RESEARCH ARTICLE

Fine-tuning Substrate--Catalyst Halogen--Halogen Interactions for Boosting Enantioselectivity in Halogen-Bonding Catalysis

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Abstract: A new approach towards highly enantioselective halogen-bonding catalysis has been developed. In order to circumvent the intrinsic issues of the halogen-bond (XB) nature and consequent unresolved limitations in asymmetric catalysis, fine-tuned halogen--halogen interactions between the substrate and XB-donor were designed to pre-organize the substrate in the catalyst's cavity and boost enantiocontrol. The present strategy exploits both the electron cloud (Lewis base site) and the sigma (σ)-hole site of the halogen-substituent of the substrates to form a tight catalyst--substrate--counteranion chiral complex. Thus, this enables a controlled induction of high levels of chirality transfer. Remarkable enantioselectivities of up to 95:5 e.r. (90% *ee*) have been achieved in a model dearomatization reaction of halogen-substituted (iso)quinolines with tetrakis-iodotriazole multidentate anion-binding catalysts.

Introduction

In the last few years, halogen bonding[1] has emerged as a powerful tool in supramolecular[2] and medicinal chemistry,[3] and created new possibilities towards selective recognition[4] and organocatalysis.[5,6] Important contributions in enantioselective recognition of neutral and anionic substrates have been reported with different chiral rotaxanes,[7] halotriazole- and halotriazolium-based halogen-bond (XB)-donors,[8] among others. However, most of the XB processes thus far rely on achiral donors,[1] and enantioselective applications,[7,8] especially in catalysis,[9-15] are still in their infancy. In this regard, there are some challenges that have to be overcome to effectively implement XB in enantioselective processes. Hence, the high directionality of roughly 180° between the halogen through its sigma (σ)-hole[16,17] and the bound substrate (Lewis base = LB); together with the size of the halogen atom, commonly iodine, result in a longer distance between the catalyst chiral backbone and the substrate to attain high chirality transfer. As a consequence, only few examples of chiral XB-donors applied in the asymmetric catalysis have been reported so far.

The first enantioselective cases were described by the groups of Tan[11] and Arai,[12] who used XB in dual catalysis as a secondary interaction among multiple noncovalent and/or Lewis acid/base activation units. More appealing but challenging is the use of XB, and in general σ-hole activation, as primary interaction, which remains underrepresented in asymmetric catalysis. In 2020, Huber and co-workers published the first example of asymmetric induction purely based on XB-activation with a chiral bidentate bis-iodoimidazolium XB-donor bearing large side arms to create a chiral environment close to the substrate (Figure 1a, left).[14] An enantioselectivity up to 33% *ee* in a Mukaiyama aldol reaction with

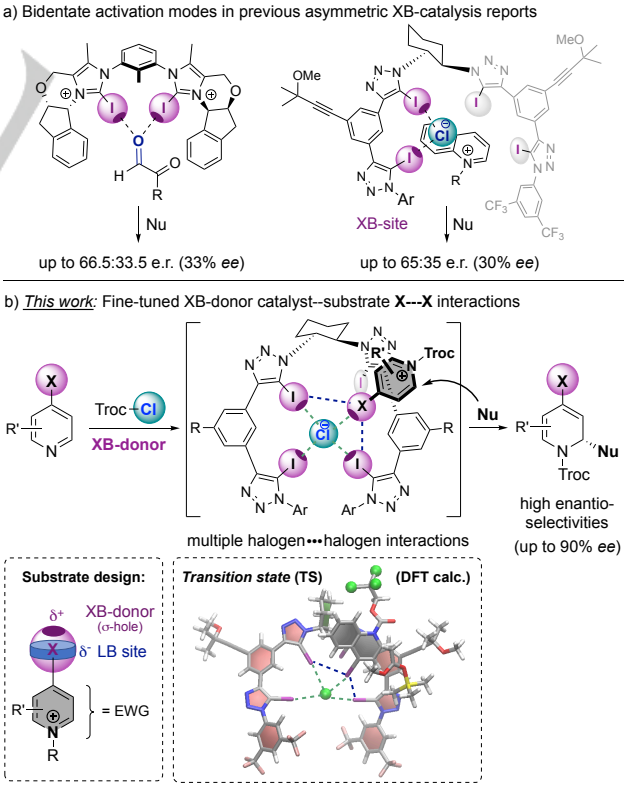


Figure 1. a) State-of-the-art enantioinduction in XB-catalysis. b) *This work*: Fine-tuning substrate--catalyst halogen interactions with triazole XB-donors for chirality induction enhancement in XB anion-binding catalysis supported by quantum chemical calculations.

glyoxal derivatives could be achieved. Shortly after, our group reported a chiral tetrakis iodo-triazole system[15] for enantioselective anion-binding catalysis,[18] reaching a similar low enantioinduction in a Reissert-type reaction (Figure 1a, right).[15,19] Quantum chemical calculations performed in this study revealed a bidentate binding of only one catalyst arm to the chloride in the catalyst-substrate ion-pair complex.

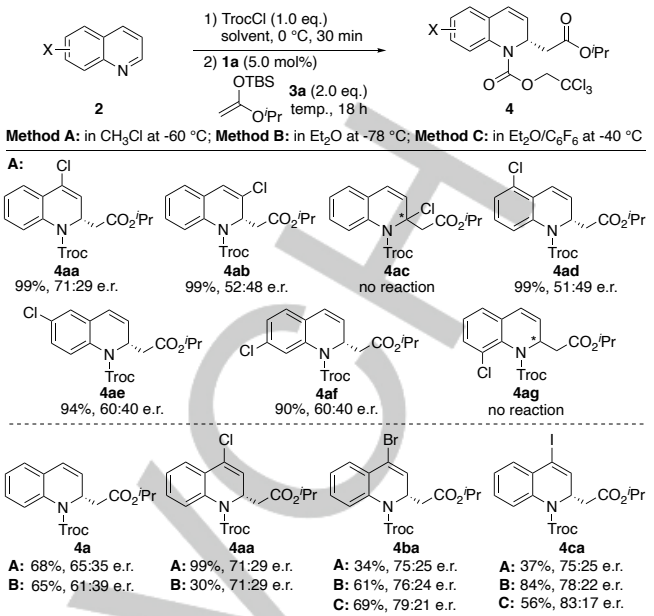
In order to solve some of the current limitations in asymmetric σ-hole catalysis, we aimed at a better fixation of the substrate and, thus, a more efficient chirality transfer to achieve synthetically useful enantioselectivities. To this purpose, we envisioned additional substrate--catalyst halogen interactions as a strategy to boost enantioselectivity in XB catalysis. For the proof-of-principle, we explored this approach in a related Reissert-type anion-binding catalyzed prototypical reaction (Figure 1b). In particular, we proposed *N*-arenium-type substrates bearing additional halogens (X), which can act simultaneously as Lewis bases within their electron cloud (LB site, in blue) and σ-hole donors (XB site, in dark purple), to allow for fine-tuned multiple halogen--halogen contacts with the XB-catalyst. DFT calculations on the plausible transition state (TS) of a model system supported a halogen-interactions interplay as key feature to enable high levels of enantiocontrol, and suggest the participation of four σ-hole interactions with the chloride-counteranion of the substrate and two halogen--halogen contacts between the substrate and catalyst. Based on this new strategy in XB-catalysis, we herein report the asymmetric dearomatization of halogen-substituted (iso)quinolines with tetrakis-iodotriazole anion-binding catalysts, reaching high enantioselectivities up to 95:5 e.r. (≤ 90% *ee*).

Results and Discussion

Optimization of the Reaction: Halide Substitution Effect

To explore our hypothesis on the enhance of stereocontrol by additional halogen-interaction between the catalyst and the substrate bearing a Lewis basic site on the scaffold, several haloquinolines were initially tested (Scheme 1). After standard pre-activation with TrocCl to the *N*-acylquinolinium chloride salts, the reaction with the silyl ketene acetal **3a** was conducted in $CHCl_3$ at -60 °C in the presence of 5 mol% of tetraiodo-triazole catalyst **1a** (*Method A*). By rotating a chloride atom around the quinoline core, a strong influence on the enantioselectivity outcome of the reaction could be observed. Thus, the best results were obtained with 4-Cl-quinoline, which provided the product **4aa** in an excellent 99% yield and a good 71:29 e.r. in favor of the (*S*)-enantiomer. Other substitution patterns, such as for 3-Cl (**2ab**), 5-Cl (**2ad**), 6-Cl (**2ae**) and 7-Cl-quinolines (**2af**), led to diminished enantioinductions (≤ 60:40 e.r.), even lower than for the parent unsubstituted quinoline (**4a**). Moreover, no reaction was observed for 2-Cl and 8-Cl-quinolines. In these two cases, the substituent might hamper the nucleophilic attack by blocking the C-2 position, directly or through constraining the free rotation of the *N*-Troc protecting group, respectively.

Next, the effect of introducing heavier halogen substituents in the 4-position was investigated. We were pleased to see an increasing enantioselectivity when going from a 4-Cl to 4-I substitution, which might indicate a stronger halogen bonding and/or better interaction with the softer, more polarized iodine-atom. Hence, the dearomatized products **4ba** and **4ca** were obtained in 75:25 e.r., but in only moderate yields (34 and 37%,



Scheme 1. Screening of the effect of the incorporation of a halogen substituent into the substrate **2**. All reactions were conducted on a 0.1 mmol scale in the corresponding solvent (0.05 M; methods **A-C**) and under argon atmosphere. Isolated yields given. E.r. determined by chiral SFC or HPLC analysis.

respectively). This was the result of a competitive halogen-exchange side-reaction with the present Cl-counter anion of the *N*-Troc quinolinium substrate. To avoid or minimize this process, the solvent was changed to Et_2O (*Method B*). Fortunately, the desired products were then obtained selectively (> 90%) and with slightly improved enantioselectivity, reaching a 78:22 e.r. for **4ca** with the 4-iodo substitution.

In order to further improve the enantioselectivity while repressing the I–Cl-atom exchange, a solvent screening was conducted with 4-iodoquinoline (**2ca**) (see S.I. for full screening). It turned out that the best solvent system was a 2:1 mixture of Et_2O/C_6F_6 at -40 °C (*Method C*), providing the product **4ca** in 56% yield and a notably enhanced 83:17 e.r., while low or not observable halogen-exchange to the 4-chloro-byproduct takes place (4-I/4-Cl selectivity > 95%).

Computational Study: Substrate-Catalyst X-Interactions

Intrigued by our initial observations and in order to gain more insights into the key interactions leading to the enantioselectivity enhancement by the introduction of halogen-atoms in the substrate, computational investigations at density functional theory (DFT) level were performed. In particular, M06-2X[20] functional with 6-31G(d,p)[21] and LANL2DZ[22] basis sets for iodine atoms were used for optimizations with further solvent and energy corrections (see S.I. for more details).

The catalyst **1a** and 4-iodoquinoline (**2ca**), together with a model silyl ketene acetal (((1-methoxyvinyl)oxy)trimethylsilane) as nucleophile, were used to study the halogen interactions between the XB catalyst and substrate along the reaction pathway towards the formation of both (*S*)- and (*R*)-products (see S.I. for complete picture). Among ten different reaction pathways, one of the most probable routes to build the observed major (*S*)-product involves multiple XB-induced stabilizations in the transition state **ts1S** (Figure 2). Conversely to the previously observed bidentate modus (see Figure 1a, right),[15] the catalyst **1a** presents a tridentate XB-type binding to the chloride anion in **ts1S**.

Furthermore, the acylated iodo-quinolinium substrate, which can also act as weak halogen donor, shows an additional XB to the chloride anion (with a Natural Bond Orbital[23] NBO-stabilization energy = 13.7 kcal mol^{-1}). This XB contact through the σ-hole of the substrate is presumably enhanced by I--I-interactions with two iodo-triazoles of **1a** (type I,[24] with angles θ_1 =134° and θ_2 =113° with **CL-I**, and θ_1 =131° and θ_2 =114° with **OR-I**), presenting similar NBO stabilization energies of 0.8 and 0.7 kcal mol^{-1}, respectively. The stabilization of the XB between the outer-left iodo-triazole (**OL-I**) and the chloride is significantly weaker than for the other iodo-units of the catalyst (**CL-I** and **OR-I**) and substrate (7.9 vs. ~12-14 kcal mol^{-1}). This observation could be interpreted as a driving force for the catalyst's tridentate mode for chloride binding in **ts1S**. Thus, the additional XBs between the substrate and catalyst-anion complex play a crucial role for achieving a more efficient substrate fixation and chirality transfer, favoring the (*S*)-product formation pathway and leading to the observed enhanced enantioselectivities.

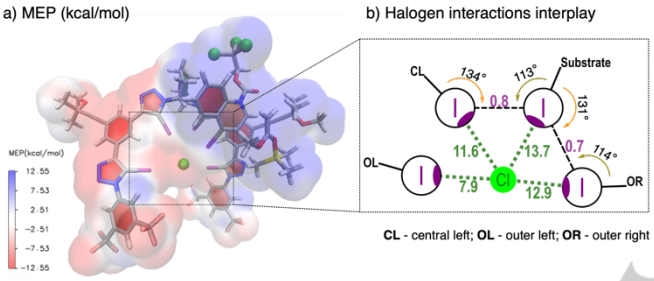


Figure 2. a) Molecular electrostatic potential (MEP) of the key transition state **ts1S**; b) outlined cooperative XB and halogen--halogen interactions between catalyst **1a**, chloride anion and substrate within **ts1S**; MEP and stabilization energies in kcal mol^{-1}.

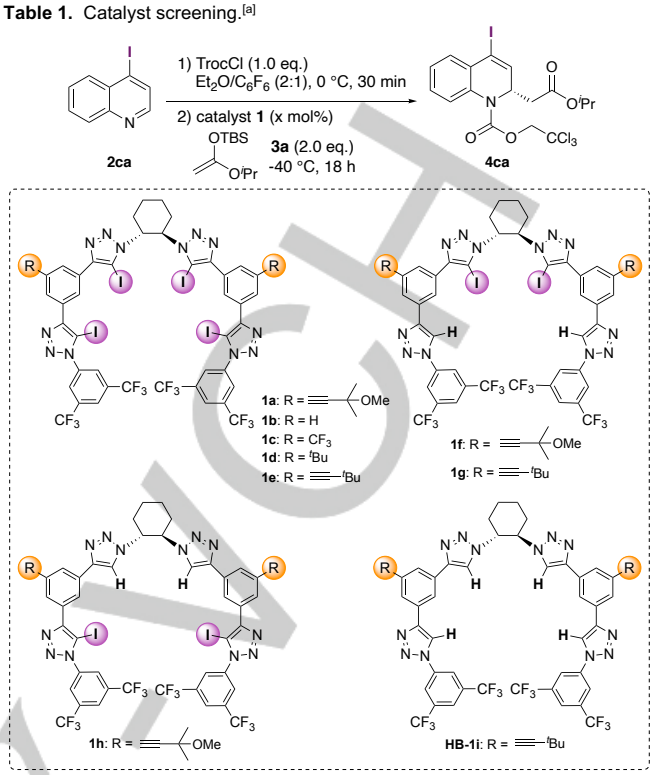
Catalyst Screening

Motivated by the obtained results and insights on the halogen interaction network, other triazole-based XB-catalysts **1** were next explored in the model reaction of **2ca** in Et_2O/C_6F_6 at -40 °C (Table 1). A variety of tetra-iodo XB-donors **1a-e** bearing different residues on the side chain were first used. While the absence of side chain substitution led to a lower enantioinduction (**1b**: 71:29 e.r. vs. **1a**: 83:17 e.r., entries 1 and 2), other groups such as CF_3 or *t*Bu provide a similar good enantioselectivity (**1c**: R = CF_3, 80:20 e.r.; **1d**: R = *t*Bu, 84:16 e.r., entries 3 and 4, respectively). The best result was obtained with the tetra-iodo XB-donor **1e** bearing a *tert*-butyl-acetylene rest, reaching 85:15 e.r. (entry 5).

Next, bis-iodo triazoles at the "inner" (**1f-g**) or "outer" sites (**1h**) were tested. Similar enantioselectivities were observed with **1f** and **1g** (85:15 and 81:19 e.r., entries 6 and 7), in this case being superior the dimethylmethoxy substitution at the acetylene side chain. Interestingly, the opposite (*R*)-enantiomer was favored with the "outer" bis-iodo triazole catalyst **1h**, resembling the results obtained with the proto-tetrakis triazole systems (21:79 e.r., entries 8 and 9).[19] This indicates that the presence of two large iodine atoms in the "inner" site of the catalyst hinders the formation of the same helical catalyst-anion complex.

After having identified **1e** as the XB-donor of choice and to rule out possible strong competitive H-bonding with the mixed bis-iodo systems, the catalyst loading was screened. While the use of just 2.5 mol% of **1e** led to the product in an increased yield of 80% and 86.5:13.5 e.r. (entry 10), the use of 10 mol% catalyst

Table 1. Catalyst screening.[a]



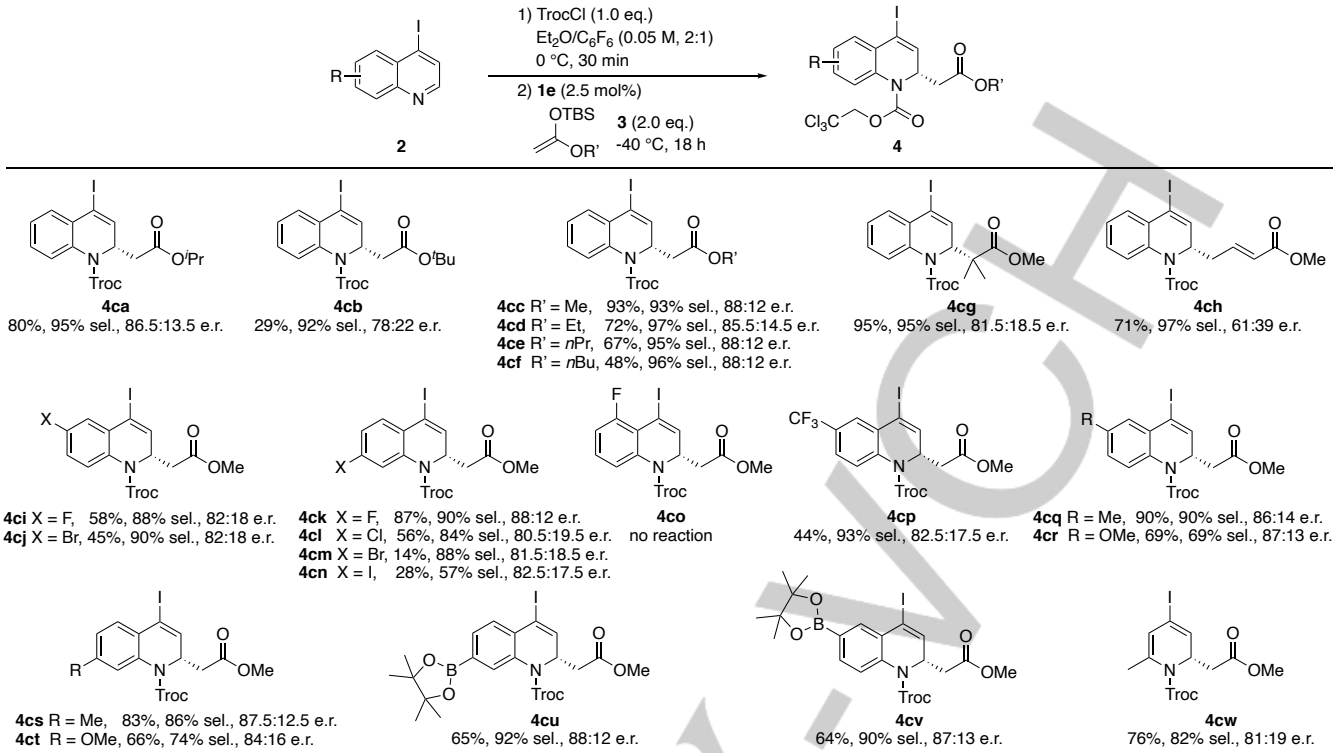
Entry	Catalyst (mol%)	Yield (%)[b]	Selectivity (%) (4-I *vs.* 4-Cl)[c]	e.r.[d]
1	**1a** (5)	56	96	83:17
2	**1b** (5)	68	95	71:29
3	**1c** (5)	66	96	80:20
4	**1d** (5)	67	96	84:16
5	**1e** (5)	60	96	85:15
6	**1f** (5)	54	92	85:15
7	**1g** (5)	54	90	81:19
8	**1h** (5)	60	92	21:79
9	**HB-1i** (5)	77	90	21:79
10	**1e** (2.5)	80	95	86.5:13.5
11	**1e** (10)	67	95	84:16

[a] All reactions were conducted on a 0.1 mmol scale in dry Et_2O/C_6F_6 (2:1, 0.05 M) and under argon atmosphere. [b] Isolated yields. [c] Determined by NMR of the crude reaction. [d] Determined by chiral SFC analysis.

loading did not provide any improvement (entry 11). Therefore, further reactions were performed using 2.5 mol% of **1e** in the optimized solvent system.

Scope of the Reaction with Iodo-Quinolines

We continued the study by exploring the scope and limitations of the method (Scheme 2). First, differently substituted silyl ketene acetal nucleophiles were screened. Keeping the TBS-group, the more sterically demanding *t*Bu residue in **3b**, led to significantly lower yield and enantioselectivity compared to the parent nucleophile **3a** bearing an *i*Pr substitution (**4cb**: 29%, 72:18 e.r., vs. **4ca**: 80%, 86.5:13.5 e.r.). In contrast, linear alkyl groups provided better results. With the exception of the ethyl derivative **3d** (**4cd**: 85.5:14.5 e.r.), the methyl, *n*-propyl and *n*-butyl



Scheme 2. Scope of the reaction with quinolines **2**. All reactions were conducted on a 0.1 mmol scale. Isolated yields given. E.r. determined by chiral SFC or HPLC analysis. Selectivity of 4-I/4-Cl product formation determined by ^{1}H NMR of the crude mixture.

substitution provided an improvement in terms of enantioselectivity, reaching an 88:12 e.r. in all cases. However, the commercially available OMe-nucleophile **3c** was more reactive, building the product **4cc** in a high 93% yield. Finally, the dimethyl substituted trimethylsilyl ketene acetal **3g** and TBS dienolate **3h** gave the corresponding products **4cg** and **4ch** in moderate to high yields (70-93%), but with notable lower enantiomeric inductions (81.5:18.5 e.r. and 69:31 e.r., respectively).

Next, the substrate scope for a variety of substituted 4-Iodo-quinolines with the nucleophile **3c** was investigated. The presence of a second halogen in the C6 and C7 position was compatible, leading to the products (**4ci-4cn**) in moderate to good yields, and similar enantioselectivities as for the parent substrate **2ca** (81:19 – 88:12 e.r.). Conversely, the C5-fluoro derivative showed no reactivity, which might indicate inefficient additional XB interactions of the neighbor C4-iodo atom in the transition state. Moreover, both electron withdrawing substituents such as a trifluoromethyl (**4cp**) and electron donating groups such as methyl (**4cq** and **4cs**) or methoxy (**4cr** and **4ct**) were also well-tolerated, providing similar levels of enantioinduction. Interestingly, the pinacolborane products **4cu** and **4cv**, which allow for orthogonal cross-coupling reactions, were built in good yields and high enantioselectivities up to 88:12 e.r. Finally, it should be noted that the reaction with pyridines such as 4-iodo-2-methylpyridine also proceeded smoothly, providing the corresponding product **4cw** in 76% yield and 81:19 e.r.

The robustness of the method was confirmed by a 10-fold upscaling of the reaction of **2ca** with **3c** (Figure 3a). Thus, under the standard conditions, the reaction of **2ca** (255.5 mg, 1.0 mmol) with **3c** provided the product in similar high yield (90% vs. 93% for 0.1 mmol) and same enantiomeric ratio of 88:12 e.r.

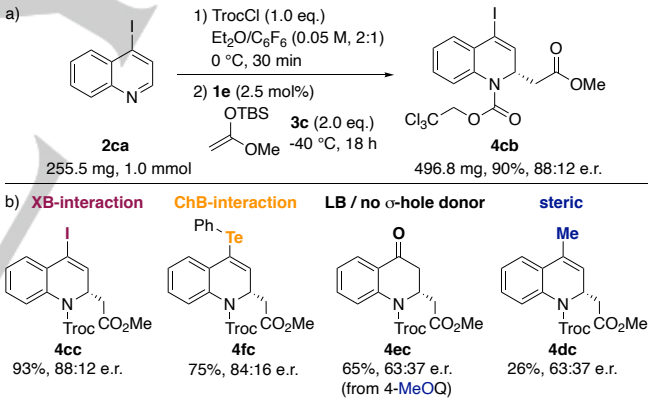


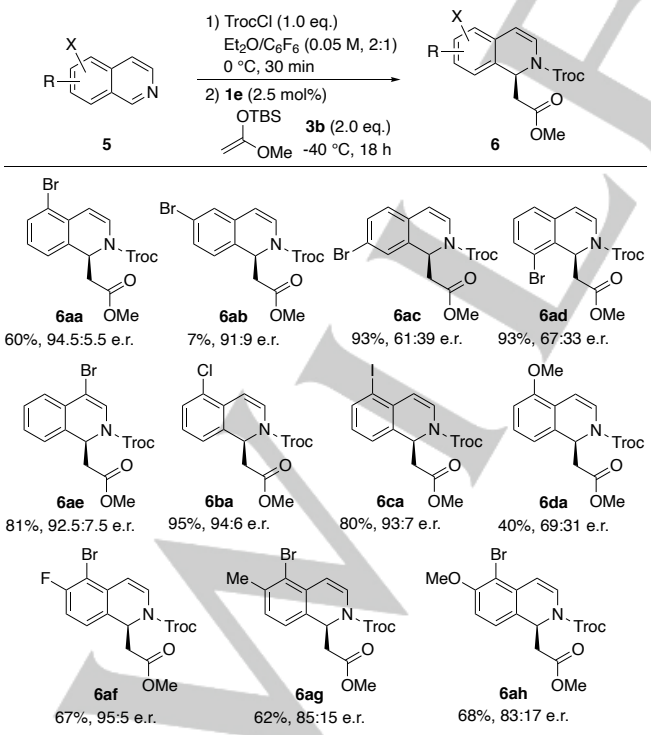
Figure 3. a) Upscaling of the reaction of **2ca** with **3c**, and b) comparison of the effect of different C4-substitited quinolines.

Finally, in order to better differentiate the role of the 4-iodo group of the substrate as σ-hole donor or Lewis base site, differently C4-substituted quinolines were examined (Figure 3b). The reaction with a quinoline containing a phenyl tellurium group, able to undergo chalcogen-bonding (ChB) with the catalyst or anion-binding complex, was carried out. In this case, the product **4fc** was formed in 75% yield and a similar 84:16 e.r. Conversely, a methoxy group, which can act as a Lewis base while it is not a good σ-hole donor, or a 4-methyl substitution provided the products **4ec** and **4dc** in a notable lower enantioselectivity (63:37 e.r.), comparable with the one of unsubstituted quinoline. These observations are in line with the computational studies (see **ts1S**, Figure 2), and indicates that the catalytic system is not only operating with halogen-bonds, but can also be conveyed towards other σ-hole interactions such as chalcogen-bonds.

Extension to Isoquinolines

We next expanded our substrate--catalyst halogen-interaction approach for the reaction with the related isoquinolines (Scheme 3). Once again, the optimal position of the additional halogen in the substrate was explored by rotating a bromine-atom on the isoquinoline core. Pleasantly, this type of substrates proved even more suitable, providing the dearomatized products in generally higher enantiomeric ratios than the parent quinolines. Hence, the 5-bromo derivative led to the best results (**6aa**: 60%, 94.5:5.5 e.r.), followed by the 4-bromo and the 6-bromo isoquinolines (**6ae**: 81%, 92.5:7.5 e.r.; **6ab**: 7%, 91:9 e.r.), while the 7- and 8-substitution **6ac** and **6ad** provided only poor enantiomeric inductions. On basis of these results, 5-chloro (**5b**) and 5-iodo (**5c**) were also explored. In this case, only a negligible difference could be observed between the chloro-, bromo- and iodo-substitution (ranking from 93:7 to 94.5:5.5 e.r.). It is also important to note that the halogen-exchange to the 5-chloro isoquinoline products is extremely low compared with the 4-haloquinoline products. Moreover, a diminished chiral induction was obtained with the 5-methoxy isoquinoline (**6da**: 69:31 e.r.). This is aligned with our hypothesized required additional halogen-interaction between the substrate and catalyst--anion complex for attaining high enantioselectivity.

Taking into account their more readily accessibility, a few 5-bromo quinolines containing an additional electron-withdrawing, electron-donating or neutral substituent at the C6-position were finally reacted under the standard conditions. The 5-bromo-6-methyl and 6-methoxy derivatives provided the products **6ag** and **6ah** in slightly lower enantioselectivities than the parent 5-bromoisoquinoline (85:15 e.r. and 83:17 e.r., respectively). To our delight, the introduction of a fluorine at the C6 position provided an excellent enantiomeric ratio of 95:5 (**6af**).



Scheme 3. Scope of the reaction with halo-isoquinolines **5**.

Conclusion

In conclusion, the long-standing issue of inefficient chirality transfer in halogen-bonding catalysis has been in part resolved by introducing fine-tuned halogen--halogen interactions between the substrate and XB-donor. Within this approach, a model asymmetric dearomatization reaction of halogen-substituted *N*-hetereoarenes such as (iso)quinolines using tetrakis-iodotriazoles as multidentate anion-binding catalysts was investigated. Computational studies suggested additional halogen interactions of the substrate through both its electron cloud (Lewis base site) and σ-hole site to the chloride--catalyst-complex. Furthermore, enhanced halogen-bond properties *via* iodine--iodine interactions were also revealed. Lastly, the comparison with substrates containing a MeO- (Lewis base) or a PhTe-group (σ-hole donor) further supports the crucial role of a σ-hole-type bonding from the substrate for an efficient enantioinduction. Hence, high enantioselectivities up to 95:5 e.r. have been achieved, which are well beyond the state-of-the-art in XB-catalysis.

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Keywords: Halogen-Bonding • Asymmetric Catalysis • Halogen--Halogen Interactions • Organocatalysis • Anion-Binding

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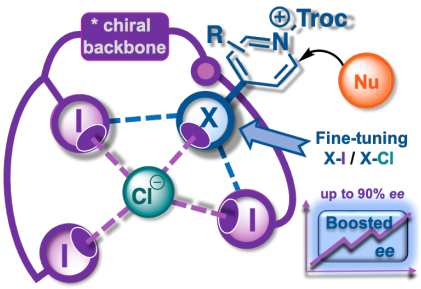

A new strategy towards boosted enantioselectivities in primary halogen-bonding catalysis is presented. Fine-tuned multiple halogen-halogen interactions between the substrate and halogen-bond (XB)-donor catalyst, through both the electron cloud (Lewis base site) and the sigma (σ)-hole site of the incorporated halogen-substituents, allows for enantioselectivities of up to 90% *ee* in model anion-binding-catalyzed dearomatization reactions.

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