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Halogen-Bond-Promoted Double Radical Isocyanide Insertion under Visible-Light Irradiation: Synthesis of 2-Fluoroalkylated Quinoxalines

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S *Supporting Information*

ABSTRACT: A halogen-bond-promoted double radical isocyanide insertion with perfluoroalkyl iodides is reported. With perfluoroalkyl iodides as halogen-bond donors and organic bases as halogen-bond acceptors, fluoroalkyl radicals can be generated by a visible-light-induced single electron transfer (SET) process. The fluoroalkyl radicals are trapped by *o*-diisocyanoarenes to give quinoxaline derivatives. This mechanistically novel strategy allows the construction of 2-fluoroalkylated 3-iodoquinoxalines in high yields under visible-light irradiation at room temperature.

Halogen bonding (XB) is an attractive non-covalent interaction between terminal halogen atoms in compounds of the type R—X and Lewis bases (LBs) (Figure 1).[1] R—X acts as the halogen-bond donor, where X is any halogen atom with an electrophilic region and R is a group covalently bound to X. LB is the halogen-bond acceptor, typically a molecular entity possessing at least one nucleophilic region. Compared with another common intermolecular non-covalent interaction, hydrogen bonding,[2] halogen bonding offers some potential advantageous features:[3] (1) higher directionality; (2) larger and more polarizable interacting atoms compared with hydrogen; and (3) different solubility profiles, as halogen-bond donors are typically based on different fluorinated groups. Halogen bonding itself has been known for a long time and has garnered dramatically increased interest from chemists exploring crystal engineering,[4] supramolecular chemistry,[1c−e,5] and drug design[6] since the early 1990s.

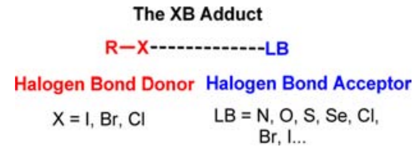

Figure 1. Introduction of the XB adduct.

Unlike hydrogen bonding, which plays an important role in non-covalent catalysis, XB has to date found very limited applications in organic synthesis.[7] The first report in which halogen-bond donors were used as organocatalysts was published by Bolm and co-workers in 2008.[7a] In this work, the quinolone derivatives were reduced, catalyzed by iodoperfluoroalkanes ($C_8F_{17}I$). Huber[7e−h] and others[7] also performed a series of excellent experiments on XB-mediated organic transformations. Despite these advances, XB-mediated synthetic chemistry is still in its infancy and needs further investigation.

Recently, our group has been interested in the development of non-covalent bond-mediated radical reactions.[8] Typically, a non-covalent interaction, such as an electron donor−acceptor interaction, can be used to initiate a single-electron-transfer (SET) transformation.[9] On the other hand, we have recently developed visible-light-promoted radical isocyanide insertions to synthesize azaarenes.[10] These processes are normally catalyzed or initiated by photocatalysts under visible-light irradiation.[11] As some non-covalent interaction complexes can be excited by absorbing visible light,[9a] we were interested in whether radical isocyanide insertions could be induced by non-covalent interaction complexes, e.g., XB complexes, under visible-light irradiation.[12]

With this idea in mind, we focused on the synthesis of quinoxaline derivatives, which are useful but synthetically challenging targets. It was envisaged that the quinoxaline skeleton could be constructed using double radical isocyanide insertions of *o*-diisocyanoarenes with perfluoroalkyl halides. Thus, we started our investigation by using 1,2-diisocyano-4,5-dimethylbenzene (**1a**) and perfluoroalkyl iodide **2a** as the model substrates. After a quick screening, we were pleased to find that 2-perfluoroalkylated quinoxaline **3a** could be generated when a solution of **1a** (1 equiv) and **2a** (2 equiv) in CH_3CN was irradiated using blue light-emitting diode (LED) strips in the presence of an amine (1 equiv) (Table 1, entries 1−3). Both tertiary and secondary amines were suitable, and dibenzylamine proved to be the best donor, giving **3a** in 65% yield. The dosage of dibenzylamine could be reduced to 0.2 equiv. However, the

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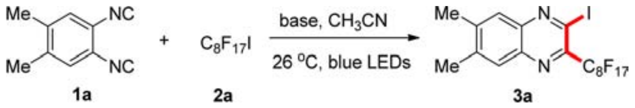
Table 1. Discovery of XB-Mediated Double Radical Isocyanide Insertion[a]



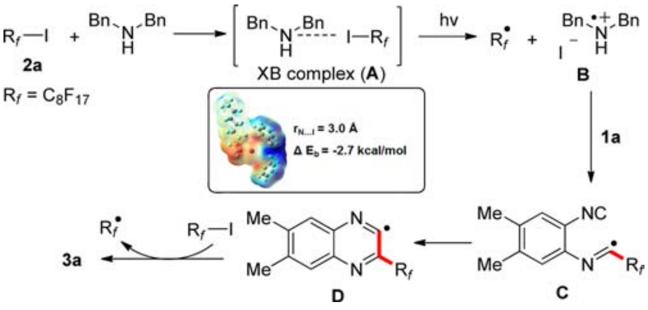
entry	base	yield(%)[b]	entry	base	yield(%)[b]
1	DABCO[c]	52	4[d]	Bn_2NH	0
2	**Bn_2NH**	**65**	5[e]	Bn_2NH	62
3	DIPEA	50	6	none	17

[a] Reaction conditions: a solution of **1a** (0.10 mmol), **2a** (0.20 mmol), and base (0.10 mmol) in the indicated solvent (2.0 mL) was irradiated using blue LED strips for 24 h. [b] Isolated yields. [c] DABCO (0.05 mmol) was used. [d] No visible-light irradiation. [e] The reaction was irradiated through a 400−650 nm short-pass filter.

yield decreased to 57% (for full screening conditions, see the Supporting Information). Control experiments showed that light was necessary. Without light irradiation, the starting materials were fully recovered (entry 4). When the reaction mixture was irradiated using blue LED strips through a 400−650 nm short-pass filter, a comparable yield was obtained (entry 5 vs 2). Furthermore, the action spectrum indicated that 459 nm light was the most effective in this reaction, giving a 63% yield (Figure S6). These phenomena exclude trace UV light as the real light source. When the reaction was carried out without a base, the desired product was still generated in 17% yield (entry 6).

On the basis of the fact that an XB adduct can be formed between an amine and a perfluoroalkyl iodide[13] as well as the aforementioned experimental phenomena, a mechanism is posited, as shown in Scheme 1. When Bn_2NH is present, it engages in an encounter complex **A** through XB with perfluoroalkyl iodide **2a**. Reversible electron transfer (ET) in the XB adduct **A** is activated by visible-light irradiation, leading to the irreversible collapse of complex **A** into the perfluoroalkyl radical R_f·, Bn_2NH^{+}·, and iodide anion. The fluoroalkyl radical R_f· adds to diisocyanide **1a**, and this is followed by radical cyclization to produce radical intermediate **D**, which abstracts an iodine atom from perfluoroalkyl iodide **2a** to give the final product **3a**.

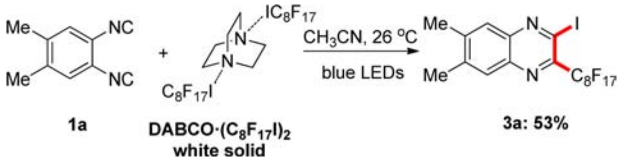
Scheme 1. Proposed Mechanism for the Double Radical Isocyanide Insertion



In order to verify the existence of the proposed XB adduct, a series of NMR experiments were performed using a solution of **2a** and Bn_2NH in $CDCl_3$. The formation of an XB adduct between **2a** and Bn_2NH was strongly supported by the ^{19}F NMR titration experiments. The resonance corresponding to the F of the CF_2I group (−59.104 ppm) was shifted to the upfield regime as Bn_2NH was added to the $CDCl_3$ solution of **2a** (Figure S1). The binding constant for the XB complex (K_a = 0.151) was determined using the Benesi−Hildebrand method based on ^{19}F NMR spectroscopy (Figure S2).[14] Furthermore, the 1:1 donor:acceptor molar ratio in solution for the XB complex was readily established using Job's method (Figure S3).[15]

The halogen-bonded adduct between DABCO and two $C_8F_{17}I$ molecules can be isolated as a solid.[7c] When a solution of **1a** and the preformed solid adduct DABCO·$(C_8F_{17}I)_2$ in CH_3CN was irradiated using blue LED strips, the desired quinoxaline **3a** was obtained in 53% isolated yield (Scheme 2). This result also strongly supports the crucial role played by the XB complex in this double radical isocyanide insertion.

Scheme 2. Synthesis of 2-Fluoroalkylated Quinoxalines by the Halogen-Bonded Adduct DABCO·$(C_8F_{17}I)_2$[a]



[a] Reaction conditions: a solution of **1a** (0.10 mmol) and DABCO·$(C_8F_{17}I)_2$ (0.15 mmol) in dry CH_3CN (2.0 mL) was irradiated using blue LED strips for 24 h. The isolated yield is shown.

The radical nature of this reaction was confirmed by electron paramagnetic resonance (EPR) experiments using *tert*-butyl-α-phenylnitrone (PBN) as a spin trap (Figure 2). When PBN was introduced into the reaction mixture, a spectrum signal attributed to the spin adduct C_8F_{17}−PBN (**5**) appeared as a triplet of singlets. In the absence of amine, the signal was weakened. Without light, almost no signal was observed. These phenomena strongly suggest that the perfluoroalkyl radical is the key intermediate and that the generation of the intermediate heavily relies on the presence of light and amine.

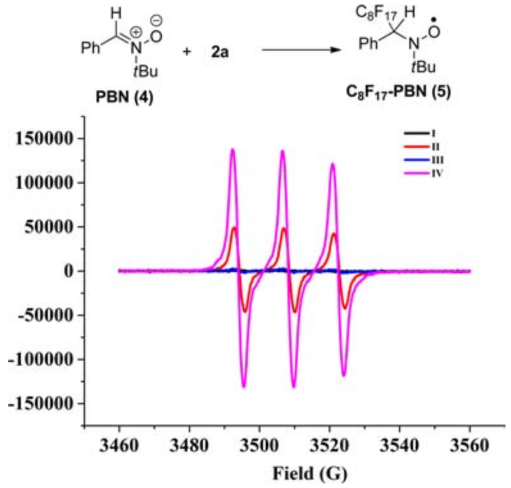


Figure 2. EPR spectra obtained in DMF at 298 K in the presence of PBN: (I) PBN in DMF; (II) a solution of **1a**, **2a**, and PBN in DMF after irradiation with blue LEDs for 1 h; (III) a solution of **1a**, **2a**, Bn_2NH, and PBN in DMF without irradiation; (IV) a solution of **1a**, **2a**, Bn_2NH, and PBN in DMF after irradiation with blue LEDs for 1 h.

To better understand the mechanism of this reaction, a series of DFT calculations were carried out using the Gaussian 09 program.[16] Molecular geometries of the reactants, intermediates, transition states, and products were optimized with the B3LYP functional. The 6-311+G(d,p) basis set was used for C, H, O, N, and F, and LANL2DZ was used as the effective core potential for I. All of the stationary points were tested by frequency calculations. The polarizable continuum model (PCM) was employed to consider the solvent effect of CH_3CN. The formation of the XB adduct was demonstrated from electron delocalization in the frontier molecular orbitals and binding energy in Figure 3. The calculated N···I distance of 3.0 Å is smaller than the sum of the van der Waals radii of N and I atoms (3.7 Å). The binding energy (ΔE_b) was calculated as the difference between the energy of the XB adduct (E_{adduct}) and the sum of the energies of the halogen-bond donor (R−X) and acceptor (LB) (E_{R-X} and E_{LB}, respectively). The binding energy of $C_8F_{17}I\cdots Bn_2NH$ is −2.7 kcal/mol. Both the LUMO (denoted as L) and the HOMO (denoted as H) are delocalized between R−X and LB to different degrees in comparison with the frontier orbitals of the individual $C_8F_{17}I$ and Bn_2NH units. The H−L energy gap of $C_8F_{17}I\cdots Bn_2NH$ is 5.48 eV. More detailed frontier molecular orbital information on the adducts and their individual parts and the other molecular electrostatic potentials and N···I bond distances of the halogen-bonded adducts are presented in the Supporting Information.

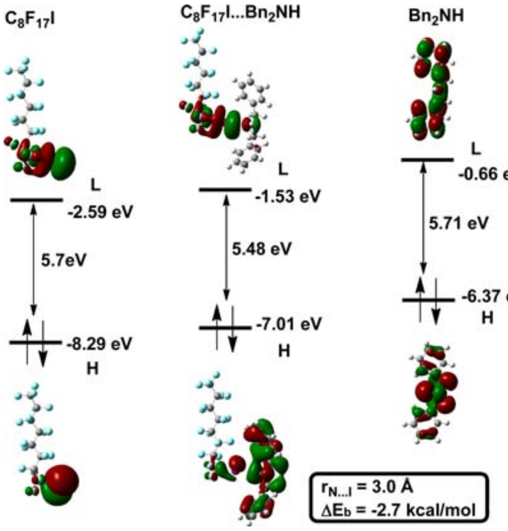


Figure 3. Detailed frontier molecular orbitals and N···I bond distance of $C_8F_{17}I\cdots Bn_2NH$.

Furthermore, we calculated the possible reaction paths of the double radical isocyanide insertion reaction. The relative free energies (ΔG) with zero-point energy (ZPE) corrections are reported in Figure 4. In the C−I homolysis pathway, the theoretical calculations indicated that the major pathway of the XB-mediated double radical isocyanide insertion was energetically more favorable by 13.7 kcal/mol than the minor pathway of visible-light-only-promoted double radical isocyanide insertion (for details of the minor pathway, see the Supporting Information). The C−I heterolytic pathway of **2a** (**A**) to give I^- and **B** is unfavorable with a high energy barrier of 65 (60.2) kcal/mol (for details, see the Supporting Information).

We next explored the substrate scope of this XB-induced double radical isocyanide insertion. First, perfluoroalkyl iodides were examined (Scheme 3). A variety of perfluoroalkyl iodides with different chain lengths underwent this transformation smoothly (**3a**−**g**). Diisocyanides with different substituents did not affect this reaction either (**3h**−**k**). Gaseous CF_3I was also suitable in this transformation to give 2-trifluoromethyl-3-iodoquinoxalines **3l** and **3m** in satisfactory yields. The structures of **3i** and **3j** were established unambiguously by single-crystal X-ray diffraction analysis.

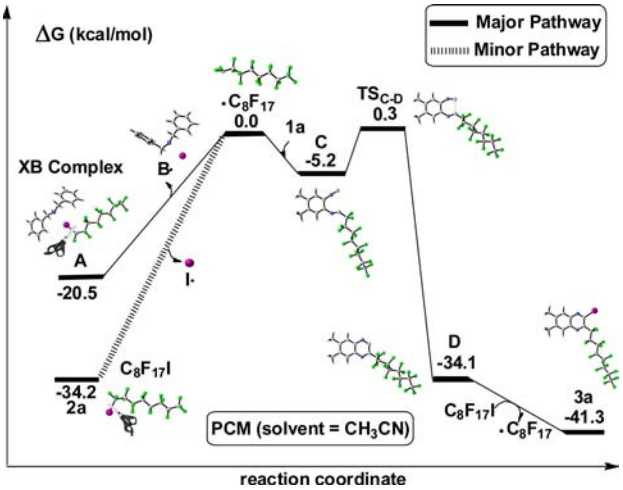
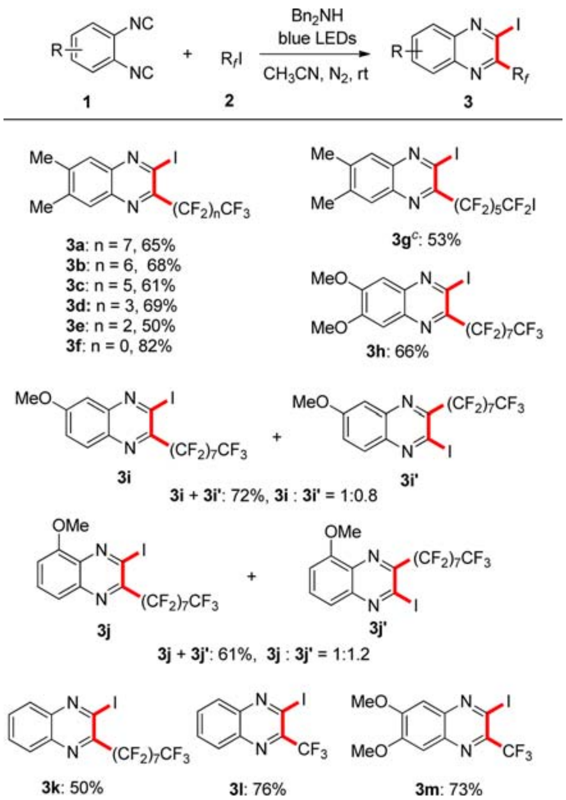


Figure 4. Free energy curves for XB-mediated double radical isocyanide insertion (major pathway) and visible-light-only-promoted double radical isocyanide insertion (minor pathway).

Scheme 3. Synthesis of 2-Perfluoroalkyl-3-iodoquinoxalines[a,b]

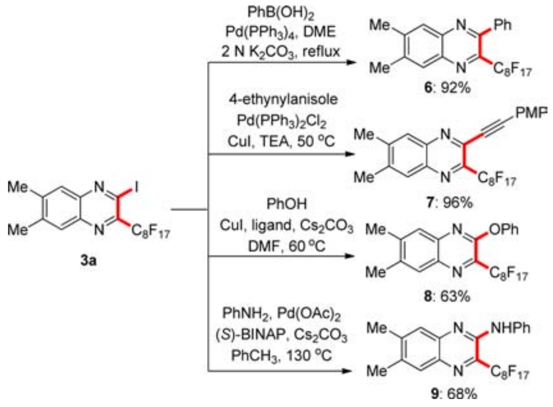


[a] Reaction conditions: a solution of **1** (0.10 mmol), **2** (0.20 mmol), and Bn_2NH (0.10 mmol) in dry CH_3CN (2.0 mL) was irradiated using blue LED strips for 24 h. [b] Isolated yields are shown. [c] 0.3 mmol of iodide **2** was added.

In order to demonstrate the practicability of this transformation, the resultant 2-fluoroalkyl-3-iodoquinoxalines could be easily modified further (Scheme 4). Iodide **3a** could undergo

Suzuki, Sonogashira, and Buchwald–Hartwig couplings to give quinoxalines **8–11** with different 3-functionalities.

Scheme 4. Synthetic Utility



In summary, we have developed an XB-promoted double radical insertion of diisocyanides with perfluoroalkyl iodides. A series of 2-fluoroalkyl-3-iodoquinoxalines could be synthesized under visible-light irradiation. The existence of an XB complex and the proposed mechanism were investigated experimentally and theoretically. The resultant quinoxaline skeleton is a biologically important building block for synthetic and medicinal chemists. The iodide at C3 facilitates further modifications. Further explorations of the synthetic applications of XB adducts are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02271.

Experimental procedures, spectral data, calculation details, and complete ref 16 (PDF)
Crystallographic data for **3i** (CIF)
Crystallographic data for **3j** (CIF)

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Notes

The authors declare no competing financial interest.

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