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Halogen Bond-Catalyzed Povarov Reactions

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Abstract. The use of a bidentate halogen bond donor to catalyse Povarov reactions of imines derived from aryl aldehydes and anilines is reported. Dienophiles used in these reactions included 2,3-dihydrofuran, *N*-vinyl-2-pyrrolidone and *N*-Cbz-protected 2,3-dihydropyrrole. Very high isolated yields of the desired 1,2,3,4-tetrahydroquinoline products were obtained with low catalyst loadings (0.01 equivalents) and short reaction times (minutes to hours) at ambient temperature. Notably, the bis(benzimidazolium iodide)-based catalyst used in these reactions proved to be more efficient than analogous bromine and chlorine functionalized compounds, as well as a related monodentate benzimidazolium iodide. These observations are similar to what has been reported by others regarding halogen bond organocatalysis, and may prove useful in guiding catalyst design as the field moves forward.

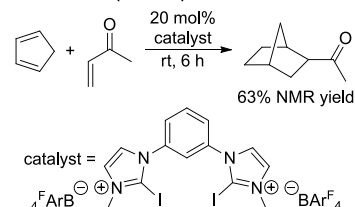
Keywords: halogen bond; organocatalysis; Povarov reaction; cycloaddition; tetrahydroquinolines

Halogen bonds are non-covalent interactions that can be considered to be functionally analogous to hydrogen bonds,^[1] and the use of organic halides as halogen bond donors to catalyse organic reactions has been examined recently.^[2] In this context organic halides have been used to activate quinolines,^[3] imines,^[4] carbon-halogen bonds,^[5] silicon-halogen bonds,^[6] aldehydes and ketones,^[7] Michael acceptors,^[8] thioamides,^[9] trichloroacetimidates,^[10] hydantoin,^[11] nitroalkenes,^[12] alkoxyallenes,^[13] ethers,^[14] and iodonium ylides^[15] in various transformations. With regards to the reactions studied, one area of focus has been cycloaddition reactions, and numerous variations of Diels-Alder reactions have been reported to be catalyzed by organic halide halogen bond donors (Figure 1).^[16]

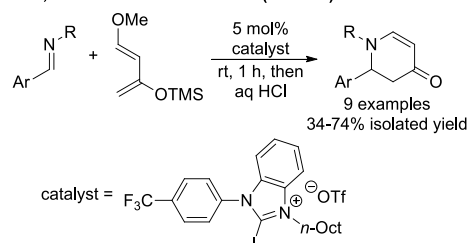
In the context of halogen bond catalysis, we previously reported the use of bidentate bis(benzimidazolium iodide) salt **1** to catalyse Friedel-Crafts reactions between aldehyde and ketone electrophiles and indole nucleophiles to form bis(indolyl)methanes (Figure 2a).^[17,18] Now we wish to report that **1** is also efficient as a catalyst for

Povarov reactions^[19,20] of imines derived from arylaldehydes and anilines with a range of dienophiles to form 1,2,3,4-tetrahydroquinolines in high isolated yields using mild reaction conditions and low catalyst loadings (Figure 2b).^[21]

a) Huber and co-workers (ref. 16a):

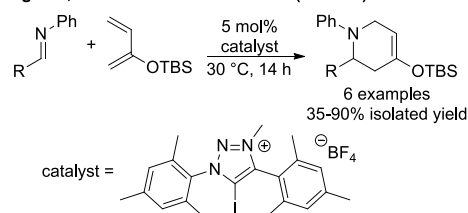


b) Takeda, Minakata and co-workers (ref. 16b):



Kanger and co-workers later studied halo-1,2,3-triazolium salt catalysts in a similar reaction (ref. 16c).

c) Haraguchi, Fukuzawa and co-workers (ref. 16d):



d) Arai and co-workers (ref. 16e):

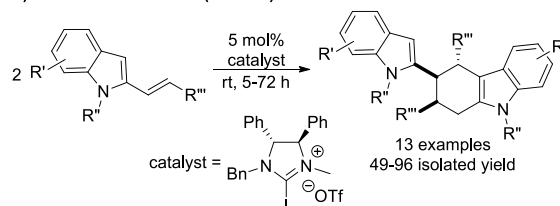


Figure 1. Halogen bond-catalyzed Diels-Alder reactions.

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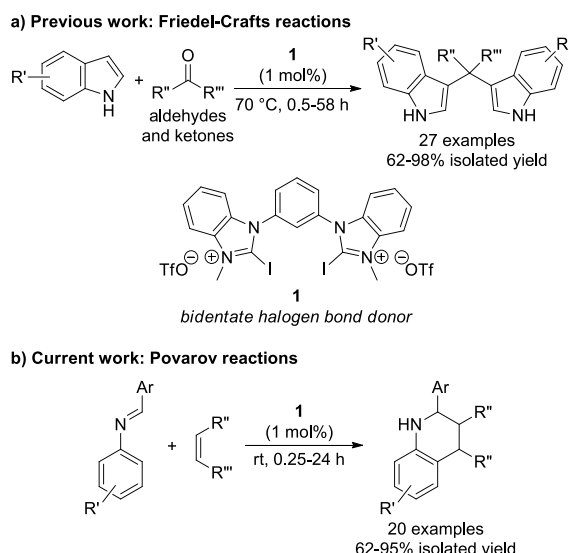


Figure 2. Halogen bond-catalyzed Friedel-Crafts and Povarov reactions.

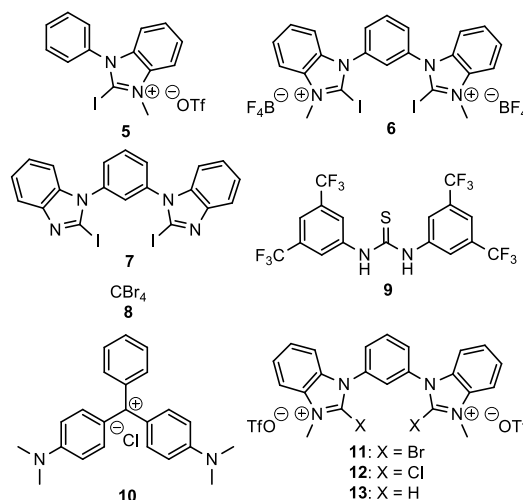
As the starting point for this project we chose to study the reaction between imine **2a** and 2,3-dihydrofuran (**3**) (Table 1), and since the use of 1 mol% of **1** in acetonitrile worked well in the aforementioned Friedel-Crafts reactions, we applied these conditions to this reaction as well. Gratifyingly a separable mixture of *endo* and *exo* isomers of **4a** was formed in very high isolated yield after only 0.5 hour at room temperature (entry 1). The *endo:exo* ratio was determined by ^1H NMR analysis of the crude reaction mixture, before the isomers were separated by chromatography for characterization, and was found to be typical for this reaction.^[22] When **1** was omitted from the reaction mixture, no reaction was observed (entry 2). Replacement of **1** by monodentate analogue **5** resulted in a lower yield of **4a** (entry 3), as was the case in our Friedel-Crafts reactions, in which case even using 2 mol% of **5** did not provide the catalytic efficiency of 1 mol% of **1**.^[17] When the triflate anions of **1** were replaced with tetrafluoroborate anions in **6**, the yield of **4a** was even lower (entry 4). The reason for the lower yield in this reaction is unclear at this point, but it has previously been noted that counter ion effects in halogen bond catalysis of such reactions is complicated and rather unpredictable.^[16c] Neutral analogue **7** was unable to catalyse the reaction, as were simple hydrogen bond donor CBr_4 (**8**), hydrogen bond donor thiourea **9**, and organic cation malachite green (**10**) (entries 5–8).

A series of control reactions was then performed in order to provide evidence that halogen bonding was indeed operative in the reaction between **2a** and **3** in the presence of **1**. Replacing the iodine atoms of **1** with bromine atoms in catalyst **11** afforded **4a** in slightly lower yield (entry 9), and with chlorine atoms in catalyst **12** the yield of **4a** was lower still (entry 10). Omitting the halogen atoms altogether in **13** resulted in no desired product being formed in its presence (entry 11). This reactivity trend of $\text{I} > \text{Br} > \text{Cl}$ is the

same as what was observed in the halogen bond-catalyzed aza-Diels-Alder reaction reported by Kanger and co-workers (Figure 2b).^[16c] Furthermore, addition of 0.1 equivalents of Bu_4NI to the reaction mixture completely shut down the formation of **4a**, as might be expected (entry 12). While the addition of the bases pyridine, $i\text{Pr}_2\text{EtN}$ or K_2CO_3 did not dramatically affect the outcome of the reaction in terms of yield (entries 13–15), diastereoselectivity did seem to

Table 1. Povarov reactions between **2a** and **3**.^[a]

entry	catalyst	additive	yield ^[b]	<i>endo:exo</i> ^[c]
1	1	nil	90	60:40
2	nil	nil	0	-
3	5	nil	55	56:44
4	6	nil	23	59:41
5	7	nil	0	-
6	8	nil	0	-
7	9	nil	0	-
8	10	nil	0	-
9	11	nil	82	58:42
10	12	nil	65	60:40
11	13	nil	0	-
12	1	$\text{Bu}_4\text{NI}^{[d]}$	0	-
13	1	pyridine	85	73:27
14	1	$i\text{Pr}_2\text{EtN}$	83	75:25
15	1	K_2CO_3	78	76:24
16	1	BHT ^[e]	89	65:35
17 ^[f]	1	nil	91	63:37



^[a] General reaction conditions: **2a** (1.0 mmol), **3** (4.0 mmol), catalyst (0.01 mmol), additive (0.001 mmol) in MeCN (2 mL), rt, 0.5 h.

^[b] Combined isolated yield of *endo* and *exo* isomers of **4a**.

^[c] Determined by ^1H NMR analysis of crude **4a**.

^[d] Reaction was performed using 0.1 mmol Bu_4NI .

^[e] Reaction was performed using 0.02 mmol of BHT.

^[f] Reaction performed using **2a** (10.0 mmol), **3** (40.0 mmol), and **1** (0.1 mmol) in MeCN (20 mL) at rt for 0.5 h.

improve slightly for reasons that we cannot explain at this point. These results indicate that the presence of adventitious acid was likely not responsible for the observed catalysis. Furthermore, the addition of BHT to the reaction mixture also did not significantly alter the outcome of the reaction (entry 16), indicating that a radical mechanism was unlikely. Finally, to examine the scalability of the reaction we performed on a 10-fold larger gram-scale and obtained similar results in terms of yield and selectivity (entry 17).

Having established that **1** can indeed act as an efficient catalyst for Povarov reactions, we next examined the range of imines that can be used in such transformations. Imines **2b-j**, bearing either an electron-donating or electron-withdrawing substituent on one or both of the aromatic rings, were all successfully used, and we were able to prepare 1,2,3,4-tetrahydroquinolines **4b-j** in good to very high isolated yields in generally short reaction times using the optimized reaction conditions (0.01 equivalents of **1** in MeCN at room temperature) (Figure 3). Only the reaction involving chlorine-substituted imine **2c** was a bit of an outlier, and afforded relatively low yield (62%) of **4c**, with some recovered starting material, after a longer reaction time (24 h), compared to all of the other reactions performed (80-93% yield, 1-2 h).

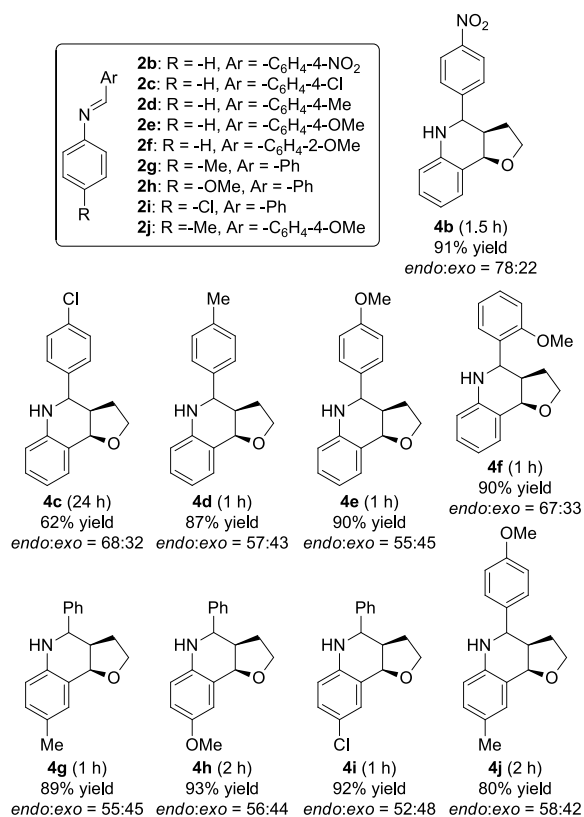


Figure 3. Povarov reaction products using **3**.

We next looked at what other dienophiles could be used in our Povarov reactions, and found that both *N*-vinyl-2-pyrrolidone (**14**)^[23] and *N*-Cbz-protected 2,3-dihydropyrrole (**15**)^[24] were suitable, and allowed for the production of 1,2,3,4-tetrahydroquinolines **16a-g**

and **17a-c**, respectively (0.01 equivalents of **1** in MeCN at room temperature) (Figure 4). The reactions with **14** were generally a bit more sluggish than the reactions with **3**, while the reactions with **15** were very efficient. Even when chlorine-substituted **2c** was the imine reaction partner for **15**, product **17b** could be isolated in 92% yield after only 1 hour. It should be noted that for products **16a-g**, the *cis:trans* ratios could only be estimated in some cases due to the very high diastereoselectivity observed that is consistent to what has previously been reported.^[23]

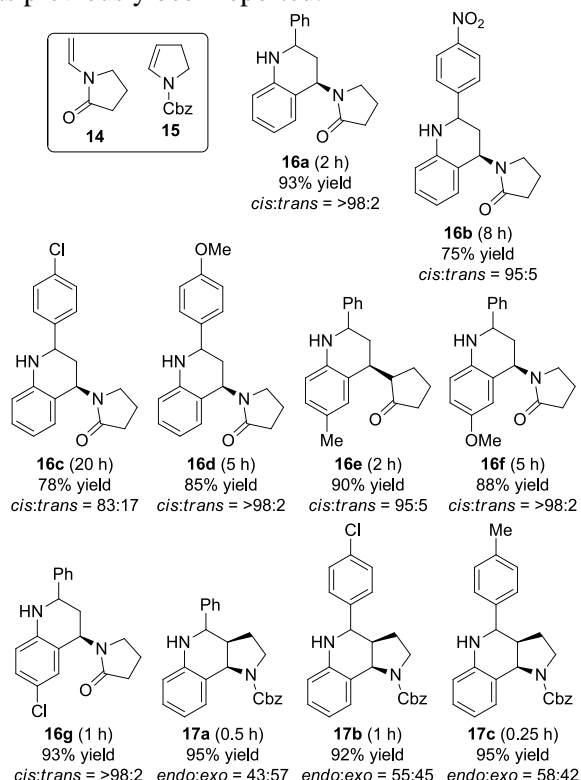


Figure 4. Povarov reaction products using **14** and **15**.

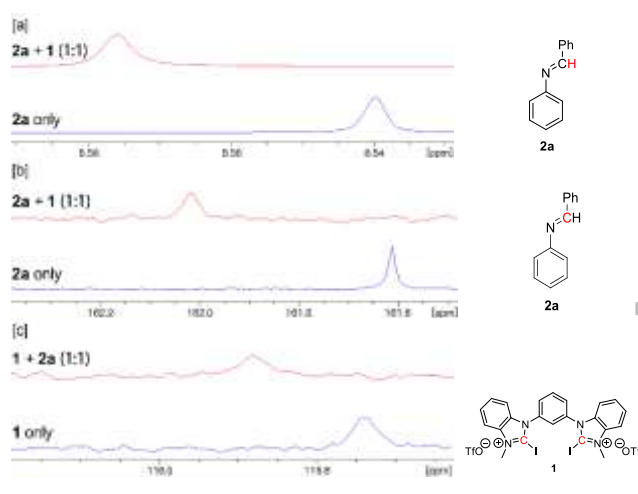


Figure 5. NMR studies.

Additional evidence for halogen bonding between **1** and the imine substrate **2** being responsible for the observed catalysis in our reactions was obtained from a series of NMR experiments (Figure 5). The imine proton of **2a** clearly shifted downfield slightly when in the presence of 1 equivalent of **1** (Figure 5a), as did the imine carbon atom of **2a** (Figure 5b). Furthermore, the same was true for the iodine functionalized carbon atoms of **1** when 1 equivalent of **2a** was added (Figure 5c).^[7d]

Based on our results, we believe that **1** is able to catalyse Povarov reactions of imines **2** by formation of complex **A** (Figure 6). The greater catalytic efficiency of **1** compared to that of **5** (Table 1, entry 1 vs. entry 3) seems to indicate that both iodine atoms of **1** are involved in substrate activation. Reaction of the dienophile at the imine carbon is thus facilitated so that the Povarov reaction can occur by either a concerted or stepwise mechanism to form the observed 1,2,3,4-tetrahydroquinoline products.

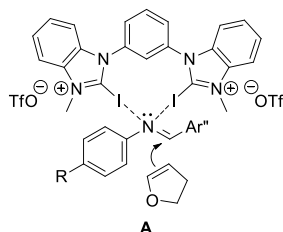


Figure 6. Halogen bond activation of imines **2** by **1**.

In summary, we have found that bidentate **1** is an efficient catalyst in a variety of Povarov reactions for the synthesis of 1,2,3,4-tetrahydroquinolines. Our observations in this research project agree with what has previously been reported, by both us and others; that bidentate catalysts are much more efficient than monodentate ones, and organic halides functionalized with iodine atoms are more effective as catalysts than bromine or chlorine containing analogues. Hopefully these observations will drive catalyst design in the future, and thus lead to a broadening of the utility of halogen bond catalysis.

Experimental Section

General Procedure: Catalyst **1** (8.9 mg, 0.01 mmol) and dienophile **3**, **14**, or **15** (4.0 mmol) were placed in a dry 1 dram vial equipped with a magnetic stirring bar. Acetonitrile (2.0 mL) was added, followed by imine **2** (1.0 mmol). The resulting solution was stirred at rt and monitored by TLC analysis. When the reaction was determined to be complete, the solvent was removed *in vacuo*, and the crude product was analyzed by ¹H NMR analysis to determine the *endo:exo* ratio. The crude product was then purified by silica gel chromatography (EtOAc/hexane) to afford both isomers of product **4** or **17**. For product **16**, only the major isomer was isolated.

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