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Non-bonding Electron Pair versus π-Electrons in Solution Phase Halogen Bond Catalysis: Povarov Reaction of 2-Vinylindoles and Imines

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Abstract. The non-bonding electron pair (n-pair) of heteroatoms and π-electrons are both efficient halogen bond (XB) acceptors. In solid and gas phase studies, n-pairs generally prevail over π-bonding orbitals as XB acceptors, whereas few studies have been conducted regarding the preference in solution phase. Herein, the Povarov reaction via the C–I···N XB interaction and [4+2] cycloaddition via the C–I···π XB interaction were evaluated, revealing that the n-pair was more dominant in the XB catalysis system in solution. The XB donor-catalyzed Povarov reaction gave diverse indolyl-tetrahydroquinoline derivatives in good yields. Synthesis of indolyl-quinolines was also developed.

Keywords: Halogen bond; Povarov reaction; Tetrahydroquinoline; Quinoline; Indole; Iodine

Halogen bond (XB) is a non-covalent interaction between a σ-hole of an electron-deficient halogen atom (XB donor) and a Lewis base (XB acceptor).[1] X-ray crystallographic studies conducted by Hassel in the 1950s were crucial in identifying the structural features of these non-covalent interactions, revealing that both the non-bonding electron pair (n-pair) of a heteroatom and aromatic π-electrons acted as efficient XB acceptors in the solid phase (Figure 1A).[2] When both an n-pair and π-electrons are present in the XB acceptor (e.g., 2,2-bipyridine), the n-pair is preferentially involved in XB formation.[3] This phenomenon is observed in various solid phase studies where n-pairs generally prevail over π-bonding orbitals as XB acceptors.

As with the solid phase studies, n-pairs are more dominant than π-systems in gas phase studies.[4] Interestingly, exceptional examples were reported by Legon for complexes of relatively electron-rich aromatic compounds such as furan and thiophene with chlorine monofluoride (Figure 1B, left).[5] In those

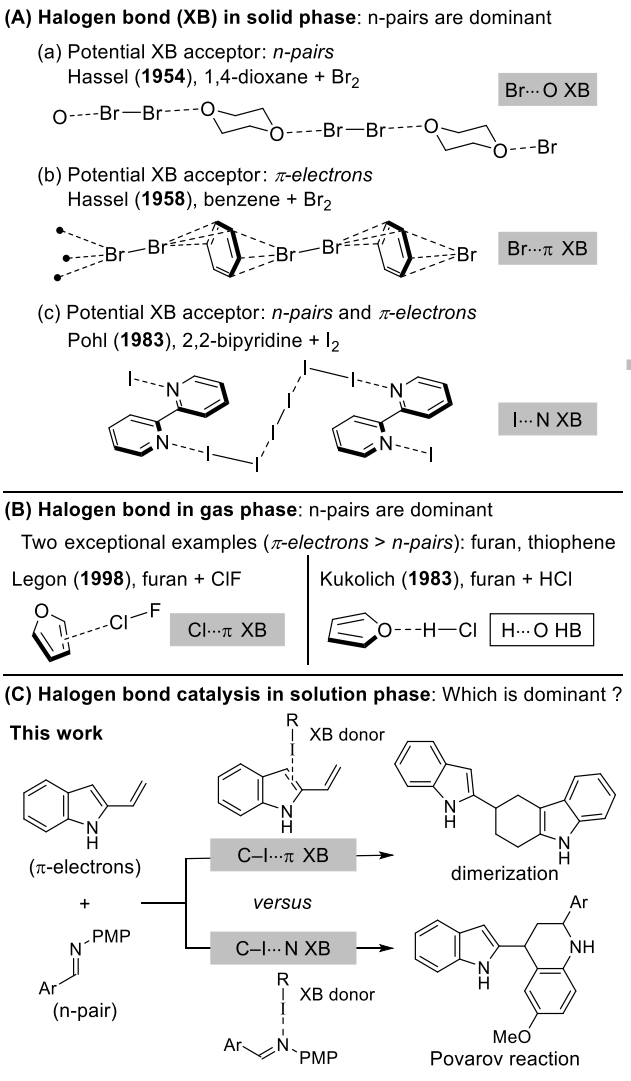

Figure 1. Halogen bond in solid, gas and solution phases.

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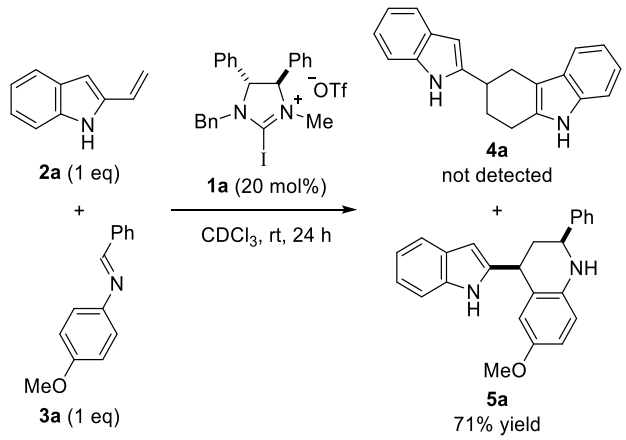
aromatic systems, π-electrons dominated over the n-pairs as XB acceptors. When the XB donor was replaced with hydrogen chloride, a Cl−H···O complex was formed through a hydrogen bond (HB), which is a unique difference between XB and HB (Figure 1B, right).[6]

Unlike these solid state and gas phase studies, the preference for n-pairs and π-electrons as XB acceptors in the solution phase has not been extensively investigated, despite various applications of XB in molecular recognition and catalysis.[7,8,9] As the first example of the use of C−I···π XB in catalysis, electrophilic activation of 2-alkenylindoles by cationic XB donors for [4+2] cycloadditions was developed.[9x] To evaluate which is dominant in catalysis in the solution phase, in this study, C−I···π XB-catalyzed dimerization was selected as a benchmark reaction. By adding *N*-*p*-methoxyphenyl (PMP) imines to the [4+2] dimerization system as n-pair type XB acceptors, a competitive reaction between the dimerization via C−I···π XB and the Povarov reaction via C−I···N XB would be investigated (Figure C).

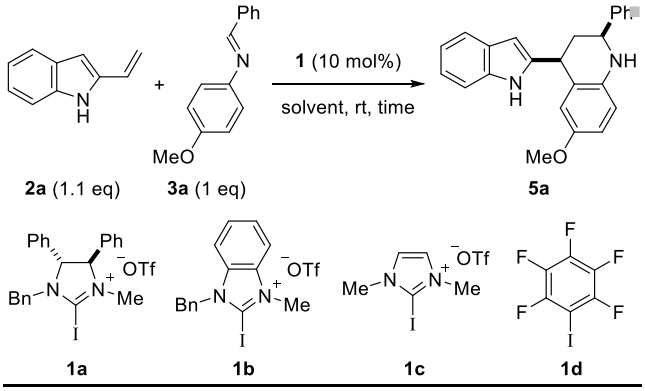
The competitive reaction (Scheme 1, **2a**+**2a**→**4a** versus **2a**+**3a**→**5a**) was performed using XB donor **1a** which was previously found to be the optimum catalyst for dimerization of **2a**.[9x] The Povarov reaction was found to be dominant (**4a**: 0% yield versus **5a**: 71% yield, single diastereomer), suggesting that, in accordance with previous studies in the solid and gas phases, C−I···N XB was also preferred in the solution phase. Several Brønsted acid or Lewis acid catalyzed Povarov reactions of 2-alkenylindoles with *N*-arylimines have been reported.[10]



Scheme 1. Competitive reaction between **2a**+**2a** and **2a**+**3a** by XB catalysis.

This highly selective promotion of the Povarov reaction by XB catalysis stimulated us to further optimize the reaction conditions (Table 1). We evaluated several XB donors (10 mol%), along with the non-catalyzed reaction, in the presence of 2-vinylindole (**2a,** 1.1 eq) and *N*-PMP imine (**3a,** 1 eq) in $CHCl_3$ (entries 1-5). Cationic XB donors **1a-c** efficiently promoted the reaction, whereas pentafluoroiodobenzene **1d**, which is known as a neutral XB donor, showed negligible catalytic activity. Among the cationic XB donors applied, 2-iodoimidazolium salt **1c** showed better catalytic activity to give **5a** in 79%. CH_2Cl_2 was the best solvent to give the product, although **1c** was not completely solved in the reaction media. An increased amount of **2a** and a shorter reaction time resulted in formation of **5a** in 89% yield, thus these were chosen as the optimum reaction conditions (entry 12). When the yields of **5a** were low in Table 1, unreacted starting materials were remained and dimerization of **2a** was not observed.

Table 1. Optimization of reaction conditions.



Entry	**1**	Solvent	Time (h)	Yield (%)[a]
1	none	$CHCl_3$	23	19
2	**1a**	$CHCl_3$	22	74
3	**1b**	$CHCl_3$	21	78
4	**1c**	$CHCl_3$	21	79
5	**1d**	$CHCl_3$	21	7
6	**1c**	hexane	21	65
7	**1c**	toluene	22	78
8	**1c**	THF	21	31
9	**1c**	CH_3CN	22	50
10	**1c**	MeOH	21	15
11	**1c**	CH_2Cl_2	22	80
12[b]	**1c**	CH_2Cl_2	13	89

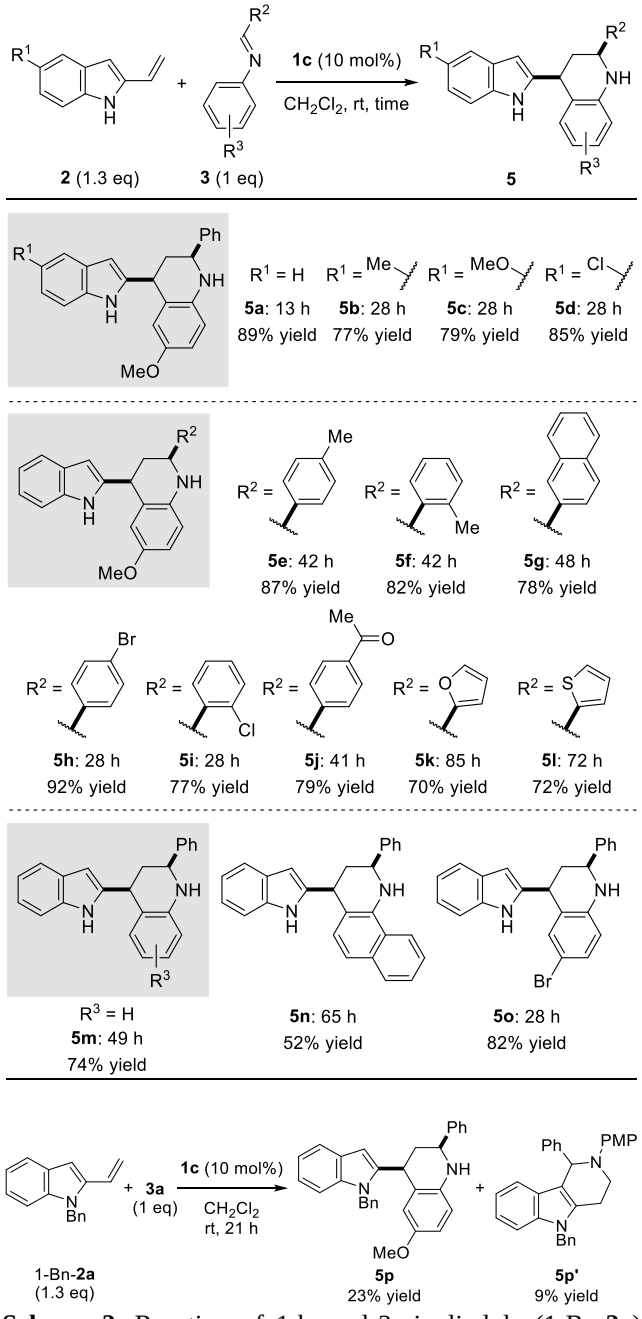
[a] Isolated yield. [b] 1.3 eq of **2a** were used.

We next investigated the substrate scope on the XB catalyzed Povarov reaction of 2-vinylindole with imines (Table 2). Neither electron-donating nor electron-withdrawing substituents at the 5-position of 2-vinylindole influenced the reaction outcome (**5b-d**). *N*-PMP imines having *p*-tol, *o*-tol, 2-naphthyl, *p*-Br-C_6H_4, *o*-Cl-C_6H_4, *p*-acetyl-C_6H_4, 2-furyl, and 2-thiophene groups were all well tolerated to give desired products (**5e-l**) in high yields. *N*-Phenyl, *N*-1-naphthyl, and *N*-*p*-Br-C_6H_4 imines were also acceptable to furnish the products in good to moderate yields (**5m-o**). When 1-benzyl-2-vinylindole (1-Bn-**2a**) was used, tetrahydroquinoline **5p** and tetrahydro-γ-carboline **5p'**

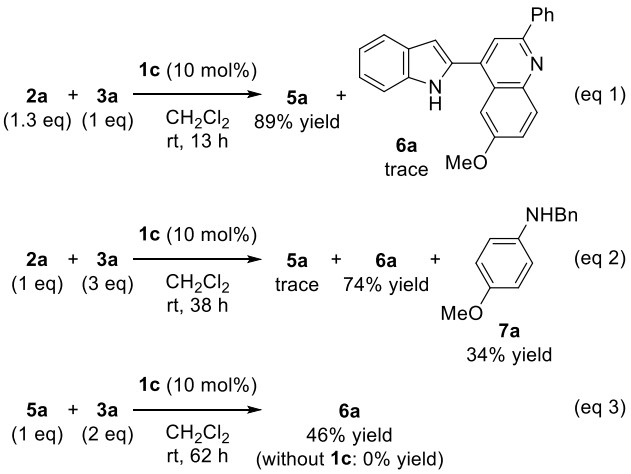
were obtained in 23% and 9% yield respectively, together with unidentified byproducts (Scheme 2).[10b] Dimerization of 2-vinylindoles was not observed in all cases.

In the course of the development of the XB-catalyzed Povarov reaction, indolyl-quinoline **6a** was detected as a byproduct (Scheme 3, eq 1).[11] We assumed that indolyl-tetrahydroquinoline **5a** was transformed into **6a** by dehydrogenation, while the *N*-PMP imine functioned as a formal hydrogen acceptor.[12] To verify this hypothesis, a reaction using 1 equivalent of **2a**, 3 equivalents of **3a**, and 10 mol% of **1c** was performed in CH_2Cl_2 for 38 hours (Scheme 3, eq 2). The yield of indolyl-tetrahydroquinoline **5a** drastically decreased to a trace amount, while indolyl-quinoline **6a** was obtained in 74% yield, along with 34% yield of amine **7a**, which could be generated by hydrogenation of *N*-PMP imine **3a**. This result suggests that selective formation of either indolyl-tetrahydroquinoline **5a** or indolyl-quinoline **6a** can be easily controlled by adjusting the amounts of 2-vinylindole and *N*-PMP imine. To check whether the transformation of **5a** into **6a** is accelerated by XB donor or not, **1c** was added to the mixture of 1 eq of **5a** and 2 eq of **3a** (Scheme 3, eq 3). While no reaction occurred without **1c**, indolyl-quinoline **6a** was obtained in 46% yield after 62 h in the presence of **1c** which indicated that the second step was also promoted by the catalyst.[9a,9d,9p]

Table 2. Synthesis of indolyl-tetrahydroquinolines catalyzed by XB donor.



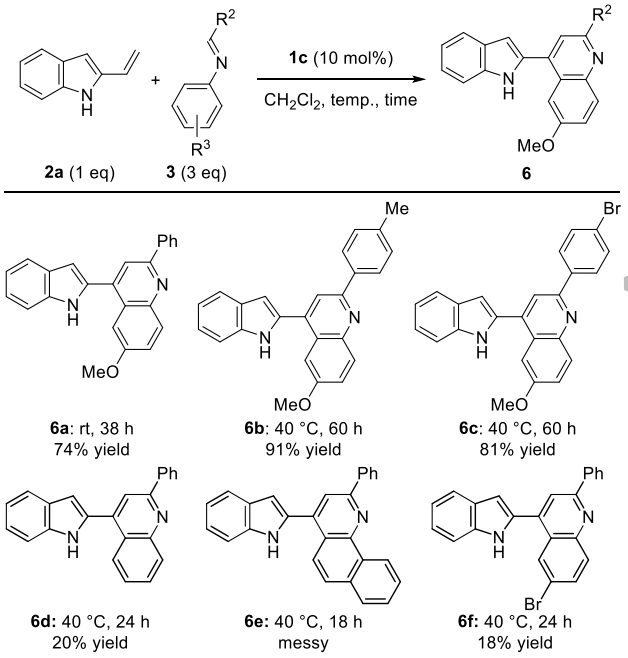
Scheme 2. Reaction of 1-benzyl-2-vinylindole (1-Bn-**2a**) and **3a**.



Scheme 3. Product switching controlled by the equivalent of imine.

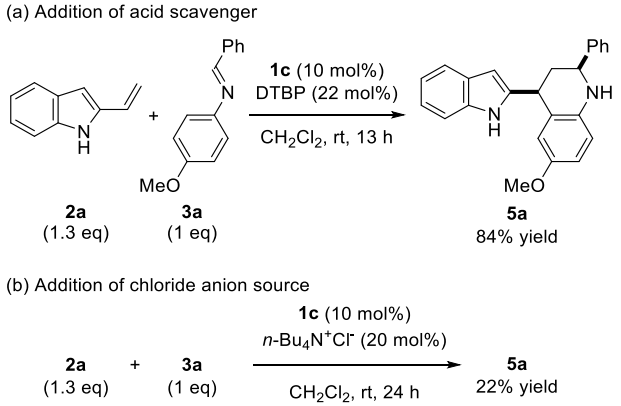
Additional examples for the synthesis of indolyl-quinolines were investigated as shown in Table 3.

Table 3. Synthesis of indolyl-quinolines catalyzed by XB donor.



The introduction of *p*-tol or *p*-Br-C_6H_4 groups at R^2 had no effect on the reaction, and the corresponding indolyl-quinolines **6b** and **6c** were obtained in 91% and 81% yields, respectively, by conducting the reaction at 40 °C for 60 hours. The indolyl-quinolines **6d** and **6f** were also obtained from *N*-phenyl and *N*-*p*-Br-C_6H_4 imines in 20% and 18% yields, but the reaction went messy when *N*-1-naphthyl imine was employed.

Several supporting experiments were performed to confirm that this Povarav reaction was promoted by XB catalysis (Scheme 4). The addition of DTBP (2,6-di-*tert*-butylpyridine) did not disturb the reaction, suggesting that a hidden Brønsted acid, which could be generated through hydrolysis of the XB donor, was not the catalyst (Scheme 4a).[13] In the presence of a chloride anion source, the reaction slowed down to give 22% of **5a** with remaining of the starting materials (Scheme 4b).[9c] (The similar results are obtained using **1a** and **1b**. See the details in the supporting information.) These results indicated that the XB was important to smoothly catalyze the reaction.



Scheme 4. Supporting experiments for reaction promotion by XB.

In summary, we evaluated the preference between the C–I···N XB and C–I···π XB interactions in solution, by performing a competitive reaction between the XB-catalyzed dimerization of 2-vinylindole and the Povarov reaction of 2-vinylindole with *N*-PMP imine. The Povarov reaction was selectively promoted by a cationic XB donor catalyst to furnish a series of indolyl-tetrahydroquinolines in moderate to high yields, indicating that the C–I···N XB interaction was dominant in solution phase as with previous studies in the solid and gas phases. In addition, the reaction system could be modified to synthesize indolyl-quinolines by changing the ratio of 2-vinylindole and imine. We hope that the present study will contribute to further development of XB catalysis for achieving efficient organic synthesis.

Experimental Section

General procedure for XB-catalyzed Povarov reaction of 2-vinylindoles 2 with *N*-arylimines 3.

To a mixture of 2-vinylindole **2** (0.13 mmol, 1.3 eq) and *N*-arylimine **3** (0.1 mmol, 1 eq) in CH_2Cl_2 (0.5 mL) in a round bottom screw vial containing a stir bar was added catalyst **1c** (0.01 mmol, 10 mol%). The vial was flushed with argon and the mixture was stirred for the appropriate time at room temperature. The solvent was removed under reduced pressure and the resulting mixture was purified by preparative thin-layer chromatography or silica gel column chromatography using hexane/acetone = 4/1 as an eluent to afford the product **5**.

General procedure for XB-catalyzed synthesis of indolyl-quinolines 6.

To a mixture of 2-vinylindole **2** (0.1 mmol, 1 eq) and *N*-arylimine **3** (0.3 mmol, 3 eq) in CH_2Cl_2 (0.5 mL) in a round bottom screw vial containing a stir bar was added catalyst **1c** (0.01 mmol, 10 mol%). The vial was flushed with argon and the mixture was stirred for the appropriate time at room temperature. After the solvent was removed under reduced pressure, the resulting mixture was purified by preparative thin-layer chromatography or silica gel column chromatography using hexane/acetone = 4/1 as an eluent to afford the product **6**.

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