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Halogen-Bonding-Induced Hydrogen Transfer to C═N Bond with Hantzsch Ester

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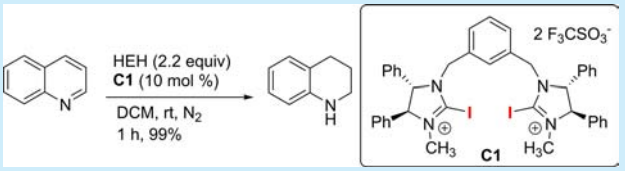
Supporting Information

ABSTRACT: Several bidentate dihydroimidazolines were prepared and investigated as catalysts for hydrogen transfer reduction of C═N bond with Hantzsch ester. Highly efficient reactions were observed for quinolines and imines with low catalyst loading of 2 mol %. The presence of halogen bonding was elucidated using NMR studies and isothermal calorimeric titrations. Binding constants of the XB donors were also measured using isothermal calorimeric titrations (ITC).



Halogen bonding (XB) is the directional interaction between a covalently bound halogen atom (X) and a Lewis base.[1] This noncovalent interaction was conclusively revealed by Hassel through X-ray crystallographic studies of dihalogen molecules with Lewis bases.[2] Halogen bonding has impacted research fields which require control of intermolecular recognition and self-assembly processes.[3] In particular, it has found applications in crystal engineering and supramolecular chemistry.[4] These observations are generally under thermodynamic control. Initially, this process is reversible under experimental conditions, and it will terminate until the assembly with XB is formed under thermodynamically favorable state.

As it is highly directional, halogen bonding has potential to be used in catalytic processes.[5] Bolm[6] and Huber[7] were the first to recognize that XB can be exploited for organocatalysis. Bolm reported that haloperfluoroalkanes can be used as catalysts for the reduction of 2-phenylquinoline using a Hantzsch ester.[6] *N*-Heterocycles such as quinolines are well-known as efficient XB acceptors in the study of halogen bonding.[8] Huber developed charge-assisted imidazolium XB donors to activate benzhydryl bromide for a Ritter-type reaction with acetonitrile.[7a] These bidentate donors have strong interactions with halogen atom, with constant binding in the order of 10^6. Stoichiometric amounts of these XB donors are required to promote the reaction. Huber further developed neutral polyfluorinated arenes as catalysts for the addition of ketene silyl acetal to 1-chloroisochroman.[5a] Unlike the previous example, in which the leaving halide binds to the XB donor, this reaction uses a silyl to trap the leaving halide, allowing the XB donors to be regenerated in the reaction.

Inspired by their work, we designed a series of bidentate dihydroimidazoline XB donors (Figure 1, **C1**–**C6**). The synthesis of **C1** began from commercially available chiral diamine (Scheme 1). The imidazolidine intermediate was obtained in high yield through condensation with glyoxylic acid, followed by oxidative decarboxylation with NBS.[9] The diimidazolidine framework was assembled using *m*-xylylene dibromide. Neutral iodoimidazoline was obtained next, and

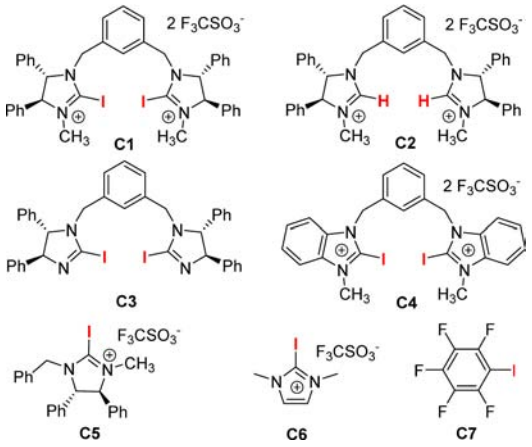
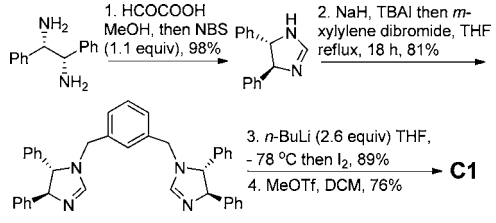


Figure 1. Halogen bond donors **C1**–**C7**.

Scheme 1. Synthesis of Halogen Bond Donor C1



subsequent methylation resulted in the cationic imidazolium **C1**. Through similar routes, other XB donors **C2**, **C3**, **C4**, and **C5** were also obtained in good yields (see the Supporting Information for details). These donors were purified with flash chromatography followed by recrystallization. Notably, the imidazolium **C1** has much better solubility in organic solvents than imidazolium **C4**.

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The structure of **C1** was confirmed using the X-ray crystallographic method (Figure 2). The interaction between the XB donor with the triflate counterions (2.868 Å) can be clearly observed, which is below the sum of the van der Waals radii.[7a]

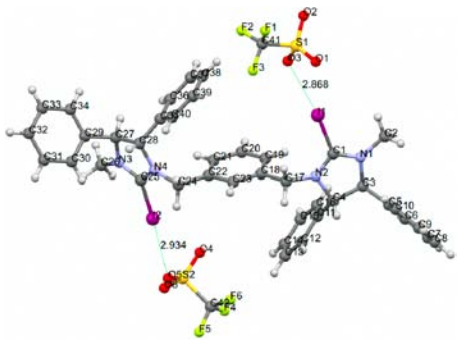


Figure 2. X-ray structure analysis of the XB donor C1 (elipsol at 50% probability); selected bond lengths (Å) and angles (deg): C1–I1 2.088(10), C1–N1 1.309(9), C1–N2 1.322(10), C3–N1 1.499(8); N1–C1–N2 114.0(8).

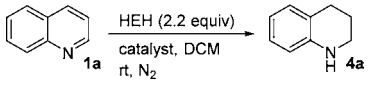
The hydrogen-transfer reaction of C=N, using Hantzsch ester as hydrogen source, is a mild method to reduce nitrogen-containing compounds.[10] Brønsted acids were shown to be particularly good catalysts to promote this reaction.[11] XB donors can act as Lewis acids in the presence of pyridines and heterocycles; it is likely to be an efficient catalyst for this reaction. The effectiveness of a XB donor as a catalyst probably follows the "goldilocks" principle. A weak XB donor might not be sufficiently Lewis acidic to decrease the HOMO of C=N, while a strong XB donor may bind too tight to the product/reagent of the reaction and inhibit the catalytic cycle. A suitable XB catalyst is thus a dynamic XB donor.

We selected the reduction of quinoline **1a** as a model for our initial investigation (Table 1). With 10 mol % of imidazolium **C1** as the catalyst, we obtained complete reaction within 1 h, and the resulting amine was obtained with an isolated yield of 92% (entry 1). For imidazolium **C2**, the deiodo version of **C1**, a non-XB donor, the reaction was not completed after 24 h (entry 2). After 1 h, only about 10% of the reduced adduct was detected using GC. The neutral imidazoline **C3**, nonmethylated variant of **C1**, was also unable to complete the reaction within 24 h (entry 3). Both the presence of the iodo group and the electron-withdrawing tendency of the imidazolium cationic core are essential for the reactivity of the catalyst **C1**. Solubility of imidazolinium **C4** is poor and may contribute to its ineffectiveness as a catalyst (entry 4). XB donor **C5**, the monodentate version of **C1**, was able to catalyze the reaction with some efficiency (entry 5). We were not able to detect any product when imidazolium **C6** was used (entry 6). When a well-known XB donor pentafluoroiodobenzene was used as the catalyst, sluggish reactivity was observed (entry 7). To remove the doubt that the reaction is catalyzed by residual acid present in the catalyst, 20 mol % of K_2CO_3 was added to a separate experiment, which proceeded smoothly (entry 8). In the absence of catalyst, only a trace amount of product was detected within 19 h (entry 9).

With further optimization, we found that quinoline **1a** can be catalyzed with 2 mol % of **C1** (Table 2, entry 1). Under the optimized reaction conditions, a variety of mono and disubstituted quinolines were reduced with high yields (entries 2–9). Both electron-withdrawing and electron-donating substituents are suitable.

In the presence of 5 mol % of **C1**, 1,10-phenanthroline **1j** can be reduced to the corresponding 1,2,3,4-tetrahydro-1,10-phenanthroline **4j** (Scheme 2, eq 1). Reduction of unactivated pyridine is nontrivial, and there are only a limited number of reports.[12] With our methodology, 3-carbonylpyridine **1k–l** can be reduced in high yield to tetrahydropyridines **4k–l** albeit with long reaction time (Scheme 2, eq 2).

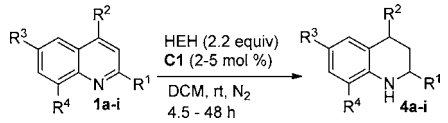
Table 1. Transfer Hydrogenation of Quinolone 1a with Hantzsch Ester in the Presence of Different Catalysts[a]



entry	catalyst (mol %)	time (h)	yield[b] (%)
1	**C1** (10)	1	99 (92)[c]
2	**C2** (10)	24	68
3	**C3** (10)	24	45
4	**C4** (10)	19	78
5	**C5** (10)	3	91
6	**C6** (10)	21	trace
7	**C7** (10)	67	30
8[d]	**C1** (10)	2.5	99
9	–	19	trace

[a]HEH: diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate). [b]Determined using GC–MS. [c]Isolated yield in parentheses. [d]20 mol % K_2CO_3 added.

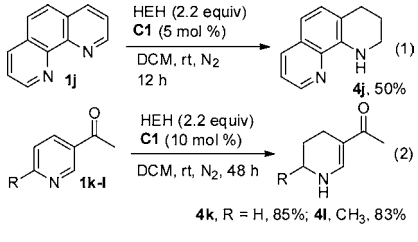
Table 2. Transfer Hydrogenation of Quinoline Derivatives in the Presence of C1[a]



entry	**1**	$[R^1,R^2,R^3,R^4]$	**C1** (mol %)	time (h)	yield[b] (%)
1	**1a**	[H,H,H,H]	2	4.5	99
2	**1b**	[Me,H,H,H]	2	24	95
3	**1c**	[H,Me,H,H]	5	48	95
4	**1d**[c]	[Ph,H,H,H]	2	5	95
5	**1e**	[4MeOC$_6$H$_4$, H,H,H]	2	5	93
6	**1f**	[Ph,H,Br,H]	2	15	95
7	**1g**	[Ph,H,NO$_2$,H]	2	3	90
8	**1h**	[Ph,H,Me,H]	2	24	90
9	**1i**	[Me,H,H,OH]	5	7	90

[a]HEH: Hantzsch ester. [b]Isolated yield. [c]The enantiometric excess of the product is zero.

Scheme 2. Transfer Hydrogenation of Pyridine Derivatives in the Presence of C1



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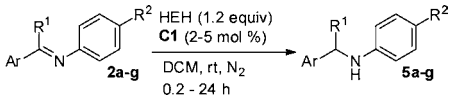
Next, we examined the reduction of imine derivatives in the presence of **C1** (Table 3). In most cases, the imines can be reduced in good yields within 2 h (entries 1−5). For imines with highly electron-withdrawing substitution, no reduction was observed (entry 6).

Table 3. Transfer Hydrogenation of Imine Derivatives in the Presence of C1



entry	2	[Ar,R^1,R^2]	**C1** (mol %)	time (h)	yield[a] (%)
1	**2a**	[Ph,H,H]	2	1	90
2	**2b**	[4ClC$_6$H$_4$,H,H]	5	1	92
3	**2c**	[4MeC$_6$H$_4$,H,H]	2	1	90
4	**2d**	[1-naphthyl,H,H]	2	2	86
5	**2e**	[4NO$_2$C$_6$H$_4$,H,Me]	2	0.2	90
6	**2f**	[4NO$_2$C$_6$H$_4$,H,NO$_2$]	2	24	n.r.[b]
7	**2g**	[Ph,Me,H]	5	24	93

HEH: Hantzsch ester. [a]Isolated yield. [b]No reaction.

In order to verify the presence of the proposed *N*-halogen interaction, we conducted several NMR experiments (Figure 3).

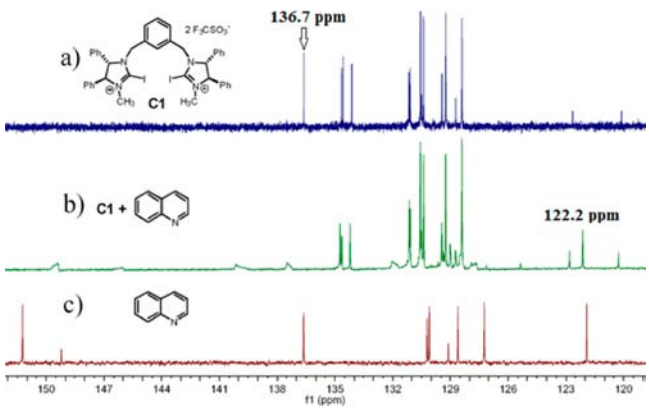
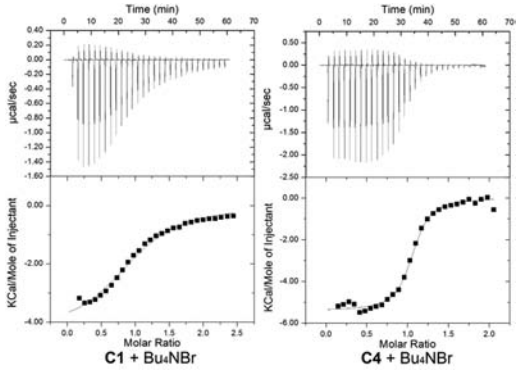


Figure 3. ^{13}C NMR spectra of **C1** and **1a** in CD_2Cl_2: (a) **C1**; (b) **C1** + **1a** (1:1); (c) **1a**.

Through DEPT and 2D NMR (HMQC and HMDC), we concluded that the iodine-carrying carbon of **C1** has a δ = 136.7 ppm in the ^{13}C NMR (Figure 3, Spectra a). When 1.0 equiv of **1a** is added to **C1**, the peaks of **1a** were much reduced (spectra b). On closer inspection, it seems that the peaks of **1a** had broaden, indicating a presence of a number of nonequivalent conformations. At the same time, the iodine-carrying carbon of **C1** shifts upfield by 14.5 ppm. Such an observation was not present when triflic acid (TfOH) was added to **1a** (see the Supporting Information for details). The NMR experiments provide an indication that there is a clear interaction between the nitrogen atom of **1a** and iodine atom of **C1**. Resnati and co-workers reported the ^{19}F NMR study of the halogen bonding between haloperfluorocarbons (XB donor) and a heteroatom (XB acceptor).[13] Because of the halogen-bonding interaction, it was also observed that the ^{19}F peak of the XB donor shifted upfield significantly. Huber and co-workers also made similar observations in the ^{13}C NMR spectra of the imidazolium XB donor with its acceptor.[7a]

Isothermal titration calorimetry (ITC) was developed by Huber to determine the halogen bond strength of XB donors.[7d] Using a similar approach, we measured the binding constants of **C1** and **C4** with bromide (Table 4); they are 3.29 × 10^4 and 4.57 × 10^5 M^{-1}, respectively.

Table 4. Isothermal Calorimetric Titrations of Halogen Bond Donors with Halide[a]



entry	guest	host	K (mol^{-1})	ΔH (kJ/mol)	$T\Delta S$ (kJ/mol)
1	**1a**	**C1**			
2	Bu$_4$NBr	**C1**	3.29E4	−18.0	7.8
3	Bu$_4$NBr	**C4**	4.57E5	−22.6	9.7

[a]Conditions: halogen bond donors (0.2 mM), halide (2 mM).

In conclusion, we have prepared a series of novel halogen-bonding donors based on a bidentate dihydroimidazoline core. One of these donors, imidazolium **C1**, was found to be an efficient catalyst for the hydrogen-transfer reduction of the C=N bond with Hantzsch ester. Highly efficient reactions were observed for quinolines and imines with low catalyst loading of 2 mol %. The presence of halogen bonding was elucidated using NMR studies and isothermal calorimeric titrations. Binding constants of the XB donors were also measured using isothermal titration calorimetry (ITC).

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data, X-ray structural analysis, and ITC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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