N-Heterocyclic Iod(az)olium Salts - Potent Halogen-Bond Donors in Organocatalysis

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Abstract

This article describes the application of $N$-heterocyclic iod(az)olium salts (NHISs) as highly reactive organocatalysts. A variety of mono- and dicationic NHISs are described and utilized as potent XB-donors in halogen-bond catalysis. They were benchmarked in seven diverse test reactions in which the activation of carbon- and metal-chloride bonds as well as carbonyl and nitro groups was achieved. $N$-Methylated dicationic NHISs rendered the highest reactivity in all investigated catalytic applications with reactivities even higher than all previously described monodentate XB-donors based on iodine(I) and (III) and the strong Lewis acid BF$_3$.

Keywords

halogen bonding • hypervalent iodine • $N$-heterocycles • cyclic iodonium salts • organocatalysis

Introduction

Halogen bonding (XB) is a non-covalent interaction between an electrophilic halogen donor (XB-donor) and a Lewis basic acceptor (XB-acceptor). Halogen bonds are important intermolecular interactions which find widespread applications in crystal engineering, functional materials and in molecular recognition.\textsuperscript{1–9} In recent years XB was found to be an innovative concept in organic synthesis and in this regard XB-donors have been established as versatile catalysts.\textsuperscript{10–12} The vast majority of XB-donors are based on monodentate iodine(I) derivatives with either a polyfluorinated or a $N$-heterocyclic backbone, e.g. the triazolium derivative 1 or the pyridinium derivative 2 (Figure 1, a), with cationic species being typically more reactive than neutral derivatives.\textsuperscript{13–17} Bidentate XB-donors such as imidazolium 3 have been described as well and were found to have a significantly higher reactivity than monodentate analogues.\textsuperscript{18}

Besides monovalent iodine(I) species, hypervalent iodine(III) derivatives, in the form of (cyclic) diaryliodonium salts, received growing attention as XB-donors, due to the high Lewis acidity of the hypervalent iodine atom.\textsuperscript{19} This Lewis acidity was severely investigated in a plethora of theoretical\textsuperscript{20–22} and experimental studies.\textsuperscript{23} After an initial
report in 2015 by Han and Liu about the use of diaryliodonium salts as catalysts for a solvent-free Mannich reaction, Huber and co-workers investigated iodonium salts 4 (Figure 1, b) in the Ritter-type solvolysis of benzhydryl chloride and [4+2] cycloadditions. Further XB-mediated halide abstractions for the initiation of a cationic polymerization or for the activation of a metal halogen bond followed.

Although these iodonium salts only act as monodentate XB-donors, their performance in most reactions is comparable to bidentate iodine(I) derivatives, underlining their high potential. Thiophene-based bidentate iodonium salt 5 as well as perfluorinated iodonium salt 6 were recently described by Huber and co-workers, which so far show the highest reactivity among all literature-described iodine(I) and iodine(III) XB-donors.

Figure 1. Selected examples of XB-donors based on iodine(I) with cationic $N$-heterocyclic backbones (a) and iodine(III) XB-donors (b).

In our group, we are strongly interested in the influence of $N$-heterocyclic substituents on the chemical properties of hypervalent iodine compounds, in particular aryl-$\lambda^3$-iodanes. We focus our investigations on the stability and the reactivity of these so far underrepresented reagents, always in direct comparison to well-established non-stabilized or $O$-stabilized derivatives. In this regard, we recently introduced $N$-heterocycle-stabilized iodanes (NHIs) and found a remarkable reactivity of these reagents which outcompetes well known iodanes in a plethora of oxidative couplings - even in catalytic applications. (Figure 2, a). We also developed chiral $N$-heterocycle-substituted iodoarenes as chiral iodane precursors and applied them in a plethora of highly enantioselective couplings (Figure 2, b). Very recently, we were able to introduce iodolopyrazolium salts as a unique class of $N$-heterocycle-based iodonium salts. In our initial report, we demonstrated their potential reactivity as XB-donors. Inspired by this initial, although only moderate activity, in XB catalysis, we herein want to use this structural motif and present the first systematic investigation of
N-heterocyclic iod(az)olium salts (NHISs) in general and their successful application as highly reactive XB-donors.

Results and Discussion

In our initial report, we described iodolopyrazolium triflates 7a and 7b. Even though these compounds could be isolated in high yields following a fast and robust synthesis, we were not able to receive structural information which would be important for a further rational variation with the goal to improve their XB-donor properties. We were meanwhile able to obtain single crystals of the chloride salt of 7a (7c) directly from the reaction media. As the most relevant structural information, X-ray analysis revealed a significantly shorter I-Cl bond length para to the pyrazole of 2.965 Å (79% of the sum of the vdW radii) than para to the phenyl core of 3.015 Å (81% of vdW), indicating this to be the more active site for halogen-bonding interactions (Figure 3). Thus, enhancing the electron deficiency of the N-heterocycle should increase the reactivity of the iodonium salt as a XB-donor.

In our previous investigations we elaborated, that diazole-substituted iodanes show an excellent relationship between reactivity and stability. We therefore started our

Figure 2. N-Heterocycle-substituted iodanes and aryl iodides and their applications.

Figure 3. Previously synthesized iodolopyrazolium salts 7a+b and crystal structure (ORTEP drawing) of 7c (CCDC 2082275) including the coordination of a second chloride to exemplify differences in the I-Cl bond length. Thermal ellipsoids displayed with 50% probability. Selected bond length: I1-C5: 2.135 Å; I1-C2: 2.063 Å; I1-Cl1: 2.965 Å; I1-Cl1: 3.015 Å. Selected bond angles: C2-I1-C5: 80.28°; C5-I1-Cl1: 161.48°; C2-I1-Cl1: 168.47°.
systematic search for better XB-donors through the synthesis of different diazole-containing NHISs. Beside the previously described iodolopyrazolium triflates 7a+b we generated novel NHISs (triflates and BArF salts) based on C- and N-bound pyrazoles 7d+8a-b, imidazoles 9+10a and imidazopyridine 11a. (Figure 4, a).

![Diagram](image)

Figure 4. Investigated mono- (a) and dicationic (b) N-heterocyclic iodonium salts.

Beside those monocationic species, we further wanted to decrease the electron density at the N-heterocycle to strengthen the XB-donor capability of the hypervalent iodine atom through an increased electron pull initiated by a charged N-heterocycle. This was achieved by the synthesis of the respective N-methylated, dicationic derivatives 7e-f, 8c-d, 10b-c, and 11b-c (Figure 4, b).

These structurally diverse NHISs were initially tested on the well-established Ritter-type solvolysis of benzhydryl chloride 12 to acetamide 13 as a typical benchmark reaction for XB-donors.25,43–45 The reaction was performed in wet acetonitrile, but at a lower concentration than previously described, to minimize influences of precipitating iodolium chlorides and to make the reaction even more challenging (Figure 5).25,40

Under these modified conditions iodolium triflate 4a, as a literature known standard, gave 42% yield after 72 h of the amide 13, while iodolopyrazolium triflate 7a yielded 72%, indicating a two times higher initial rate constant ($k_{rel}$). The exchange of the counterion to BArF (7d) had no significant effect on the reaction rate. The strong electron-withdrawing CF$_3$-substituted derivative 7b drastically increased the initial conversion rate with a seven times higher $k_{rel}$ value compared to the unsubstituted pyrazole 7a, yielding acetamide 13 in 54% yield after only 24 h. Next,
we investigated the \( N \)-bound pyrazole 8a which performed better than the \( C \)-bound derivative 7a, giving 13 in 77% after 24 h and nearly quantitative yield (96%) after three days. In contrast, imidazoles 9 and 10a yielded only low amounts of 13 with 24% and 5%, respectively. Instead, benzhydrol was formed in significant amounts. The imidazopyridine 11a appeared to be insoluble in acetonitrile and therefore did not promote the desired reaction.

We then investigated the dicationic \( N \)-methylated derivatives 7e, 8c, 10b and 11b. Although the \( C \)-bound \( N \)-Me-pyrazole 7e showed a higher initial reactivity, the overall performance was lower compared to the unsubstituted \( N \)-bound pyrazole 8a with 86% yield after 72 h. In comparison, the three other \( N \)-Me species showed a significantly higher reactivity. In contrast to the low performance of the imidazole 10a and the incompatibility of imidazopyridine 11a, \( N \)-Me imidazole 10b appeared to be among the best XB-donors giving 13 in 90% yield after only 24 h. The \( N \)-Me imidazopyridine 11b was even more reactive (95% after 24 h). However, following the already high reactivity of the unsubstituted pyrazole 8a, the \( N \)-Me derivative 8c outperformed all other XB-donors with 90% yield after only 4 h and nearly quantitative yield (99%) after 24 h, indicating an 174 times higher \( k_{rel} \) value compared to iodolium triflate 4a, as one of the hitherto best XB-donors tested in this transformation so far. It is worth mentioning, that the application of only 50 mol\% of XB-donor 8c still gave 13 in 78% yield after 72 h (see ESI – Figure S3).
Following the high performance of our $N$-heterocyclic iod(az)olium salts in the Ritter-type solvolysis of benzhydryl chloride (12), we were eager to test the much more challenging activation of $\alpha$-methylbenzyl chloride (14), of which only the easier bromide variant has been studied.\textsuperscript{29} In this reaction no conversion of the starting material 14 was observed using 4a, whereas with the best non-methylated $N$-HetAr-derivative, pyrazole 8a, 18% of the acetamide 15 was obtained after three days (Figure 6). With 23% yield after 72 h $C$-bound $N$-Me pyrazole 7e only performed slightly better. In contrast, $N$-Me imidazole 10b gave 79% within a similar time span. For the more reactive $N$-Me imidazopyridine 11b nearly the same yield (77%) was already observed after only 24 h. $N$-Methyl pyrazole 8c again proved to be top of its class with 92% conversion after 24 h and full conversion (99% yield) after 66 h. Compared to the non-methylated derivative 8a, 8c showed an approx. 35 times higher initial rate constant ($k_{rel} = 34.5$), underlining its performance as the best reported XB-donor for these types of halide abstractions to date.

![Figure 6](image-url)

**Figure 6.** Yield-vs.-time profile for the XB-mediated Ritter-type solvolysis of $\alpha$-methylbenzyl chloride (14) over the course of 72 h employing stoichiometric amounts of several cyclic iodonium salts as potential activators in wet CD$_3$CN. Yields determined via $^1$H-NMR spectroscopy.

Following their outstanding performance in the activation of C-Cl bonds, the activation of a metal-Cl bond was investigated in the gold(I)-catalyzed cyclization of propargylic amide 17 to oxazoline 18 (Figure 7). To overcome solubility issues in this reaction and since the corresponding tetrakis(3,5-bistrifluoromethyl)borate (BARF) derivatives proved to be more reactive in previous reports,\textsuperscript{27} the $N$-heterocyclic iodonium salts 7f, 8b+d, 10c and 11d were prepared by anion exchange for further investigations. $N$-
Methyl pyrazole 8c and imidazole 10b proved to be troublesome. By abstracting a 3,5-bis(trifluoromethyl)phenyl group from the borate and subsequent ring opening of the iodazole core, the formation of acyclic iodonium salts was observed as a major side reaction. After prolonged reaction time iodonium salt 16 was obtained in 74% yield (Scheme 1). In contrast, C-bound derivatives 7d and 11b showed a significantly lower affinity for this undesired side reaction and were successfully isolated as the corresponding BArF salts 7f and 11c. Switching the anion from BArF to tetrakis(pentafluorophenyl)borate finally solved the issue for the N-bound derivatives 8d and 10c.

Scheme 1. Ligand exchange and ring opening towards acyclic iodonium salt 16 as the major side reaction during anion exchange.

With the BArF salts in hand, the activation of the gold(I)-catalyst was investigated. In contrast to the previous results, iodolopyrazole 7b showed a lower reactivity with 78% conversion after 10 h \(k_{\text{rel}} = 0.6\) compared to iodolium salt 4b giving 18 in 93% conversion after the same time span (Figure 7). Again, a much higher reactivity was observed for the N-bound pyrazole 8b with 90% conversion after 3.5 h. All N-Me derivatives 7f, 8d, 10c and 11c showed only a slightly better performance than 8b, presumably as an indicator for a “close to maximum” conversion rate.

Figure 7. Conversion-vs.-time profile for the gold(I)-catalyzed cyclization of propargylic amide 17 in the presence of different cyclic iodonium salts as the activators. Yields determined via \(^1\)H-NMR spectroscopy with tetraethyl silane as the internal standard.
Imidazole 10c was determined to be the most efficient activator with 92\% conversion of amide 17 after 2.5 h and full conversion after around 6 h, with a four times higher initial rate constant than iodolium salt 4b.

We turned our focus towards the Diels-Alder cycloaddition of cyclopentadiene (19) and methyl vinyl ketone (20) as another benchmark reaction.\(^{15}\) Here, iodolium salt 4b has been previously investigated.\(^{25}\) We again performed a slight adaption of the initial reaction conditions by reducing the amount of cyclopentadiene 19 to only 4 equivalents. Under these conditions the blank reaction was neglectable after the investigated reaction end point of 3 h (Figure 8). Iodolium salt 4b provided 13\% yield (\(k_{\text{rel}} = 3.5\)), while iodolopyrazole 7b already gave 21 in 26\% yield (\(k_{\text{rel}} = 8\)). N-Bound pyrazole 8b again showed a significantly enhanced reactivity with 83\% yield after nearly 3 h (\(k_{\text{rel}} = 47\)). An even better performance was observed for C-bound N-Me pyrazole 7f with a full conversion after 2.5 h (\(k_{\text{rel}} = 91\)). However, N-methyl imidazopyridine 11c was by far the most efficient XB-donor in this transformation with a full conversion after only 10 min reaction time.

Following these promising results, we were eager to investigate the more challenging Diels-Alder reaction between cyclohexadiene (22) and MVK (20), in which the bidentate iodolium salts 5 was reported to be the so far only active XB-donor and nearly approached the activity of the strong Lewis acid BF\(_3\).\(^{28}\) In contrast, to the literature report, we started the investigation with a catalyst loading of 15 mol\% instead of 30 mol\%. Under these conditions, pyrazole 8b showed a low reactivity with only 2\% yield after 12 h (Figure 9). In comparison, all N-Me species 7e, 8d, 10c and 11c
showed high and nearly equal performances giving 23 in around 80-85% yield after 12 h. Furthermore, they even showed a slightly higher initial conversion rate than BF₃ etherate, although just falling short in overall reactivity (see the supporting information Figure S15 for this catalyst loading). To our delight, it then became apparent that the catalyst loading for the N-Me derivatives could be reduced to 5 mol% without significant loss in reactivity with yields between 76-83% after 12 h (Figure 9). Especially imidazopyridine 11c showed an outstanding reactivity with 40% yield after just 0.5 h and 83% after 12 h. Furthermore, at this catalyst loading even BF₃ etherate was outperformed (70% after 12 h), indicating imidazopyridine 11c to be the most active XB-donor for this transformation described so far. Additionally, even at only 2.5 mol% catalyst loading, 11c still gave 23 in 66% yield after 12 h. At last, a stability test with this catalyst was conducted due to the described slow side reaction with the BArF counterion during anion exchange. For this, an additional equivalent of both starting materials was added after 10 h, revealing nearly the same conversion profile in the second run as in the first one (see supporting information Figure S17+S18), proving the possible side reaction to be of minor influence. The acyclic iodonium salt 16 showed a completely different conversion profile with a lower overall activity.

![Figure 9](image.png)

**Figure 9.** Yield-vs.-time profile for the XB-mediated Diels-Alder reaction between cyclohexadiene (22) and MVK (20) over the course of 12 h employing iod(az)onium salts as potential activators in CD₂Cl₂. Yields determined via ¹H-NMR spectroscopy using tetraethyl silane as the internal standard.

As another carbonyl-activating benchmark reaction, the Michael addition between 1-methylindole (24) and trans-β-crotonophenone (25) to 26 was investigated.¹⁸,²⁸,⁴⁶,⁴⁷ Due to the high performance in previous reactions, we started our investigation with
only 5 mol% catalyst loading. As reported for 4b, both non-methylated pyrazoles 7d and 8b showed no catalytic activity (Figure 10), whereas N-Me pyrazole 7e gave 26 in 52% yield after almost 5 h. Similar to their high performance in the Ritter-type reactions 8d, 10c and 11c showed outstanding reactivity with close to quantitative yields after 1-1.5 h. We further decreased the catalyst loading of 8d and 11c to 1 mol% and were delighted to observe a high reactivity for both XB-donors as well, with 8d clearly outperforming 11c with about 95% yield of 26 after only 4 h. In comparison with the reported results for the bidentate iodolium salt 5 (62% after 12 h28), this further implies pyrazole 8d to be the most potent organic XB-donor for this transformation described so far.

Finally, we investigated the nitro-Michael addition between 5-methoxyindole (27) and nitrostyrene 28.18,28 With 10 mol% catalyst loading, pyrazole 7d was nearly inactive as XB-donor (Figure 11), whereas N-Bound pyrazole 8b yielded 28 in 26% after 4 h and 61% after 24 h. When turning to the N-Me derivatives 7f, 8d, 10c and 11c, a problem was encountered. The otherwise highly reactive XB-donors 8d, 10c and 11c showed only low performances with 19-29% yield of 28 after 4.5 h. Further investigations revealed them to be incompatible with 5-methoxyindole (27). Under these conditions a plethora of different reaction and decomposition products were observed when mixing catalysts and indole 27 (see supporting information Figure S27), which limits their applicability. Only the least reactive N-Me pyrazole 7f, showed satisfying levels of activity with 61% yield after 4.5 h with 10 mol% catalyst loading and still 50% yield at
5 mol%. For the non-methylated iodonium salts 7d and 8b, no undesired side reactions were observed. Because of this, although pyrazole 7f showed the highest performance, N-bound pyrazole 8b arguably possesses the best balance between reactivity, selectivity, and stability in comparison to all hitherto investigated monodentate XB-donors.

![Chemical structure](image)

Figure 11. Yield-vs.-time profile for the XB-mediated nitro-Michael reaction between 5-methoxyindole (27) and nitrostyrene 28 over the course of 4.5 h employing several cyclic iodonium salts as potential activators in CD2Cl2. Yields determined via 1H-NMR spectroscopy using tetraethyl silane as the internal standard.

### Conclusion

In conclusion, novel N-heterocyclic iod(az)olium salts (NHISs) were synthesized and introduced as powerful XB-donors in organocatalysis. N-Methylated, dicationic derivatives showed an outstanding performance in all investigated benchmark reactions showing an even higher reactivity than all previously described monodentate organic iodine(I) and (III) donors. On top, their activation capability of unsaturated carbonyls in the Michael addition and Diels-Alder reactions surpasses the activity of bidentate iodolium salts and the strong Lewis acid BF3 with catalyst loadings of only 5 mol%. Due to their straightforward synthesis, their throughout excellent performance, and their high stability, we are confident that this novel class of XB-donors will find frequent use as organocatalysts in the near future. Further installation of chiral units should allow efficient enantioselective transformations. This further variation and their
implementation into preorganized bidentate structures is under current investigation in our laboratory.

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