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Halogen-Bond-Promoted α-C-H Amination of Ethers for the Synthesis of Hemiaminal Ethers

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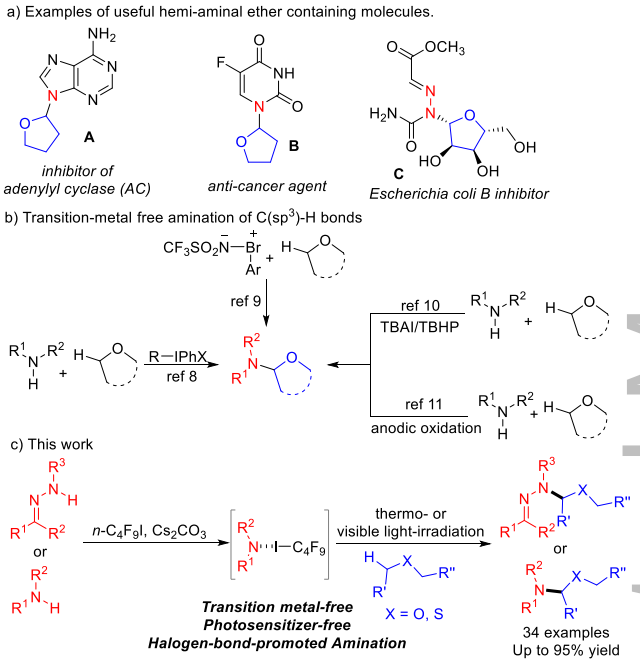
Abstract: A simple halogen-bond-promoted α-C-H amination of ether/thioether with a variety of N-H compounds has been accomplished. In the presence of low-cost and readily available perfluorobutyl iodide, a diverse range of hemiaminal ether derivatives, including the valuable hydrazone hemiaminal ethers, were quickly assembled under thermal or visible-light irradiation conditions. Mechanistic studies suggest that a halogen-bond adduct was formed and a radical chain pathway might be operative. Synthetic application of the method has been demonstrated via the preparation of the anti-viral and anti-tumor drug, Tegafur.

Keywords: halogen-bond; C-H amination; hemiaminal ether; perfluoroalkyl iodides; Tegafur

Hemiaminal ethers, especially hydrazone hemiaminal ethers, are important structural motifs commonly encountered in a large collection of biologically active natural products as well as some pharmaceutical candidates (Scheme 1a).[1-2] Given the wide prevalence of the hemiaminal framework in biological systems, the development of novel methods to access such a skeletal structure is important to the pharmaceutical industry.[3]

Traditionally, nucleophilic substitution of a halide or the protected hydroxyl group of an α-substituted ether with an amine was used to construct the hemiaminal structure.[4a] These compounds could also be prepared from hydroamination of an enol ether.[4b] Compared with conventional methods, with the advantage of avoiding the pre-installation of transformable functional groups, C-H amination represent a potentially more efficient, atom economic and environmentally friendly method. Over the past few years, the direct amination of unreactive C-H bonds has emerged as an efficient method to construct C-N bonds.[5] In this field, transition-metal-catalyzed amination of C(sp^3)-H bonds adjacent to an oxygen atom (ethers) has been intensively studied.[6] However, the transition-metal free selective



Scheme 1. Reported and our synthetic strategies.

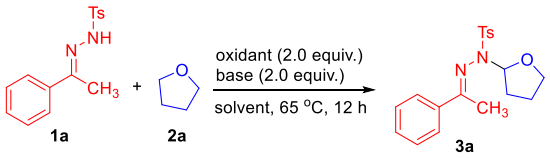
functionalization of C(sp^3)-H bonds remains a formidable challenge (Scheme 1b).[7] For examples, Guo, Feldman and Hu et al. have independently developed the non-metallic alkylation of amines with ethers in the presence of hypervalent iodine reagent.[8] In 2012, Ochiai and co-workers reported a metal-free direct amination of alkyl ethers with hypervalent sulfonylimino-λ^3-bromane serving as an active nitrenoid.[9] Du, Wang, Patel, Wang, Singh and Vidavalur et al. have demonstrated a tetrabutylammonium iodide (TBAI) catalyzed protocol for the direct C-N bond formation of ethers and azoles with *t*-BuOOH (TBHP) being the oxidant.[10] In 1986, Fuchigami et al. reported the amination of THF with alkylamines using electrochemical oxidation.[11] While impressive progress has been achieved in preparing the

corresponding hemiaminal ether compounds, some drawbacks such as the use of excess amounts of peroxide, expensive oxidation reagent, low conversions or yields and the limited substrate scopes are still the issues limiting their further applications. Moreover, to the best of our knowledge, the transition-metal-free direct C(sp^3)-H amination for the synthesis of hydrazone hemiaminal ethers has not been disclosed. In this regard, the development of a novel, mild and environmental friendly metal-free system to synthesize the hemi-amino ether compounds remains highly desirable.

Perfluoroalkyl iodides (R_FI) are known as important perfluoroalkylating reagents through the cleavage of C-I bonds and generation of perfluoroalkyl radicals.[12] The reactive and strongly electrophilic $R_F^{\bullet}$ are prone to abstract hydrogen atoms to afford hydrodehalogenation products.[13] Given the low cost, less toxicity and ready availability, the possible applications of R_FI as H-abstraction reagents for the hemiaminal ether synthesis are particularly appealing. Furthermore, due to the small reduction potential (E^0_{red} CF_3I = −1.22 V vs SCE, in DMF) compared with hypervalent iodide (E^0_{red} Ph_2I^+ = −0.2 V vs SCE, in H_2O) or peroxide (E^0_{red} t-$BuO_2^{\bullet}$ = 0.71 V vs NHE, in H_2O),[14] the sensitive functional group could be well tolerated. Nonetheless, the generation of $R_F^{\bullet}$ generally required environmentally unfriendly reagents or harsh reaction conditions, such as transition metals or UV irradiation. Generation of $R_F^{\bullet}$ without initiators under mild conditions represent a further stage of development. Recently, our group has been interested in the reactions involving perfluoroalkyl iodides,[15] we report herein an unprecedented example of a halogen-bond-promoted transition metal-free C-N bond formation reaction for the hemiaminal ether (especially hydrazone hemiaminal ether) synthesis. The active halogen-bond adduct (one kind of electron donor-acceptor complexes, EDA complexes)[16] could be formed through a transiently generated amidyl anion with perfluoroalkyl halide. Thermal or visible-light irradiation of the halogen-bond adduct induced a single electron transfer (SET),[17] thus allowing easy access to radical species. The hydrogen atom transfer (HAT) of the ether with $R_F^{\bullet}$ would generate an alkyl radical to finally afford the amination product (Scheme 1c).[18] This approach could overcome the difficulty of the previously reported methods and feature synthetic simplicity, broad substrate scope, and good functional-group compatibility.

To begin our study, the commercially available acetophenone hydrazone **1a** and tetrahydrofuran (THF) **2a** were chosen as the model substrates. The feasibility of the transformation was then tested by exposing the substrates to a mixture of n-C_4F_9I and Cs_2CO_3. Gratifyingly, the desired amination product was obtained in 67% isolated yield when the reaction was performed at 65 °C for 12h (Table 1, entry 1). Then, several control experiments were conducted and the results showed that both C_4F_9I and Cs_2CO_3 were indispensable for the reaction (Table 1, entries 2 and 3). Although polyhaloalkanes, such as C_2Cl_6, $BrCCl_3$, CCl_4, and CBr_4 have been reported to form EDA complexes with amines,[16h,16i] they were less effective than C_4F_9I in this case (Table 1, entries 4-7). Replacement of Cs_2CO_3 with other bases, such as K_2CO_3, Na_2CO_3, NaH, or t-BuOK led to diminished yields (Table 1, entries 8-11). Attempts to reduce the amount of THF failed, reactions carried out in $PhCH_3$, CH_3CN, DMF or DMSO using 10 equiv. of THF as the coupling reagent was noneffective (Table 1, entries 12-15). Finally, careful optimization of other reaction parameters revealed that the amination product could be afforded in 85% yield with 1.5 equiv. of Cs_2CO_3 and 1.5 equiv. of n-C_4F_9I at 65 °C for 12h (Table 1, entries 16-19).

Table 1. Screening of the optimal reaction conditions.[a]



Entry	Oxidant	Base	Solvent	Yield (%)[b]
1	C_4F_9I	Cs_2CO_3	THF	67
2	C_4F_9I	-	THF	NR
3	-	Cs_2CO_3	THF	NR
4	C_2Cl_6	Cs_2CO_3	THF	43
5	$BrCCl_3$	Cs_2CO_3	THF	27
6	CCl_4	Cs_2CO_3	THF	24
7	CBr_4	Cs_2CO_3	THF	45
8	C_4F_9I	K_2CO_3	THF	23
9	C_4F_9I	Na_2CO_3	THF	NR
10	C_4F_9I	NaH	THF	36
11	C_4F_9I	t-BuOK	THF	48
12	C_4F_9I	Cs_2CO_3	$PhCH_3$[c]	NR
13	C_4F_9I	Cs_2CO_3	CH_3CN[c]	NR
14	C_4F_9I	Cs_2CO_3	DMF[c]	trace
15	C_4F_9I	Cs_2CO_3	DMSO[c]	trace
16	C_4F_9I	Cs_2CO_3[d]	THF	87
17	C_4F_9I[d]	Cs_2CO_3[d]	THF	85
18	C_4F_9I[e]	Cs_2CO_3[d]	THF	55
19	C_4F_9I[d]	Cs_2CO_3[e]	THF	54

[a] Reaction conditions: under N_2, **1a** (0.3 mmol), base (0.6 mmol) and oxidant (0.6 mmol) in THF (3.0 mL) at 65 °C for 12 h. [b] Isolated yield. [c] THF (3.0 mmol) in 3.0 mL of solvent. [d] 1.5 equiv. of base or oxidant was added. [e] 1.0 equiv. of oxidant or base was used.

With the optimal reaction conditions (Table 1, entry 17) in hand, we proceeded to explore the generality of this methodology. The reaction protocol was first applied to the α-C(sp^3)-H amination of ether **2** with a wide range of hydrazone sulfonamides **1** (Table 2). Generally, acetophenone hydrazone containing either electron-donating or electron-withdrawing groups on the phenyl moiety were well tolerated and reacted smoothly to afford the corresponding products in good to excellent yields (**3b-3g**). Extension of the chain length from the methyl group to the ethyl or n-propyl group was found to have only small impact on the reactivity (**3h**

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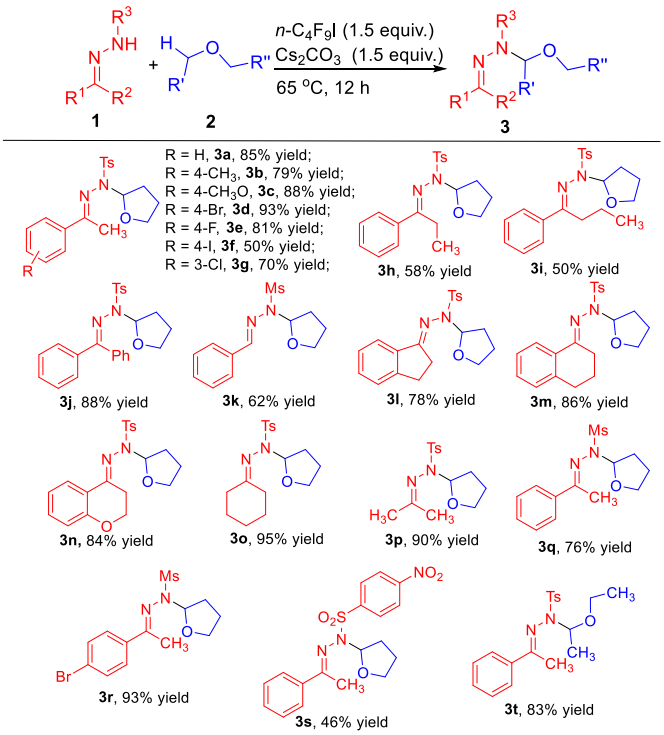
and **3i**). Replacements of the methyl group to a phenyl group or a hydrogen atom also deliver the coupling product in 88% and 62% yields, respectively (**3j** and **3k**). We then found that substrates derived from cyclic ketones could serve as suitable substrates and gave the expected products efficiently (**3l**-**3n**). Besides the aromatic substrate, the protocol was suitable for the cyclohexanone and acetone derived hydrazone (**3o** and **3p**), implying that the phenyl moiety is not indispensable for the transformation. Furthermore, in addition to the tosyl group, substrates bearing other N-protecting groups also proceeded cleanly to furnish the amination products in good yields (**3q**-**3s**). It is worth noting that with alkyl ether other than THF as the reaction partner, this method works well to give a high yield of the direct amination product (**3t**).

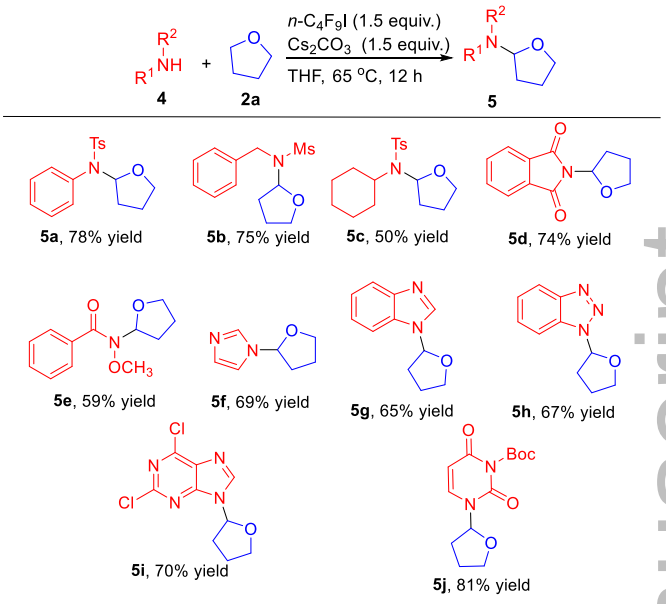
Table 2. Amination with hydrazone sulfonamides[a),b)]



[a)] Under N_2, **1** (0.3 mmol), Cs_2CO_3 (0.45 mmol) and C_4F_9I (0.45 mmol) in THF (3.0 mL) at 65 °C for 12 h. [b)] Isolated yield.

With THF **2a** used as the ether, we subsequently investigated the substrate scope to include a wide range of N-H compounds **4** (Table 3). It was observed that both aryl- and primary alkyl-substituted sulfonamides were well tolerated under the standard conditions, affording the oxidative coupling products in good yields (**5a** and **5b**). The introduction of sterically encumbered secondary alkyl cyclohexyl substituent did not affect the reaction outcome (**5c**). It is noted that the acetamide and N-alkoxyamide were good coupling partners and react smoothly to generate the amination products in 74% and 59% isolated yield, respectively (**5d** and **5e**). N-Free secondary amine without a sulfonyl or acyl group, such as NH-imidazole, benzimidazole, and benzotriazole were also suitable for the oxidative C-N coupling method (**5f**-**5h**). Notably, 2,6-dichloropurine and the nucleobase uracil were efficiently alkylated in excellent yield (**5i** and **5j**) to afford the biologically active molecules with the novel C(sp^3)-H amination protocol.

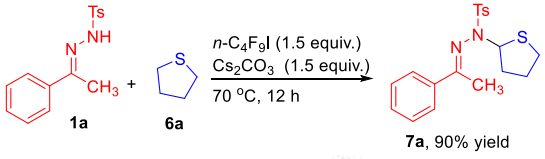
Table 3. Amination of THF with various N-H compounds [a),b)]

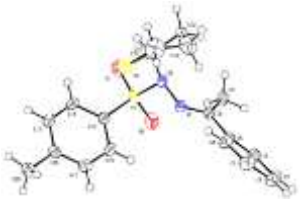


[a)] Under N_2, **4** (0.3 mmol), Cs_2CO_3 (0.45 mmol) and C_4F_9I (0.45 mmol) in THF (3.0 mL) at 65 °C for 12 h. [b)] Isolated yield.

In addition to the alkyl ether, the direct amination also worked on alkyl thioether such as tetrahydrothiophene, which afforded the coupling product **7a** in 90% yield (Scheme 2). The structure of **7a** was unambiguously confirmed by an X-ray crystallographic analysis.[19]

Scheme 2. Amination of alkyl thioether.





In order to gain preliminary insight into this transformation, we conducted additional experiments to elucidate the reaction mechanism. Some control experiments were carried out as shown in Scheme 3. The addition of a radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)[20] to the reaction mixture under the standard conditions, the reaction was completely inhibited and **1a** was recovered in 90% yield. Moreover, the TEMPO-R_F adduct **8** was observed by ^{19}F NMR spectroscopy, suggesting the involvement of a radical mechanism

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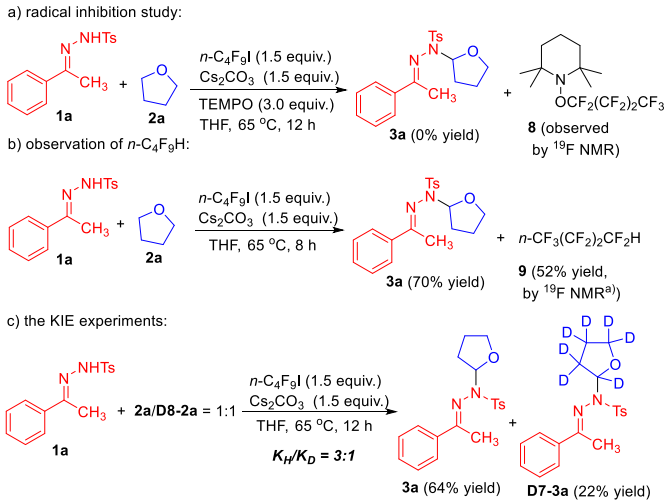
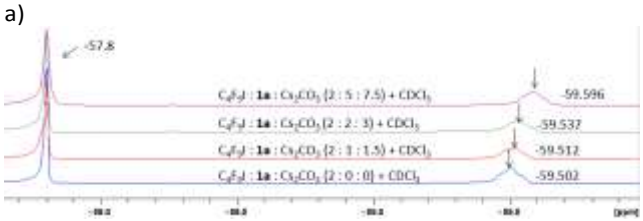
(Scheme 3a).[21] Conducting the reaction at standard conditions with a shortened reaction time, besides the target compound **3a**, R_FH **9** was afforded in 52% yield estimated by ^{19}F NMR spectroscopy, implying that *n*-C_4F_9I works as the H-abstraction reagent (Scheme 3b).[22] The result of the kinetic isotope effect (KIE) experiment indicates that cleavage of α-C(sp^3)-H bonds of ether was involved at the rate-determining step, as a significant KIE (K_H/K_D = 3) was observed in the process (Scheme 3c).

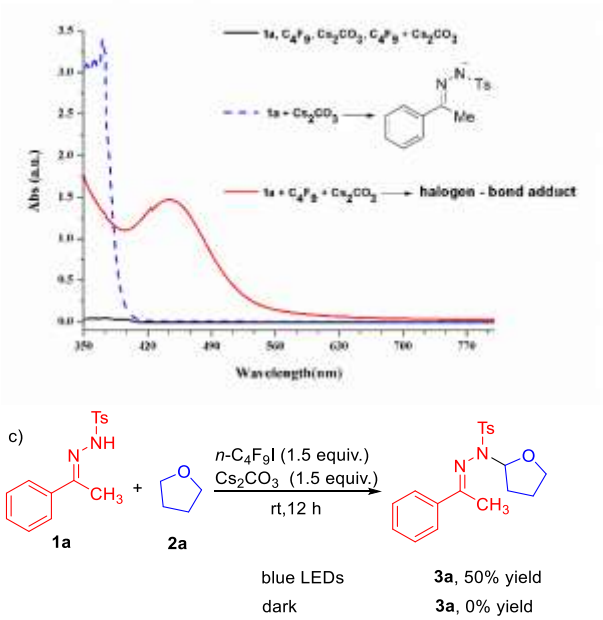
Scheme 3. Mechanism studies.



[a] The yield was determined by ^{19}F NMR with $PhOCF_3$ as an internal standard.

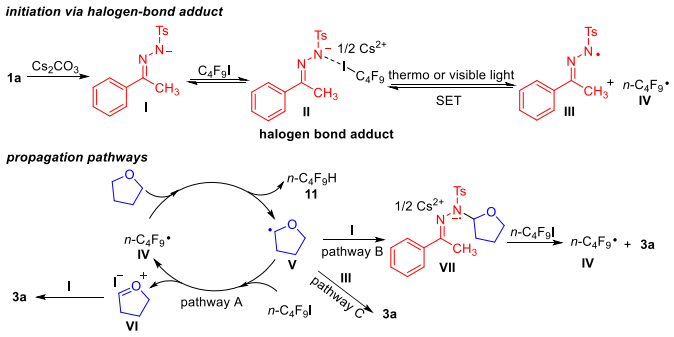
The key for the smooth transformation was the formation of the halogen-bond adduct. The existence of the halogen bonding was supported by the ^{19}F NMR titration method (Scheme 4a) and UV/Vis spectrum (Scheme 4b).[23] Moreover, the result shows that the maximum absorption peak of the halogen bond adduct lies in the visible spectral region, which suggests that the EDA complex may be irradiated by the visible light to promote a single electron transfer. Therefore, the photo promoted halogen-bond adduct enabled α-C-H amination of ethers leading to hemiaminal ethers was studied. The preliminary result indicates that the photoredox method can also be applied for the direct C-H oxidative coupling of ether and hydrazone derivatives, which afforded **3a** in 50% isolated yield at rt under blue LED irradiation (Scheme 4c). Control experiment shows that without light irradiation, no product was afforded and the starting materials were fully recovered.





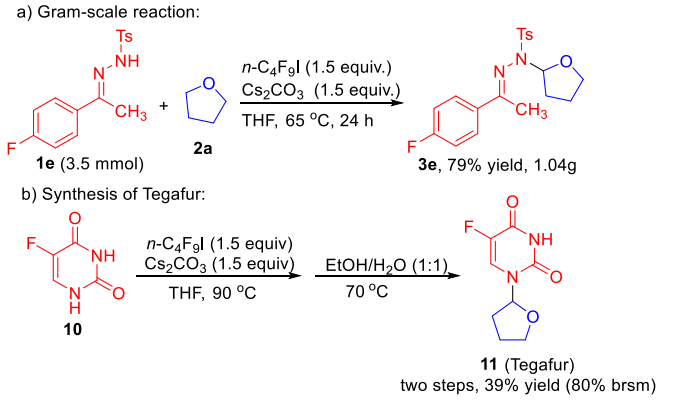
Scheme 4. Study of the halogen-bond adduct and visible light promoted reactions. a) NMR titration with $PhOCF_3$ as an internal standard. b) Optical absorption spectra recorded in THF. c) Reactions conducted under visible light irradiations.

On the basis of these results as well as the literature reports,[8,10,13,15] a plausible mechanism of chain process was proposed in Scheme 5. The interaction of transiently generated amidyl anion **I** (halogen-bond acceptor) and perfluorobutyl iodide (halogen-bond donor) first leads to the formation of a halogen-bond adduct **II**.[16] An aminyl radical **III** and a perfluorobutyl radical **IV** was generated afterwards through a thermal or visible-light-driven electron transfer. Due to the high electrophilicity and pyramidal geometry of the radical center,[13a] the in-situ generated perfluoroalkyl radical **IV** could then abstract the α-H of the surrounding ether **2a** to afford the hydrofluorocarbon **11** and alkyl radical **V**. The propagation cycle was subsequently formed through oxidation of the alkyl radical **V** by another perfluorobutyl iodide, giving an oxonium ion intermediate **VI** and another perfluorobutyl radical **IV** (pathway A). The nucleophilic attack of the deprotonated hydrazone **I** with oxonium ion intermediate **VI** would deliver the desired α-C-H amination product **3a**. On the other hand, alkyl radical **V** could react with amidyl anion **I** to form the corresponding anion-radical **VII**,[24] which is oxidized by another perfluorobutyl iodide to give the amination product **3a** and regenerate the perfluoroalkyl radical **IV** (pathway B). Although coupling of the aminyl radical **III** and an alkyl radical **V** could lead to the formation of **3a**, this pathway was less likely due to the low concentration of both radical species (pathway C).



Scheme 5. Proposed reaction mechanism.

To further demonstrate the synthetic value of the novel method, the gram-scale preparation of **3e** was conducted, which afforded the expected oxidative C-N coupling product in 79% isolated yield (Scheme 6a). Tegafur **11** was an anti-viral and anti-tumor prodrug of 5-fluorouracil **10**, featuring high lipophilicity and water solubility.[25] By using the methodology developed here, tegafur **11** could be easily prepared in moderate yield (the yield based on the recovered starting material (brsm) was as high as 80%) through a one-pot, two-step procedure without the requirement of the protection of 5-fluorouracil (Scheme 6b).



Scheme 6. Application of the synthetic methodology.

In summary, we have developed an unprecedented halogen-bond-promoted transition metal-free C-N bond formation with low-cost and readily available perfluorobutyl iodide as H-abstraction reagent. The approach allowed facile access to a diverse range of hemiaminal ether products. Especially, the valuable hydrazone hemiaminal ethers have been prepared efficiently for the first time. The mild reaction conditions, synthetic simplicity and broad substrate scope make this methodology a sustainable and promising tool for the application in the large-scale preparation of chemical feedstocks and in the complex molecule synthesis. Further investigations to uncover the detailed mechanism are currently underway in our laboratory.

Experimental Section

To a dry Schlenk tube equipped with a magnetic stir bar, was added hydrazone **1a** (0.3 mmol) and Cs_2CO_3 (0.45 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Perfluorobutyl iodide (0.45 mmol) and freshly distilled tetrahydrofuran **2a** (3 mL) was added and the reaction mixture was then stirred at 65 °C till **1a** was completely consumed (monitored by TLC). The mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* column chromatography on silica gel (4:1 hexanes/EtOAc) to afford the desired product **3a**.

Acknowledgements

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