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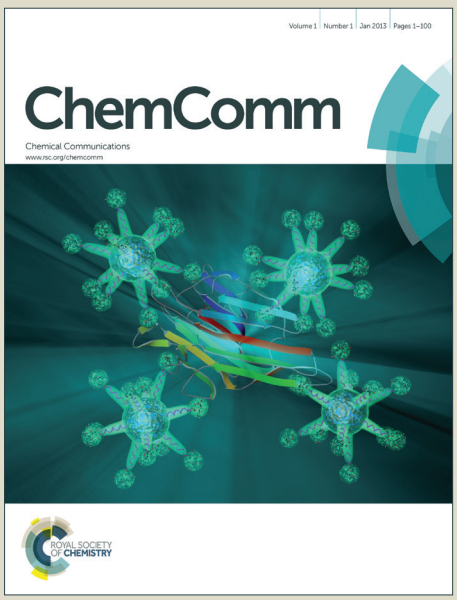

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COMMUNICATION

Organocatalytic Amination of Alkyl Ethers via *n*-Bu_4NI/*t*-BuOOH-mediated Intermolecular Oxidative C(sp^3)–N Bond Formation: Novel Synthesis of Hemiaminal Ethers†

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A novel method for constructing the hemiaminal ether framework under metal-free conditions has been developed. It involves direct organocatalytic amination of alkyl ethers through intermolecular oxidative C(sp^3)-N bond formation, with *t*-BuOOH being the oxidant and *n*-Bu_4NI as the catalyst.

Hemiaminal ether is a commonly encountered functional group present in many biologically active natural products as well as some pharmaceutical agents.[1] For example, natural product aspidophylline A known to reverse drug resistance in resistant KB cells,[2a-b] huperzine Q isolated from Huperziaserrata,[2c-d] fendleridine isolated from vallesiadichotoma RUIZ et PAV in peruandand,[2e-f] and the well-known anticancer pharmaceutical agent 5-fluorouridine[2g] all share the hemiaminal ether moiety in their respective structures.

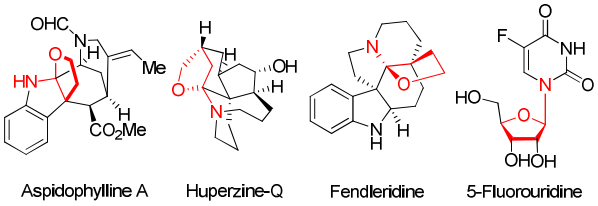
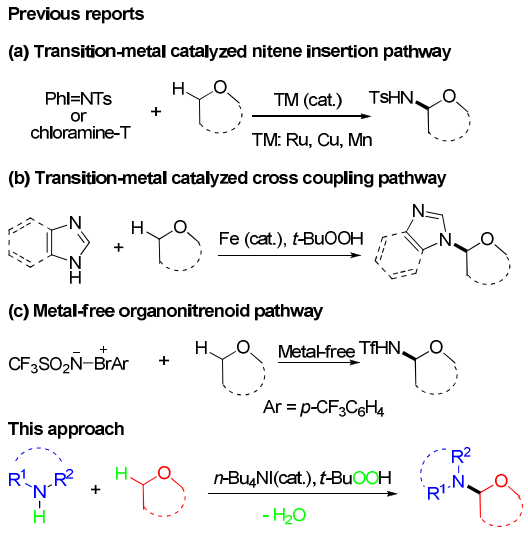


Fig. 1. Biologically Active Molecules Containing the Hemiaminal Ether Skeleton.

The prevalence of the hemiaminal ether framework in biologically important natural products and pharmaceuticals calls for the development of efficient methods for the construction of such skeletal structure. Traditionally, the hemiaminal frameworks were prepared from hydroamination of an enol ether[3a] or substitution of a halide or the hydroxyl group in an α-substituted ether by an amine.[3b] From the atom economy perspective, the C(sp^3)-H bond functionalization of alkyl ethers[4] is the most convenient and straightforward approach to access this class of compounds. One of the most studied strategies is the transition-metal catalyzed C(sp^3)-H amination of alkyl ethers induced by a nitriene precursor of either *N*-sulfonylimino-λ^3-iodane or chloramine-T (Scheme 1, pathway a).[5] An iron-catalyzed cross-dehydrogenative-coupling (CDC) reaction[6] between azoles and alkyl ethers has also been reported to form the N-alkylated azoles through the C(sp^3)-H bond functionalization of alkyl ethers (Scheme 1, pathway b).[7a,b] 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 (Scheme 1, pathway c).[8]



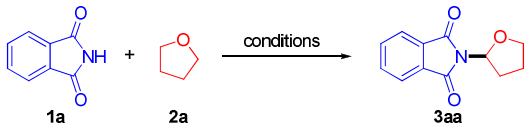
Scheme 1. Different Pathways for the Synthesis of the Hemiaminal Ether from Alkyl Ethers.

Although each of the above methodologies has its own merit in preparing the corresponding hemiaminal ether compound, the existing methods, however, all involve features of either the participation of a transitional metal or the limited scope of the applicable amines. In this regard, the search for an environmental friendly and efficient non-metallic oxidative system to realize the target compound is still very much in demand.[9] Herein, we report a novel procedure of metal-free amination of alkyl ethers by using *n*-Bu_4NI as the catalyst and *t*-BuOOH as the affordable and nontoxic oxidant.[10]

To begin our study, we chose the commercially available phthalimide **1a** and tetrahedronfuran (THF) **2a** as model substrates. Initially, hypervalent iodine reagents were tried out as oxidants to test the feasibility of this transformation.[9b,11]

However,

Table 1. Optimization of the Reaction Conditions[a]

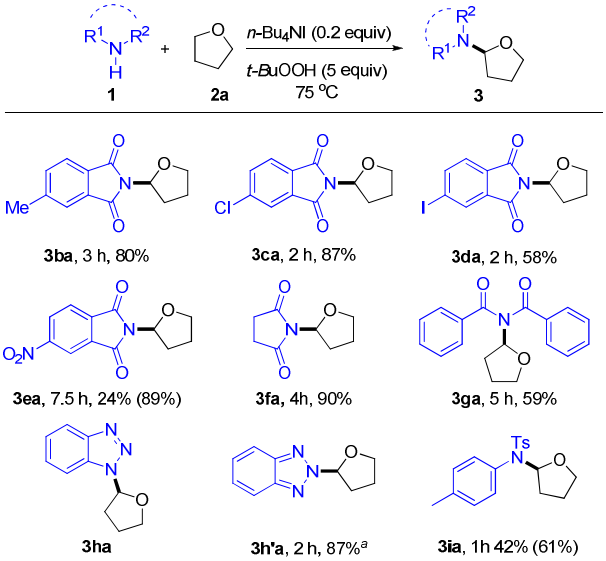


Entry	Oxidant (equiv.)	Catalyst (mol%)	Time	Yield[b]
1	PIDA (2.0)	none	12 h	NR[c]
2	PIDA (2.0)	none	12 h	5
3	PIDA (2.0)	I_2 (20)	5 h	20
4	*m*-CPBA (2.0)	PhI (20)	10 h	NR
5	H_2O_2 (2.0)	PhI (20)	10 h	NR
6	H_2O_2 (2.0)	*n*-Bu_4NI (20)	10 h	NR
7	*t*-BuOOH (3.0)	*n*-Bu_4NI (20)	2 h	85
8	***t*-BuOOH (5.0)**	***n*-Bu_4NI (20)**	**1 h**	**92**
9	*t*-BuOOH (5.0)	CuBr (20)	10 h	trace
10	*t*-BuOOH (5.0)	$FeCl_3{\cdot}6H_2O$ (20)	10 h	5%
11	*t*-BuOOH (5.0)	none	10 h	NR

[a] Reaction conditions: **1a** (1 mmol), **2a** (20 mmol), catalyst (20 mol%, 0.2 mmol) and oxidant were heated in a sealed tube at 75 °C unless otherwise stated. [b] Isolated yields. [c] RT.

no reaction occurred at room temperature for 12 h or longer after 2 equiv. of PIDA had been added to the phthalimide **1a** in THF **2a** (Table 1, entry 1). When the reaction mixture was heated and maintained at 75°C in a sealed tube for overnight, the reaction afforded a meager yield of 5% of the desired product (Table 1, entry 2). The addition of a catalyst (20 mol% of I_2) significantly improved the yield to a four-fold of 20% (Table 1, entry 3). Encouraged by this result, we set out the search of an effective catalytic oxidative reaction system, including *m*-CPBA/PhI[12] (Table 1, entry 4), H_2O_2/PhI (Table 1, entry 5), H_2O_2/*n*-Bu_4NI (Table 1, entry 6) and *n*-Bu_4NI/*t*-BuOOH[10] (Table 1, entry 7). The last combination led to a breakthrough result with the desired coupling product **3aa** being formed in an excellent yield of 85%. Further optimization showed that an increased amount of the oxidant to 5 equiv. improved the yield to 92% (Table 1, entry 8). We also checked out the transition-metal catalysts such as CuBr and $FeCl_3{\cdot}6H_2O$ which have been reported to be effective in *t*-BuOOH-mediated CDC reactions,[6] but neither of them was shown to be effective for this transformation (Table 1, entries 9-10). Control experiment showed that no **3aa** was detected when *n*-Bu_4NI was absent in the reaction system (Table 1, entry 11). Other hypervalent iodine reagents including PIFA and PhIO had also been tested out, however, only negative results of either no reaction at all or forming a complex mixture as products were observed (see ESI†).

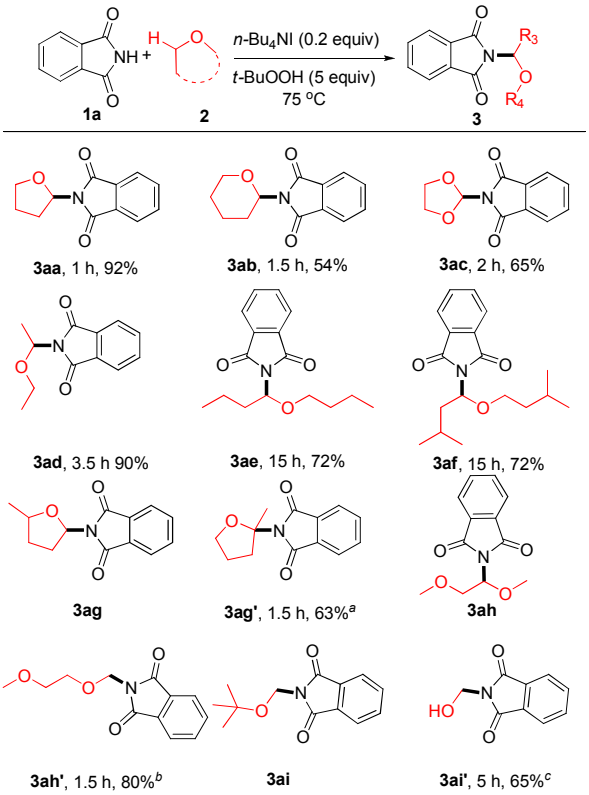
Under the most optimal reaction conditions (Table 1, entry 8), we proceeded to explore the generality of this methodology. THF (**2a**) was used as the ether reactant in the scope study of amines (Scheme 2). All phthalimide derivatives included in the study reacted smoothly and afforded the desired products **3ba**, **3ca**, **3da** in moderate to great yields, except for **3ea** in which the reaction was sluggish and only a 24% overall yield was obtained even though the yield based on recovered starting material (brsm) was as high as 89%. The large difference between the overall and brsm in the case of **3ea** seems to suggest that the strongly electron-withdrawing nitro group reduce the stability of the hemiaminal ether structure (therefore thermodynamically disfavored), but does not however affect the rate determining step (kinetically favored). Succinimide afforded product **3fa** in 90% yield, implying that the phenyl moiety in the amine substrate is not indispensable for the transformation. *N*-Benzoyl-benzamide also gave the desired coupling product **3ga** in moderate yield under the optimal conditions, indicating the lactam skeleton carried no importance in such a reaction. With benzotriazole**,** a separable mixture of two regioisomeric products **3ha**/**3h'a** was obtained. Lastly, the method was shown to be also applicable to Ts-protected *p*-toluidine, with the desired product **3ia** being isolated in moderate yield. However, certain types of amines including aniline and benzimidazole failed to give the desired products.



Scheme 2. Scope of amines [Reaction conditions: **1** (0.50 mmol), **2a** (10 mmol), anhydrous *t*-BuOOH (2.5 mmol), *n*-Bu_4NI (0. 10 mmol) at 75 °C unless otherwise stated, all the yields were isolated, yields in parentheses were isolated yields based on recovered starting marterial]. [a] Separable isomeric products, **3ha**/**3h'a** = 3.4: 1.

Similar scope studies were also carried out to the ether substrates, with phthalimide **1a** used as the amine. Results are listed in Scheme 3. Cyclic ether compounds such as tetrahedronpyran and dioxolane were found to react smoothly to generate the coupling products **3ab**, **3ac** with moderate yields. Straight chain ethers were also well tolerated and afforded the corresponding products **3ad**, **3ae**, **3af** in good to excellent yields although the reaction time was prolonged for **3ae** and **3af** containing the longer-chained alkyl substituent. Reaction of 2-methyltetrahydrofuran gave the coupling products in a separable regioisomeric mixture in a total yield of 63%, with the less steric **3ag** being the major product. To confirm the outcome with unsymmetrical substitution, we applied the reaction on another alkyl ether containing two active sites, namely, ethylene glycol dimethyl ether. Expected results were observed – a mixture of two regioisomeric products of **3ah/3ah'** (1.5:1) separable by silica gel chromatography. For the bulkier methyl *tert*-butyl ether, the yield of **3ag** was only 29%, with the major product being the

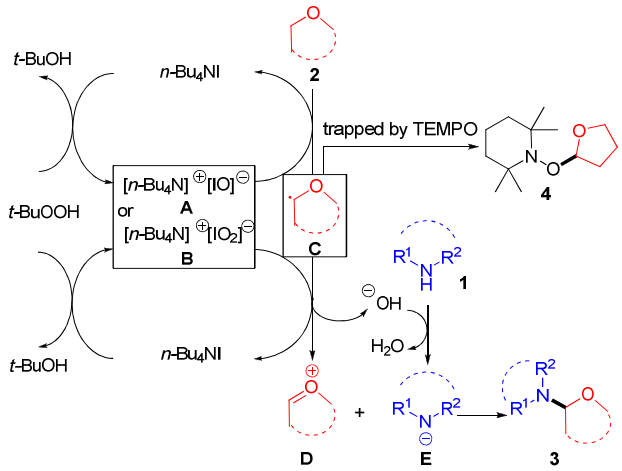
oxidative hydrolysis product **3ag'** in 36% yield.



Scheme 3. Scope of alkyl ethers [Reaction conditions: **1a** (0.50 mmol), **2** (10 mmol), anhydrous *t*-BuOOH (2.5 mmol), *n*-Bu$_4$NI (0.10 mmol) at 75 °C unless otherwise stated, all the yields were isolated yields after silica gel chromatography]. [a] Separable isomeric products, **3ag**/**3ag'** = 2.5:1. [b] Separable isomeric products, **3ah**/**3ah'** = 1.5:1. [c] Separable products, **3ai**/**3ai'** = 1:1.2.

We carried out additional experiments in order to elucidate the reaction mechanism (see ESI†). One control experiment showed that no desired product was obtained if the catalyst was switched to KI or I_2, but with a combination of I_2 and *n*-Bu$_4$NOH, the desired product was formed in 30%. This result suggests that the active hypoiodite ($[IO]^-$) or/and iodite ($[IO_2]^-$) were not only generated during the process but also played an important role in this transformation.[10e] Another control experiment was the kinetic isotopic effect (KIE) study by analyzing the ratio of **3aa** and **[D$_7$]-3aa** using ^{1}H NMR spectroscopy. Results showed k_H/k_D= 15.7 under the standard reaction conditions, indicating that the C-H bond cleavage may be the rate-determinating step (r.d.s.).

On the basis of the above results as well as literature reports,[10a,10e-g] we propose here a plausible mechanism (Scheme 3). Initially, active iodine species, ammonium hypoiodite **A** and iodite **B** were generated by oxidation of *n*-Bu$_4$NI with *t*-BuOOH. After that, hemolytic cleavage of the alkyl C–H bond was induced by **A** or **B** and gave the alkyl radical **C**, which could be trapped by TEMPO to form the coupling product **4**.[13] The alkyl radical **C** was further oxidized by active iodine species **A** or **B** to form the oxonium **D**, with a hydroxide ion being released. In the final step, the amine is deprotonated by the hydroxide ion to generate the anionic specie **E**, nucleophilic addition of specie **E** with the oxonium **D** formed the title product **3**. The proposed mechanism is in complete agreement with the observation of the nitro group effect on the reaction yields. In summary, we have demonstrated a novel *n*-Bu$_4$NI/*t*-BuOOH mediated direct



Scheme 4. The Proposed Mechanism

amination of various alkyl ethers with different amines in forming the important hemiaminal ether skeletons. The hypervalent iodine reagent was generated *in situ* by using *t*-butyl hydrogen peroxide (*t*-BuOOH) as a very affordable and also nontoxitic terminal oxidant. The beneficial features of the present approach are metal-free, organic catalytic and mild reaction conditions. Further studies on the application of the hemiaminal ether skeleton and the other oxidative coupling reactions are undergoing in our laboratory.

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