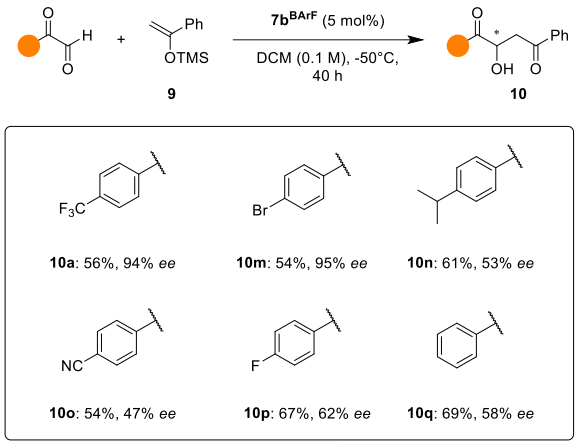


Scheme 2. Substrate screening for the reaction of various silyl enol ethers with aryl glyoxal **8**. All reactions were conducted on a 0.09 mmol scale, using dry CH_2Cl_2 under argon atmosphere, employing 2 eq. of the respective silyl enol ether. Isolated yields given. Enantiomeric excess determined by chiral HPLC analysis. Mixture of atropisomers of **7b**^{BArF} used.

Interestingly, the cyclohexyl analogue **10h** could be obtained in moderate yield and with a significant enantioselectivity of 81% *ee*, while the thiophene derivative showed slightly poorer selectivity and markedly reduced yield (Scheme 2, **10i**). On the other hand, with extended π-systems in the cases of 2-benzothiophenyl- (**10j**), 4-biphenyl- (**10k**) and 2-naphthyl- (**10l**) substituted aldol products,

excellent enantioselectivities of up to 98% *ee* were observed. While these findings confirm that outstanding selectivities can be achieved with other substrates and that good base level enantioselectivity is also observed for less suitable substrates, there appear to exist narrow requirements on the substrates to see truly exceptional enantiocontrol. This hints at a tight entanglement between catalyst and substrate in the transition state.

As we turned our attention towards the evaluation of differently substituted aryl glyoxals, the highly specific nature of the catalyst-substrate interaction turned out to be even more pronounced. Although the bromide-substituted glyoxal **10m** (Scheme 3) could be converted into the aldol product with 95% *ee* - displaying yet another case of very high enantioselectivity – all attempts to uncover the peculiar characteristics of a further substituent which enables this level of stereocontrol proved difficult: an isopropyl substituent, which has been considered as an isostere of the trifluoromethyl group,[21] resulted in 61% yield but only 53% *ee* for the aldol product **10n**. Similarly, an attempt to roughly emulate the electron-withdrawing properties[22] of the trifluoromethyl group using a cyano substituent resulted in a selectivity of just 47% *ee* in product **10o**. On the other hand, puzzlingly, the fluoride substituted product **10p** and even the non-substituted product **10q** were obtained in slightly higher selectivities of roughly 60% *ee*.



Scheme 3. Substrate screening for the reaction of aryl glyoxals with silyl enol ether **9**. All reactions were conducted on a 0.09 mmol scale, using dry CH_2Cl_2 under argon atmosphere, employing 2 eq. of silyl enol ether **9**. Isolated yields given. Enantiomeric excess determined by chiral HPLC analysis. Mixture of atropisomers of **7b^{BArF}** used.

In conclusion, a modifiable bidentate chiral halogen bond donor led to excellent enantioselectivities in a Mukaiyama aldol test reaction. A substrate screening of reaction partners revealed a significant base level of stereoselectivity for different silyl enol ethers while increased substrate specificity was observed for aryl glyoxals. Control experiments using non-iodinated congeners re-confirmed the crucial role of halogen bonding in this catalyst motif, both for activity and enantioselectivity. Thus, this constitutes the first case in which high asymmetric induction was achieved with an iodine(I)-based (and bidentate) catalyst predominantly via halogen bonding and with unbiased (non-halogen bonding) substrates. As such, it marks an important step in the further development of increasingly sophisticated organocatalyses with this interaction.

The catalyst derivatives utilized in this study represent only a fraction of the possible library of chiral halogen bond donors likely accessible in our later-stage modification approach. Work on a more extensive exploitation of this modifiable catalyst design and on applications in further promising reactions are currently underway in our laboratories.

Supporting Information

The authors have cited additional references within the Supporting Information.[23-28]

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Keywords: halogen bonding • organocatalysis • enantioselectivity • noncovalent interactions

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[16] To the best of our knowledge, there is only one report on this product, in the patent literature, in which the synthesis of product (*S*)-**10a** is postulated via a chiral Cu complex in 70% yield and 89% ee (Z. Wang, Q. Ming, J. Li, University of Science and Technology of China, CN112979523A, **2021**).

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[18] Deposition numbers 2364334 (for **10a**), 2366022 (for **SI-3**), and 2366021 (for **3**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[19] In the absence of direct crystallographic evidence (as was previously possible for **1**^{BArF}), our assignment of the atropisomers is only tentative and often, no full separation of the two isomers was possible, yielding mixtures only enriched in either atropisomer, see SI for details.

[20] The main fraction of the catalyst obtained after anion exchange to triflate (**7b**^{OTf}) consists of a ~1:2 mixture of the atropisomers, while the pure atropisomer could only be obtained in lower quantities (see SI for further details).

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