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Synthesis and Evaluation of Azolium-Based Halogen Bond Donors†

Richard A. Squitieri,[a] Keegan P. Fitzpatrick,[a] Ashley A. Jaworski,[a] and Karl A. Scheidt [a]*

Abstract: A method for the synthesis of iodinated imidazolium and triazolium *N*-heterocyclic halogen bond donor catalysts has been developed. This approach was applied to the synthesis of a variety of 1,2,4-triazolium salts to prepare a series of novel chiral halogen bond donor catalysts. The counterions of the iodinated triazoliums can be readily exchanged with chiral and achiral non-coordinating counterions to produce unique scaffolds. Their ability to promote/catalyse a conjugate addition reaction with indole was investigated. Through these initial studies, a set of general guidelines and considerations for the application of these halogen bond donors in organocatalysis have been established.

Organocatalytic reactions employing unactivated Lewis basic substrates have traditionally used Lewis or Brønsted acidic additives to coordinate and activate the electrophile (e.g., carbonyl electrophiles, Figure 1A).[1] Recently, the use of halogen-bonding additives to coordinate unactivated electrophiles has emerged as a potential alternative to conventional acid-catalyzed approaches. Specifically, iodine-containing organic molecules have been shown to promote reactions of Lewis basic substrates due to the highly polarized nature of the carbon-iodine bond, which creates an electrophilic σ-hole which can act similarly to a Lewis acid.[2] Currently halogen bonds have been widely applied to anion recognition chemistry, but the extension of their utility to organocatalysis as an alternative mode of electrophilic activation is underdeveloped. Huber first demonstrated that halogen-containing organocatalysts were competent activators of carbon-heteroatom bonds towards nucleophilic displacement in 2011.[3] Following this disclosure, reports on a variety of other reactions promoted by iodine containing halogen bond catalysts including (aza)-Diels-Alder,[4] Michael addition,[5] halide abstraction,[6] semipinacol rearrangement,[7] and cooperative catalysis by silica activation[8] have also appeared. These examples highlight the potential of halogen-bonding organocatalysts to facilitate known acid-promoted reactions, but at a more fundamental level, a clear model for their mode of action remains undefined.

Since halogen bonding by molecular I_2 has been shown to lower reaction barriers up to ~7 kcal/mol, the extension of halogen-bonding effects by organocatalysts could potentially provide sufficient energetic bias to promote a selective reaction. However, the actual energetic effects imparted by halogen-bonding motifs embedded in organic molecules have been difficult to disentangle from other dominant energetic considerations (e.g., H-bonding, pi-stacking, ionic pairing).[9] To date, there are no known examples of asymmetric organic reactions employing halogen bonding catalysts. A single chiral halogen bonding catalyst has been described previously, but it was not effective in promoting an enantioslective reaction.[10]

Most examples of electrophilic halogen bonding applied to organocatalysis have utilized monovalent halogen species, with a notable exception reported by Huber employing iodine(III) derivatives embedded in cyclic iodolium salts.[11] The majority of known halogen bonding organocatalysts are based on an iodinated imidazolium or 1,2,3- triazolium organic scaffolds (Figure 1B). These heterocyclic substructures are widely used as N-heterocyclic carbene (NHC) catalyst precursors. Isomeric 1,2,4-triazolium salts have also been studied extensively in the context of NHC catalysis, since the modular nature of their synthesis allows for incorporation of chiral motifs and tuning of the steric and electronic properties of the catalysts. Despite the wide diversity of 1,2,4-triazoliums available for NHC catalysis, the corresponding halogenated derivatives have not been reported as potential halogen-bonding organocatalysts to date. Herein, we report the synthesis of novel chiral and achiral 3-iodo-1,2,4-triazolium salts from readily available (*3-H*)-1,2,4-triazolium precursors, and an in-depth evaluation of their structure and activity as halogen bonding catalysts.

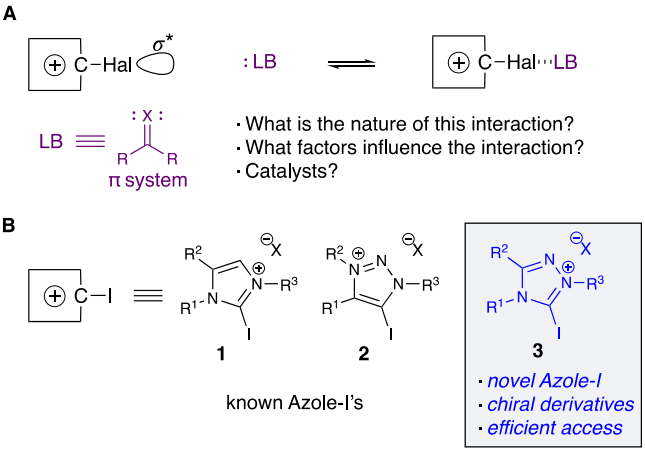

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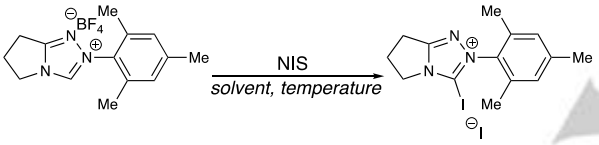
Figure 1. A) Traditional modes of carbonyl activation and halogen bonding. B) Scaffolds of previously synthesized halogen bonding catalysts and novel 1,2,4-triazolium halogen bonding catalysts.

Our initial goal was to develop a broadly applicable method that could convert a library of previously synthesized azolium salts (NHC precursors) to their corresponding XB donors. Our preliminary studies were aimed at effecting the iodination of triazolium salt **4**.[12] Starting from the conditions developed by Huber for imidazole iodination,[13] we explored a series of modified conditions using *N*-iodosuccinimide (NIS) as an iodinating reagent with 1,2,4-triazolium **4** (Table 1). Subjecting the triazolium precursor to NIS in CH_2Cl_2 and CH_3CN at room temperature offered no conversion to the iodinated product (Table 1, entries 1 and 2). Heating the reaction 60 °C in toluene also offered no conversion (Table 1, entry 3). However, under microwave irradiation in toluene at 150 °C we observed 60% conversion to the desired product (Table 1, entry 4). Nearly full conversion was obtained when the reaction was heated to 175 °C in CH_3CN, and by using an excess of NIS (5 equivalents) we observed quantitative conversion to iodinated triazolium product **5** (Table 1, entries 5 and 6).



4 **5**

Entry	Solvent	Temperature	Equiv NIS	Time	NMR Yield
1	CH_2Cl_2	23 °C	1	16 h	0%
2	CH_3CN	23 °C	1	16 h	0%
3	toluene	60 °C	2	2 h	0%
4[a]	toluene	150 °C	2	10 min	60%
5[a]	CH_3CN	175 °C	2	10 min	98%
6[a]	CH_3CN	175 °C	5	10 min	100%

[a]Reaction was run in the microwave.

Table 1. Optimization of conditions for the iodination of 1,2,4-triazolium scaffolds.

With the optimized conditions for the iodination of 1,2,4-triazoles in hand, we synthesized electronically and sterically differentiated chiral and achiral triazolium and imidazolium salts (Table 2). Several chiral triazolium salts that are prominent in NHC catalysis were iodinated in high yields, including the widely-used aminoindanol scaffold (**6**), as well as sterically hindered chiral catalysts (**7**)**,** which are known to possess vastly different electronic properties.[14] Additionally, we found the method to be general to convert other *N*-heterocyclic scaffolds used in NHC catalysis to their iodinated derivatives, for example benzimidazolium (**9**) and imidazopyridinium (**10**) derivatives were also synthesized in excellent yields using our protocol (>95%).

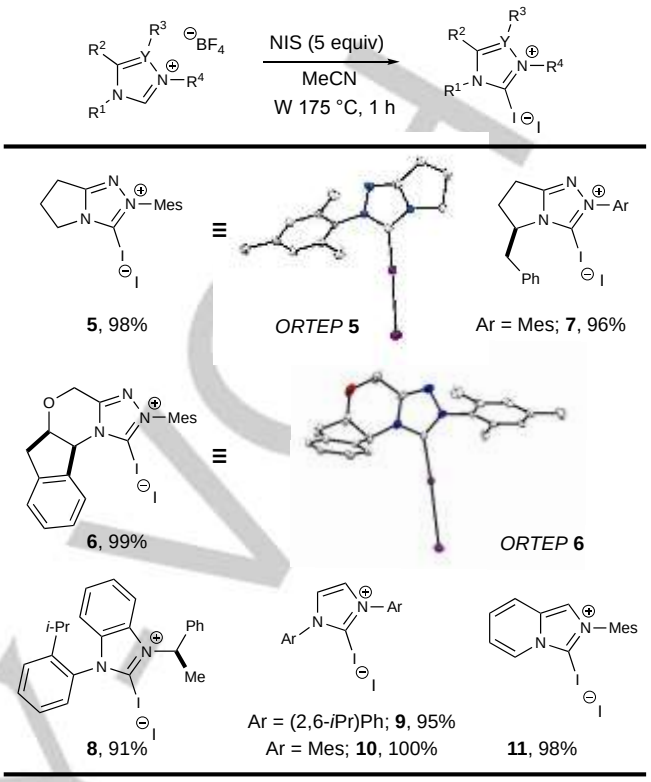


Table 2. Synthesis of iodinated imidazolium and 1,2,4-triazolium salts by microwave conditions.

Compounds **5**, **6**, and **10** were additionally characterized by X-ray crystallography, and the structures *all featured a close coordination of the iodide counterion to the σ-hole of the heteroaromatic 2-iodo substituent, an interaction similar to one which was observed by Huber with imidazolium counterparts*.[13] Due to this presumably strong association, we hypothesized that less coordinating counterions would be necessary to facilitate the possible coordination to a Lewis basic substrate for activation (Table 3). Thus, azolium **5** underwent anion exchange with silver or sodium salts of BF_4^-, PBF_6^-, SbF_6^-, and $BAr^F{}_4^-$, producing the new iodinated triazolium salts (**12**–**15**) in high yields and with a facile isolation by simple filtration. Chiral triazolium iodides **6** and **7** were also exchanged to produce their non-coordinating chiral salts in high yield. Finally, achiral triazolium iodide **5** underwent salt metathesis with the sodium salts of three chiral phosphoric acids, producing three achiral iodinated triazoliums with chiral counterions (**20-22**). The further inspection of the crystal structures for catalysts **15** and **20** confirmed that the counterions were not tightly associated with the σ-hole as was observed for the corresponding iodides which is also a feature shared with iodinated imidazoles (Figure 2).[13] We observed no additional solid state interactions with the triazolium cores of all compounds characterized, suggesting that replacement of the imidazolium C4 with nitrogen is an effective means to suppress previously observed competitive H-bonding with C4/C5 C-H bonds. These undesired interactions in previous azolium-I structures required blocking substituents at these positions.[13]

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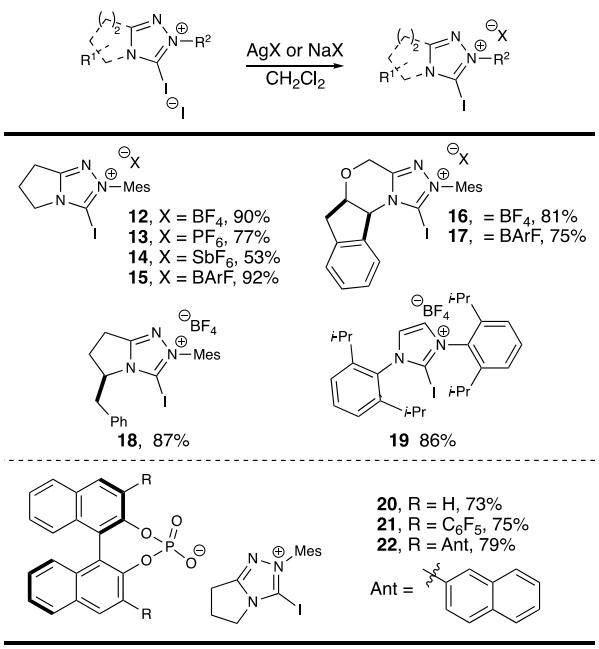

Table 3. Synthesis of 1,2,4-triazolium salts with non-coordinating anions by anion exchange.

With a variety of new iodinated triazolium derivatives, we turned our focus to surveying their catalytic properties. We first studied their ability to promote the conjugate addition of indole to crotonophenone (**23**), as this process has been shown to be promoted by related halogen-bond donor catalysts previously (Figure 3).[5a] Our initial observations indicated that catalyst **5** was also effective for promoting the conjugate addition. A survey of counterion effects showed unsurprisingly, catalyst **5** with the coordinated iodide counterion gave sluggish reactivity with only 65% conversion over 24h. The use of catalysts possessing non-coordinating counterions BF_4^- and SbF_6^- improved the reaction, giving 73% and 85% conversion respectively over 24h. Catalyst **13** with a PF_6^- counterion facilitated the conjugate addition in 100% conversion over 4 hours. Finally, catalyst **15** with a $BArF_4^-$ counterion was the most active, providing full conversion to product **25** in less than 1 hour. These results mirrored observations reported in Huber's imidazolium halogen bond donor-catalyzed conjugate addition, which showed a similar trend of increasing reactivity with the use of less coordinating counterions. Notably, we observed rapid and full conversions in these studies whereas their best catalyst is reported to facilitate the title reaction in 58% conversion after 3h and when allowed to react for several days a maximum conversion of 71% was reported.[5a] The superior reactivity of the 1,2,4-triazolium iodide catalysts when employing the highly non-coordinating $BArF_4^-$ counterion might be leveraged to maximize the relatively weak halogen bonding interaction between the catalyst and substrate in other reactions employing less reactive partners. Therefore, we proceeded to investigate this reaction in more detail to determine the basis of the observed catalytic activity of triazoliums **12-15**.

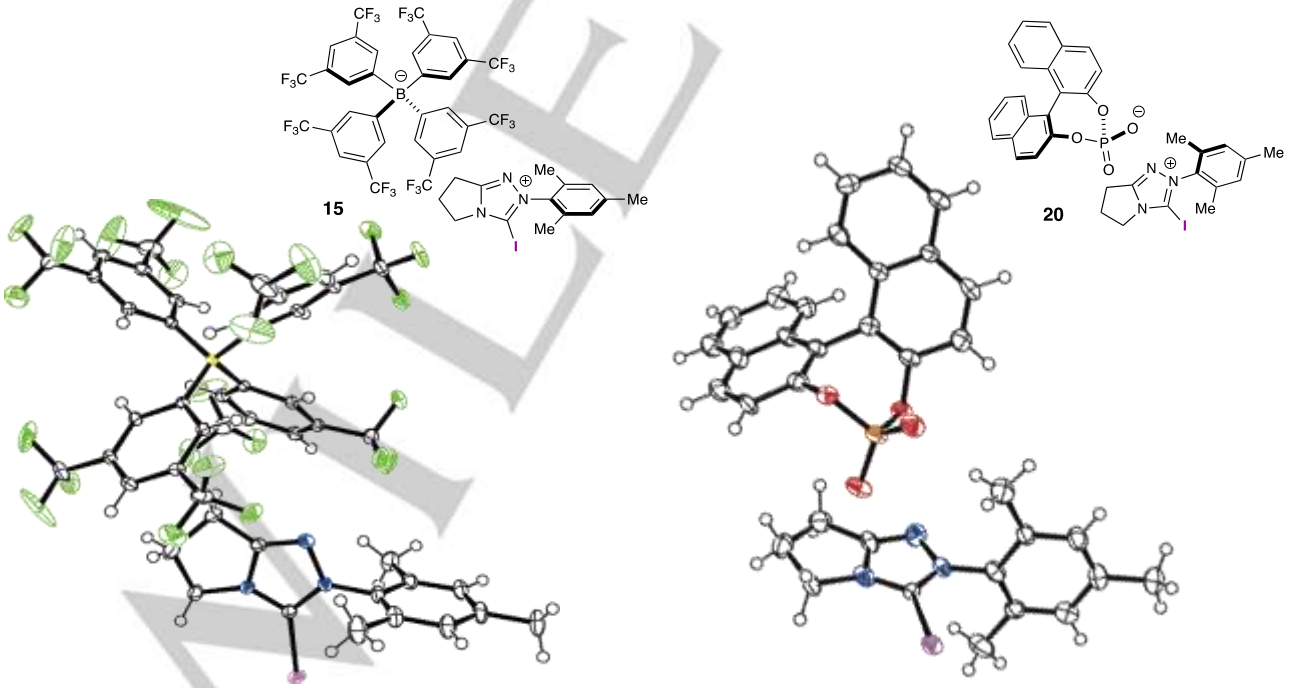

Figure 2. Crystal structure of 5,5-Mes-I with noncoordinating counterions (ORTEP **15** and **20)**.

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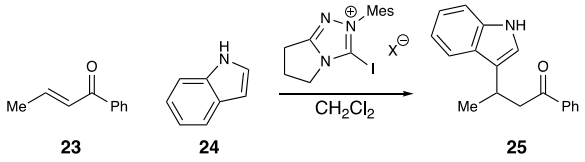

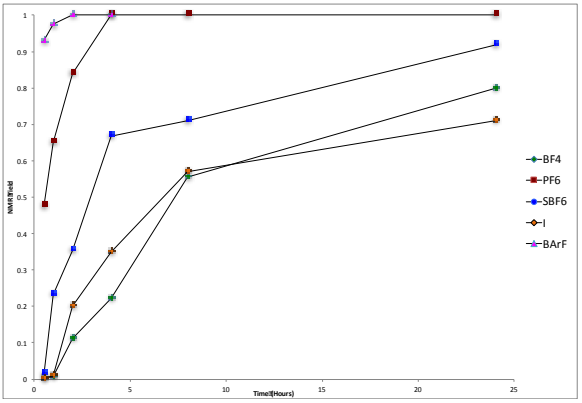

Figure 3. Kinetics plot of conjugate addition reaction using 5,5-Mes-derived iodinated catalysts with various counterions.

With an apparently very active halogen-bond donor catalyst, we began to explore the limits of its catalytic activity through presumed halogen-bonding interactions. Catalyst **15** in conjunction with a variety of pi-nucleophiles was ineffective at promoting 1,2 additions to some carbonyl and imine electrophilic partners. We also briefly examined conjugate additions of amines with maleimide, lactonizations of styrene with CO_2, hypervalent iodide-promoted aziridinations, and hetero Diels-Alder reactions using **15** with no success.

While the superior reactivity of catalyst **15** to promote a known process had been established, reaction screening of conceptually related processes did not provide satisfactory insight to formulate a hypothesis regarding the narrow substrate tolerance of this and related halogen-bonding catalysts. To better understand which potential electrophiles might best interact with these σ-hole azolium species, a ^{13}C nuclear magnetic resonance experiment (NMR) was designed to probe the coordinating effects of catalyst **15** relative to a variety of Lewis basic substrates. The goal of this study was to benchmark the limits of Lewis basicity required to observe an interaction (halogen-bonding or otherwise) with the catalyst and the results are depicted in Figure 4. We observed that the C-2 carbon of the triazolium resonates at 166.4 ppm, whereas in the presence of triphenyl phosphine and DABCO a strong coordination with the catalyst was observed, resulting in a 2.5- 2.6 ppm upfield shift at C-2. Benzophenone imine showed a substantial upfield shifts of C-2 by 1.6 ppm. Dimethylacetamide resulted in a moderate shift of 0.9 ppm and benzyl methyl ether and 4-methoxy benzoate showed a small shift of 0.5 ppm. When DBMP was allowed to equilibrate with the catalyst in the NMR no upfield shift was observed (Figure 2B). The catalyst showed no coordination to a variety of Lewis bases and π systems such as cyclohexene, *trans*-stilbene, diphenyl acetylene, styrene, and substituted benzylic carbonyls. These combined results show that the halogen bond donor is likely only sufficient enough to interact with sterically accessible Lewis bases and not π systems, establishing the substrate limitations of iodoazolium-type halogen bonding organocatalysts.

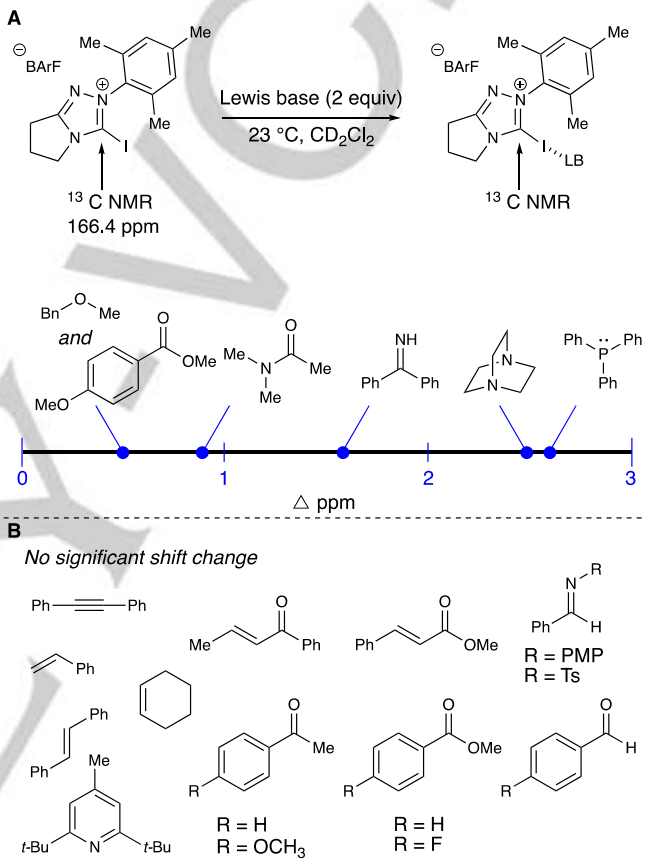

Figure 4. ^{13}C NMR shifts of catalyst **13** in the presence of a variety of electronically differentiated π bonds and Lewis bases.

The application of our iodotriazolium catalysts to novel reactions seemed somewhat implausible given the results of our ^{13}C NMR studies. We next revisited the conjugate addition reaction of indoles with enones to evaluate chiral 1,2,4-triazolium based halogen bonding scaffolds, since no one has reported enantioinduction using chiral halogen bonding catalysis. While these chiral motifs have been very successful for asymmetric NHC catalysis, compounds **6, 7, 8, 16**, **17** and **18** all failed to promote the conjugate addition reaction (Catalyst **18** produced an analytically observable amount of product which was verified as racemic).

Next, triazolium salts with chiral phosphoric acid counterions were tested in the conjugate addition reaction (Table 4). Catalyst **20** and **21** also gave no conversion to the desired product (Table 2, entries 1 & 2), whereas catalyst **22** facilitated the reaction with

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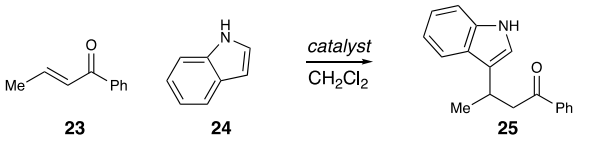
95% conversion and slight enantioenrichment (Table 4, entry 3). A brief temperature screen on this surprising result revealed that reducing the temperature shut down catalyst activity completely (Table 4, entries 4 & 5).



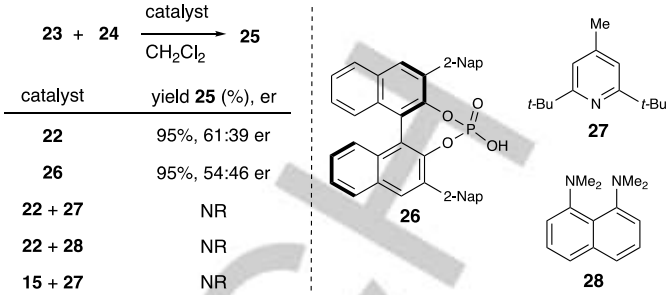
23 **24** **25**

Entry	catalyst	temp (°C)	conversion	er
1	**20**	23	0	-
2	**21**	23	0	-
3	**22**	23	95	61:39
4	**22**	0	0	-
5	**22**	-20	0	-

Table 4. Chiral phosphoric acid counter anion screening.

To further examine this result, a control reaction using just the parent chiral phosphoric acid as the catalyst facilitated the conjugate addition with similar conversion, yield and enantioselectivity as was observed using the triazolium CPA complex **22** (Scheme 4). This result indicated that the chiral counterion, not the halogen bond donor, was most likely the catalyst for this system if adventitious water was present under the reaction conditions (e.g., "hidden Bronsted acid catalysis").[15] To test this hypothesis, the reaction with catalyst **22** was repeated in the presence of proton scavengers/bases (proton sponge and 2,6-di-*tert*-butyl-4-methylpyridine (DBMP, **27**). In both cases, *no reactivity was observed supporting the hypothesis that this reaction is actually catalysed by adventitious acid*. Chiral phosphoric acids are well-known Bronsted acid catalysts, so the observation that catalyst **22'**s activity and asymmetric induction can be attributed solely to the counterion if adventitious water is present was unsurprising. However, based on this finding, we were compelled to revisit our results using active catalyst **15**. When DBMP was added to the reaction using catalyst **15** no reactivity was observed.

While it is possible that the use of Brønsted basic additives may also interrupt halogen-bonding effects,[5b, 15] DBMP shows no interaction with our azolium iodides by ^{13}C NMR spectroscopy (Figure 4). While not definitive, these results support that DBMP does not poison the catalyst, but is primarily acting as a Bronsted acid scavenger. Finally, as has been noted previously, this reaction is also efficiently catalysed by molecular iodine, and the possibility that the activity of catalysts such as **26** may also be due to the formation of trace amounts of I_2 from the parent aryl iodides and cannot be ruled out. The possibility that the combination of halogen-bond donating motifs in the presence of adventitious acid can act in a cooperative fashion may also explain of the limited examples of halogen bonding organocatalysts known to date.



Scheme 4. Chiral phosphoric acid counter anion control.

A new method for the preparation of iodinated imidazolium and 1,2,4-triazolium scaffolds has been developed and applied to a variety of chiral and achiral azolium salts. The counterions of the iodinated triazoliums can be readily exchanged with chiral and achiral non-coordinating counterions to produce unique scaffolds. Kinetic analysis of a variety of counterions shows that a BArF counterion improves the overall catalytic activity of the halogen bonding catalyst. ^{13}C NMR spectroscopic analysis of catalyst **15** indicates that the halogen bond donor is able to coordinate to several lone pair donors on the NMR time scale, but not many π bond systems. A closer inspection whether iodinated azoliums are the active catalysts in the conjugate additions investigated herein strongly indicates these specific reactions are likely promoted through a Brønsted acid pathway vs. the halogen bond donor activation. However, the overall mechanistic details for all transformations promoted by these interesting catalysts reported have yet to be fully delineated. While there are interesting and possibly unique opportunities for σ-hole interactions in catalysis, a challenge moving forward for enantioselective variants will be to be aware of and then avoid these unselective pathways (e.g., achiral Brønsted acid).

Keywords: Lewis base, catalysis, conjugate addition, halogen bonding

References:

[1] (a) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.* **2011**, *40*, 4539-4549; (b) P. D. H. Yamamoto, in *Lewis Acids in Organic Synthesis*, Wiley Online Library, **2008**.

[2] (a) O. Hassel, *Science* **1970**, *170*, 497-502; (b) M. H. Kolar, P. Hobza, *Chem. Rev.* **2016**, *116*, 5155-5187; (c) G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati, G. Terraneo, *Chem. Rev.* **2016**, *116*, 2478-2601; (d) D. Bulfield, S. M. Huber, *Chemistry* **2016**, *22*, 14434-14450; (e) R. Tepper, U. S. Schubert, *Angew. Chem. Int. Ed.* **2018**, *57*, 6004-6016.

[3] S. M. Walter, F. Kniep, E. Herdtweck, S. M. Huber, *Angew. Chem. Int. Ed.* **2011**, *50*, 7187-7191.

[4] (a) R. Haraguchi, S. Hoshino, M. Sakai, S. G. Tanazawa, Y. Morita, T. Komatsu, S. I. Fukuzawa, *Chem. Commun.* **2018**, *54*, 10320-10323; (b) Y. Takeda, D. Hisakuni, C. H. Lin, S. Minakata, *Org. Lett.* **2015**, *17*, 318-321; (c) S. H. Jungbauer, S. M. Walter, S. Schindler, L. Rout, F. Kniep, S. M. Huber, *Chem. Commun.* **2014**, *50*, 6281-6284; (d) M. Kaasik, A. Metsala, S. Kaabel, K. Kriis, I. Jarving, T. Kanger, *J Org Chem* **2019**.

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[5] (a) J. P. Gliese, S. H. Jungbauer, S. M. Huber, *Chem. Commun.* **2017**, *53*, 12052-12055; (b) D. von der Heiden, S. Bozkus, M. Klussmann, M. Breugst, *J. Org. Chem.* **2017**, *82*, 4037-4043.

[6] (a) F. Kniep, S. M. Walter, E. Herdtweck, S. M. Huber, *Chemistry* **2012**, *18*, 1306-1310; (b) F. Kniep, S. H. Jungbauer, Q. Zhang, S. M. Walter, S. Schindler, I. Schnapperelle, E. Herdtweck, S. M. Huber, *Angew. Chem. Int. Ed.* **2013**, *52*, 7028-7032; (c) S. H. Jungbauer, S. M. Huber, *J. Am. Chem. Soc.* **2015**, *137*, 12110-12120.

[7] N. Tsuji, Y. Kobayashi, Y. Takemoto, *Chem. Commun.* **2014**, *50*, 13691-13694.

[8] M. Saito, N. Tsuji, Y. Kobayashi, Y. Takemoto, *Org. Lett.* **2015**, *17*, 3000-3003.

[9] M. Breugst, E. Detmar, D. von der Heiden, *ACS Catal.* **2016**, *6*, 3203-3212.

[10] T. Arai, T. Suzuki, T. Inoue, S. Kuwano, *Synlett* **2017**, *28*, 122-127.

[11] (a) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328-3435; (b) F. Heinen, E. Engelage, A. Dreger, R. Weiss, S. M. Huber, *Angew. Chem. Int. Ed.* **2018**, *57*, 3830-3833.

[12] S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, *7*, 3873-3876.

[13] N. Schulz, P. Sokkar, E. Engelage, S. Schindler, M. Erdelyi, E. Sanchez-Garcia, S. M. Huber, *Chemistry* **2018**, *24*, 3464-3473.

[14] (a) P. C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520-3521; (b) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307-9387.

[15] T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem.* **2011**, *76*, 9353-9361.

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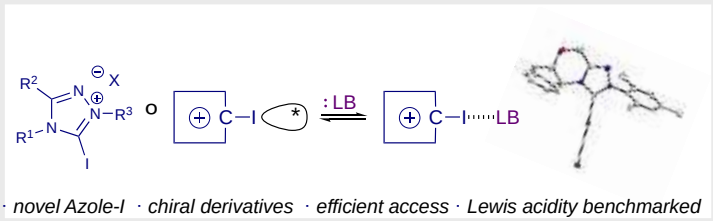

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