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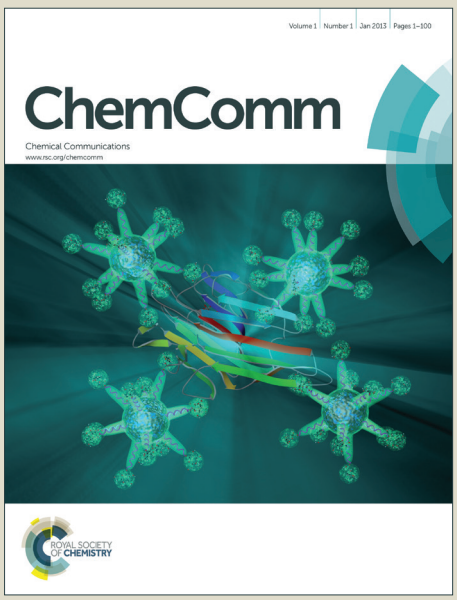

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Efficient imidation of C(sp^3)−H bonds adjacent to oxygen atoms of aryl ether under metal-free condition

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Intermolecular oxidative C–N formation reaction of aryl ether with pharmacological saccharins was realized under metal-free condition for the first time. The understanding of intrinsic characteristics between C(sp^3)−H and C(sp^2)−O bonds of aryl ether and the potential for application might promote more research interests in this area.

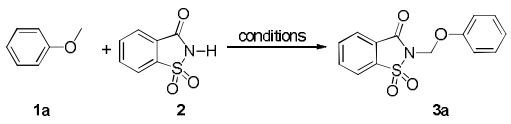
Nitrogen containing compounds are extremely important because of their abundance in various natural products as well as in synthetic organic compounds.[1] Accordingly, the construction of the C–N bond is of significant importance as it opens avenues for the introduction of nitrogen in organic molecules. The area of catalytic C−H amination has led to significant results arising both from the discovery of nitrene transfers and the combination of transition-metal-catalyzed C−H activation.[2,3] Thus far, sustainable progress has been made in the area of oxidative C(sp)−H and C(sp^2)−H couplings for various C−N bond forming reactions, In addition, several excellent examples of the amination/functionalization of the relatively active benzylic C(sp^3)–H bonds, allylic C(sp^3)–H bonds and C(sp^3)−H bonds adjacent to nitrogen atoms have been described.[4-6] Direct amination of C(sp^3)−H bonds adjacent to oxygen atoms is also a valuable goal, however, owing to the lack of reactivity under many reaction conditions, most of the current research mainly focuses on the metal-catalyzed amination of such C(sp^3)−H bond.[7]

Direct functionalization of C(sp^3)−H bonds adjacent to oxygen atoms with tetrahydrofuran and 1,4-dioxane derivatives represents one of the hot topics in the research of C(sp^3)−H bond activation, and recently, direct alkylation, alkenylation, arylation, esterification, thiolation and amination of such C(sp^3)−H bonds has been demonstrated.[8] However, to the best of our knowledge, no examples of the oxidative amidation of C(sp^3)−H bonds adjacent to oxygen atoms of methyl aryl ethers have been reported to date. Aryl ethers are structural component of natural products, pharmaceuticals, and agrochemicals.[9] Through the development of novel catalyst systems, much progress has been achieved in the direct transformation of aryl ether (O-based electrophiles) through C(sp^2)−O activation and offers a new pathway to construct diverse compounds.[10] Selective activation and direct functionalization of C(sp^3)−H bonds adjacent to oxygen atoms with aryl ethers is also a highly appealing process but remains an elusive goal. Hence, a rapid, efficient and practical access to selective activation of C(sp^3)−H bonds in common aryl ether is urgent and highly desirable. As part of our continuing interest in the construction of C−N bond,[11] we report in this paper an efficient and highly regioselective protocol for oxidative imidation of C(sp^3)−H bond adjacent to oxygen atoms with aryl ethers. In addition, cyclic and chain alkyl ethers can also give the coupling products at C(sp^3)−H α to the ethereal oxygen. More importantly, this study contributed to understand the intrinsic nature of C(sp^3)−H bond adjacent to oxygen atoms of aromatic ether, which was traditionally considered "inert" but show mysterious and attractive synthetic potential with the proper catalyst systems.

Our initial efforts focused on the direct coupling of anisole **1a** with saccharin **2** using di-tert-butyl peroxide (DTBP; *t*BuO*O*t*Bu) and Bu_4NI combination, which was usually used in radical oxidation coupling system.[12] In the presence of DTBP (4 equiv) at 120 °C with stirring for 12 h, we obtained the desired product **3a** in 35% yield (Table 1, entry 1). The yield of **3a** could be increased to 88% by employing TBHP (70% in water) as the oxidant (Table 1, entry 2). Other oxidants such as TBHP (5−6 M in decane), $K_2S_2O_8$, H_2O_2 (30% aqueous solution) were less effective (Table 1, entries 3–5). When we decreased the amount of TBHP to 2 equiv, EtOAc as the solvent, the desired product **3a** was obtained in 64% yield (Table 1, entry 6). Further screening revealed that Bu_4NI was the best choice for this reaction. Bu_4NCl, Bu_4NBr, Bu_4ONAc, and I_2 afforded **3a** in 79%, 54%, 59% and 0% yields, respectively (Table 1, entries 7–10). And no product was observed when either Bu_4NI or TBHP was absent (Table 1, entries 11 and 12). It should be noted that this facile produce was performed under environmentally benign conditions (with tert-butyl alcohol and water as by-products) as it did not require metal catalyst and the rigorous exclusion of air.

With the optimized conditions in hand (Table 1, entry 2), the substrate scope of the imidation reaction was investigated with substituted aryl ethers. As shown in Table 2, functional group compatibility was good as demonstrated with both electron-rich MeO, *t*-Bu and -deficient F, Cl, Br and CN groups which were obtained in good to excellent yields (**3b−3l**). 4-Nitroanisole gave a moderate yield in 47% (**3m**). The results of this work are significant considering that Cl, Br and CN can be converted into various functional groups under ambient conditions. It is noteworthy that 1-methoxy-4-methylbenzene gave the methyl imidated product (**3g**), while the methoxy remained intact, consistented with the previous report by Zhu's group.[13] Similarly smooth coupling was observed for aryl ethers bearing substitution groups at different positions such as 2- Cl, 3-Cl and 4-Cl and no

Table 1: Screening of Reaction Conditions[a]



Entry	Catalyst	Oxidant	Yield[%][b]
1	Bu_4NI	DTBP	35
2	Bu_4NI	TBHP	88
3	Bu_4NI	TBHP	53[c]
4	Bu_4NI	$K_2S_2O_8$	0
5	Bu_4NI	H_2O_2	21
6	Bu_4NI	TBHP	64[d]
7	Bu_4NCl	TBHP	79
8	Bu_4NBr	TBHP	54
9	Bu_4NAc	TBHP	59
10	I_2	TBHP	0
11	Bu_4NI		0
12		TBHP	0

[a]Reaction conditions: **1a** (0.5 mmol) and saccharin **2** (1.0 mmol) at 120 °C for 12 h. [b]Yield of isolated product. [c]TBHP (5−6 M in decane). [d]TBHP (70% in water) 2 equiv, EtOAc (1 mL) as the solvent.

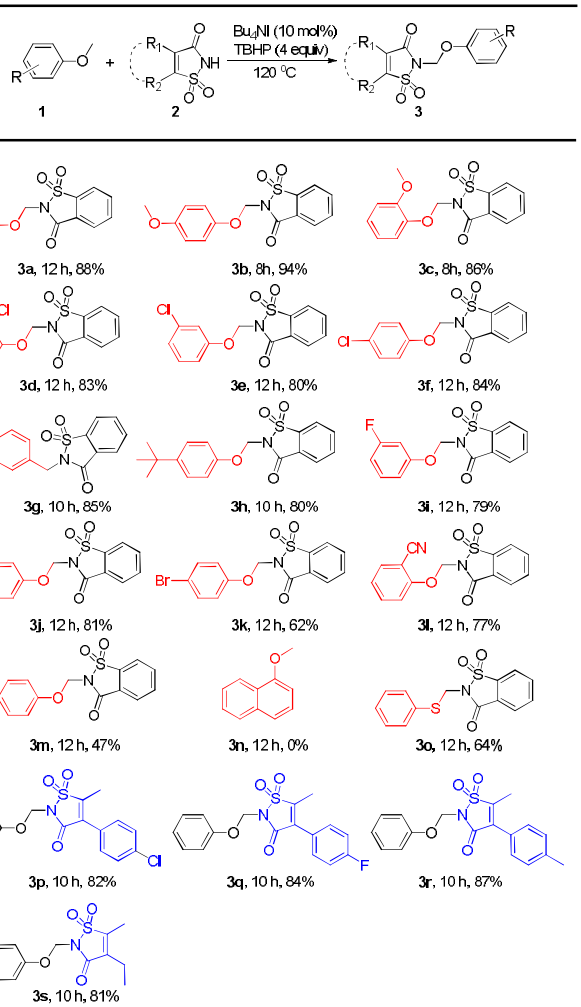
previous yield disparity was observed (**3d**, **3e** and **3f**). The fused bicyclic 1-methoxynaphthalene (**3n**) was inert during the reaction. To our delight, methyl(phenyl)sulfane was also compatible with this system and gave the desired product in 64% yield.

In fact, the saccharin moiety has been identified as an important molecular component in various classes of biologically active compounds.[14] The synthetic route for saccharin derivatives generally started from *ortho*-difunctional arenes.[15] The methodology of the formation of C−N bond directly from C(sp^3)−H bonds of aryl ether and N−H bond of saccharin will provide an attracting alternative way for the synthesis of saccharin derivatives. Therefore, other saccharin derivatives with substituents on the isothiazol-3(2*H*)-one 1,1-dioxide were also tested and some representative results are summarized in Table 2. Substrates bearing methyl and aryl groups at the 4- and 5-position of isothiazol-3(2*H*)-one 1,1-dioxide occurred efficiently to deliver **3p** to **3r** in 82–87% yields, respectively. The desired product **3s** were also obtained in good yield when 4- and 5-position of isothiazol-3(*2H*)-one 1,1-dioxide were alkyl groups.

The reaction conditions that had been optimized for aryl ether derivatives were also suitable for the imidation of cyclic and chain alkyl ethers. We select some typical compounds and the results are summaried in Table 3. Chain alkyl ethers 1,2-dimethoxyethane **4a** provided imidation products as a mixture at methyl and methane adjacent to oxygen atoms (**5a** and **5a'**). Cyclic alkyl ethers tetrahydrofuran **4b** and 1,4-dioxane **4c** were also tested to give the corresponding imidation products with saccharin (**5b** and **5c**). In contrast to previous reports about metal-catalyzed imination of alkyl ether, it is highlight that this produce is performed under environment benign metal-free conditions.

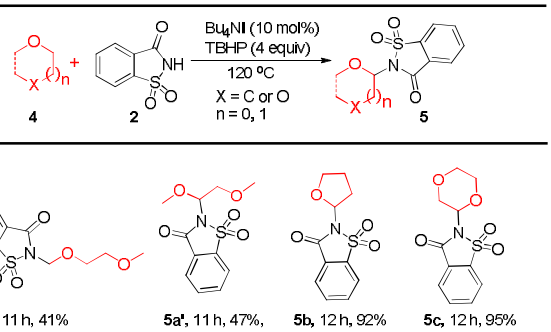
To probe the reaction mechanism, several control experiments were conducted. Intermolecular kinetic isotope effects (KIE, K_H/K_D) was carried out using equimolar amounts of tetrahydrofuran/tetrahydrofuran-d_8 and a KIE of 4.0 was observed, suggesting

Table 2: Imidation of various aryl ether with pharmacological saccharin and its derivatives[a]



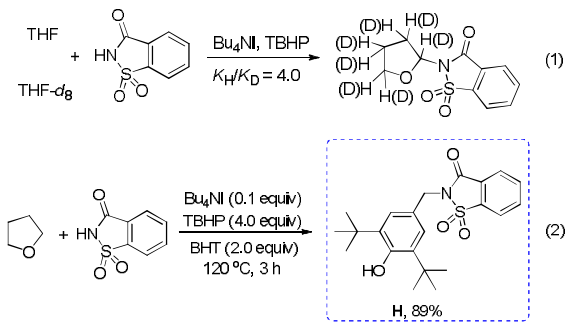
[a]Reaction conditions: **1** (0.5 mmol), saccharin **2** (1.0 mmol), Bu_4NI (0.05 mmol) and TBHP (2.0 mmol) at 120 °C for 12 h. [b]Yield of isolated product.

Table 3: Imidation of various alkyl ether with saccharin.[a]

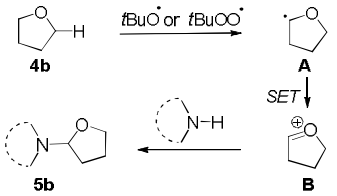


[a]Reaction conditions: **4** (0.5 mmol), saccharin **2** (1.0 mmol), Bu_4NI (0.05 mmol) and TBHP (2.0 mmol) at 120 °C for 12 h. [b]Yield of isolated product.

that C(sp^3)−H bond cleavage may be involved in the rate-determining step [Eq. (1)]. When radical inhibitor BHT (2,6-di-tert-but-



Scheme 1: Proposed reaction mechanism.



yl-4-methylphenol) and TEMPO (2,2,6,6-tetra-methyl-piperid-id-ine-*N*-oxyl) were introduced into the reaction mixture respectively, the reaction progress were completely suppressed even after longer times, unexpectedly, a methyl imidated product **H** derived from BHT was isolated in 89% yield [Eq. (2)]. Based on the experimental results and considering previous literatures about various functionalization of ether derivatives,[12c,e,k] a possible mechanism is proposed for the present catalytic reaction using tetrahydrofuran **4b** as a model substrate in Scheme 1, although further studies on the reaction mechanism are needed. The first step is likely to be the carbon-centered radical **A** adjacent to the oxygen of tetrahydrofuran can be generated by H-abstraction with a tert-butoxyl radical formed by the Bu_4NI initiated decomposition of peroxide. This radical could be further oxidized to a cation **B** through a SET (single-electron-transfer) step, whereas TBHP could react with Bu_4NI and further undergoes homolytic cleavage to afford a tert-butoxyl radical. Finally, the coupling of **B** with the nucleophile nitrogen source delivers the desired product **5b**.

In summary, we have developed a metal-free intermolecular oxidative C–N formation reaction of aryl ether with cheap and pharmacological saccharin and its derivatives using TBHP as an environmentally benign oxidant for the first time. The understanding of intrinsic characteristics between $C(sp^2)$−O bonds and $C(sp^3)$−H of aryl ether and the potential for application might promote more research interests in this fertile area. In addition, cyclic and chain alkyl ethers also reacted smoothly and afforded the desired imidation products. Considering its excellent reaction efficiency, wide substrate scope, the strategy would be highly desirable for intermolecular oxidative C–N bond formation of ether derivatives. Further investigation of the detailed mechanism and application of this protocol is currently underway in our lab.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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