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# Radical heteroarylation of unactivated remote C(sp<sup>3</sup>)–H bonds *via* intramolecular heteroaryl migration<sup>†</sup>

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The radical-mediated heteroarylation of unactivated remote  $C(sp^3)$ -H bonds *via* intramolecular heteroaryl migration is achieved, leading to a variety of heteroaryl-substituted aliphatic ketones. A library of O-/S-/ N-containing heteroaryls such as benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, oxazolyl, and thiazolyl are amenable to the migration approach. The heteroaryl migration is triggered by an azido radical-mediated hydrogen atom abstraction from unactivated aliphatic  $C(sp^3)$ -H bonds. The transformation features mild C-C bond cleavage, good selectivity for tertiary  $C(sp^3)$ -H bonds, and broad functional group compatibility.

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# Introduction

Heteroarenes are important structural motifs widely existing in natural and pharmaceutical products, and materials science.<sup>1</sup> Over the past century, tremendous efforts from organic chemistry communities have been devoted to construct heteroarenes and investigate their transformations. Notwithstanding the great progress achieved in heterocyclic chemistry, our group has a long-term interest in developing ingenious approaches to incorporate heteroarenes to target molecules by radical-mediated functional group migration.<sup>2–4</sup> For instance, radical-mediated difunctionalization of alkenes *via* intramolecular heteroaryl migration provides an efficient tactic for the concomitant installation of a heteroaryl and another functional group in an alkene.<sup>3</sup> An upgraded docking-migration strategy significantly extends the compatibility of substrates, allowing the radical heteroarylation of more general alkenes.<sup>4</sup>

Direct functionalization of inert  $C(sp^3)$ –H bonds represents a powerful and atom-economical synthetic strategy.<sup>5</sup> As a complement to transition metal-catalyzed  $C(sp^3)$ –H activation, radical-mediated site-selective functionalization of  $C(sp^3)$ –H bonds has received rapidly increasing attention,<sup>6,7</sup> and many new reaction modes have been unveiled during the last decade. It should be noted that although remote radical C-Hfunctionalization has become a heavily investigated field of the chemical community, the remote  $C(sp^3)$ -H arylation as addressed herein is particularly challenging and only very few examples have been reported complementing transition-metalcatalyzed C(sp<sup>3</sup>)-H arylation that only work for primary and secondary alkyl sites.<sup>6h,i</sup> In 2018, we disclosed a tertiary alcohol-directed radical heteroarylation of unactivated C(sp<sup>3</sup>)-H bonds via remote heteroaryl migration under photochemical conditions (Scheme 1a).<sup>8</sup> In the presence of an Ir complex as a photocatalyst and potassium persulfate as an oxidant, the nascent alkoxy radical enabled the hydrogen atom transfer (HAT) and the ensuing heteroaryl migration. Although (benzo) thiazolyl and pyridyl were readily incorporated at the δ-position of alcohols, the substrates were limited to alcohols bearing N-containing heteroaryls. Despite the fact that O/S-containing heteroaryls have also showcased the migratory aptitude,<sup>3h,i</sup> they were not tolerated under strong oxidation conditions due to their high electron density, and thus failed to generate the desired products. To address this issue, we conceive an intermolecular HAT instead of the alkoxy radicalmediated intramolecular HAT to generate the alkyl radical, and meanwhile avoid the use of harsh conditions. Considering that the azido radical is a common HAT species easily accessible under mild conditions,<sup>9</sup> we envision that the azido radicalmediated HAT might be compatible with the following O-/ S-containing heteroaryl migration, thus realizing the unprecedented O-/S-heteroarylation of unactivated C(sp<sup>3</sup>)-H bonds by a functional group migration strategy (Scheme 1b).

Herein, we provide the proof of principle for the hypothesis. Compared to the previous protocol,<sup>8</sup> the current one provides



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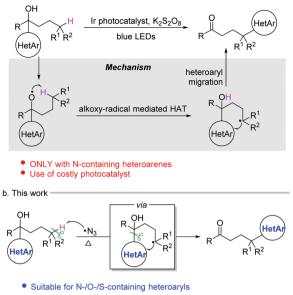
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a. Our previous work (ACIE 2018, 57, 1640)



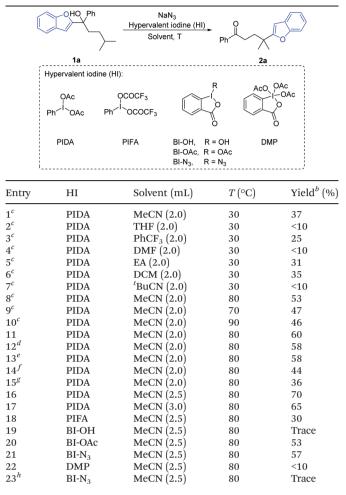
a broader substrate scope for the azido radical-mediated heteroarylation of  $C(sp^3)$ -H bonds. In addition to N-containing heteroaryls, O- and S-containing heteroaryls also readily migrate in the reaction, leading to heteroaryl-substituted aliphatic ketones in synthetically useful yields. The transformation features mild C-C bond cleavage, good selectivity for tertiary  $C(sp^3)$ -H bonds, and wide functional group compatibility.

# **Results and discussion**

We commenced the investigation with the benzofuryl-substituted tertiary alcohol 1a as a model substrate and the combination of (diacetoxyiodo)benzene (PIDA) and sodium azide as the azido radical source (Table 1). Among the screened organic solvents, MeCN delivered the highest yield of the desired product 2a (entries 1-7). Elevating the reaction temperature to 80 °C improved the isolated yield of 2a to 53% (entry 8). It was found that changing the temperature to be higher or lower did not further increase the yield (entries 9 and 10). The amounts of PIDA and NaN<sub>3</sub> were then examined (entries 11-15), showing that the use of excess PIDA and NaN3 was indeed beneficial for the reaction (entry 11). Slightly increasing the volume of MeCN to 2.5 mL resulted in a better yield (entry 16). The survey of hypervalent iodine (HI) reagents indicated that PIDA is still the most efficient reagent (entry 16, entries 18-22). Surprisingly, BI-N<sub>3</sub> capable of serving both as an oxidant and azido radical source did not provide the expected reactivity in the absence of NaN<sub>3</sub> (entry 23).

With the optimized reaction conditions in hand, the generality of the protocol was assessed (Scheme 2). A variety of tertiary alcohols bearing either an electron-rich or electron-

 Table 1
 Survey of reaction parameters<sup>a</sup>



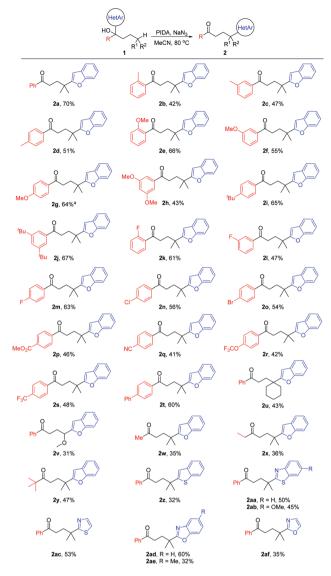
<sup>*a*</sup> Reaction conditions: **1a** (0.2 mmol), HI (4.0 equiv.), and NaN<sub>3</sub> (4.0 equiv.) in MeCN (2.5 mL), 80 °C for 12 h. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> PIDA (2.5 equiv.), NaN<sub>3</sub> (2.5 equiv.). <sup>*d*</sup> PIDA (3.5 equiv.), NaN<sub>3</sub> (3.5 equiv.). <sup>*e*</sup> PIDA (4.5 equiv.), NaN<sub>3</sub> (4.5 equiv.). <sup>*f*</sup> PIDA (4.0 equiv.), NaN<sub>3</sub> (2.0 equiv.). <sup>*g*</sup> PIDA (2.0 equiv.). <sup>*h*</sup> Without NaN<sub>3</sub>.

deficient substituent were converted into the corresponding ketone products (2a-2t). The use of substrates with para-, meta-, or ortho-substitution resulted in comparable yields (2b-2d, 2e-2g, and 2k-2m), probably suggesting that the steric hindrance of tertiary alcohols did not affect the reaction yield much. The moderate yields of products 2b-2d might be attributed to the competitive HAT with the benzylic C-H bonds of substrates.<sup>10</sup> Other tertiary C(sp<sup>3</sup>)-H bonds, such as the cyclohexyl C-H bond (2u), and the C-H bond adjacent to the O-atom (2v) were also regioselectively functionalized. Not only aryl ketones but also some dialkyl ketones were generated, albeit with decreased yields (2w-2y). In addition to benzofuryl, other heteroaryls such as benzothienyl, benzothiazolyl, thiazolyl, benzoxazolyl, and oxazolyl also readily migrated in the reaction, leading to the desired products in synthetically useful yields (2z-2af).

In order to illustrate the utility of the product, the transformations of 2a were performed. Upon treating 2a with

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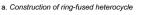
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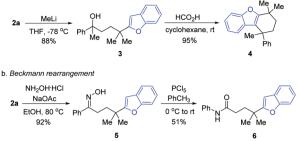


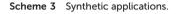
Scheme 2 Substrate scope. Reaction conditions: 1 (0.2 mmol), PIDA (4.0 equiv.), and NaN<sub>3</sub> (4.0 equiv.) in MeCN (2.5 mL), 80 °C for 12 h. Yields of the isolated products are given. <sup>a</sup>PIDA (6.0 equiv.) and NaN<sub>3</sub> (6.0 equiv.).

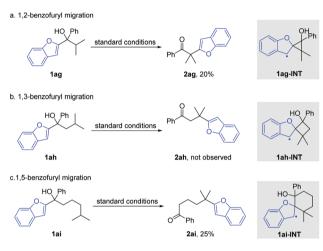
methyl lithium, the tertiary alcohol **3** was generated, which was then subjected to intramolecular annulation *via* dehydration in the presence of formic acid, leading to the valuable ring-fused heterocyclic product **4** in a high yield (Scheme 3a). Treating **2a** with hydroxylamine hydrochloride and sodium acetate generated the oxime **5**, which served as the precursor of Beckmann rearrangement to afford the corresponding amide **6** (Scheme 3b).

Afterwards, the migration distance was varied in the substrates to probe the transition states that might influence the heteroaryl migration (Scheme 4). In Scheme 2, all products were obtained *via* 1,4-heteroaryl migration, facilitated by a kinetically favoured five-membered cyclic intermediate. The 1,2-/1,5-benzofuryl migration *via* a three- or six-membered





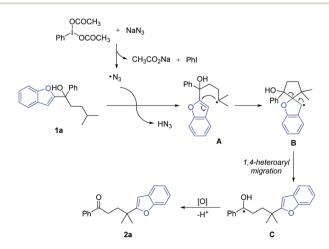




Scheme 4 Investigations on the preference of cyclic intermediates.

cyclic intermediate also proceeded, however, affording the corresponding products **2ag** and **2ai** in low yields (Scheme 4a and c). In sharp contrast, the 1,3-benzofuryl migration did not proceed owing to the disfavoured four-membered cyclic intermediate (Scheme 4b).

Based on the experimental results, a proposed mechanism is shown in Scheme 5. The interaction of PIDA with NaN<sub>3</sub> gen-



Scheme 5 Proposed mechanism.

erates an azido radical that regioselectively abstracts a hydrogen atom from the tertiary  $C(sp^3)$ -H bond with the lowest bond dissociation energy. The resulting alkyl radical intermediate **A** undergoes intramolecular cyclization to generate the spiro radical intermediate **B**. The subsequent 1,4-heteroaryl migration *via* a five-membered cyclic intermediate results in the metastable ketyl radical **C**. Finally, single-electron oxidation of **C** with PIDA followed by deprotonation furnishes the desired product **2a**.

# Conclusions

In summary, a radical-mediated remote heteroarylation of unactivated  $C(sp^3)$ -H bonds of tertiary alcohols has been disclosed, leading to a variety of useful heteroaryl-substituted aliphatic ketones. The reaction proceeds *via* a cascade of azido radical-mediated HAT and intramolecular heteroaryl migration, in which an inert C-H bond and C-C bond are consecutively cleaved under mild conditions. A library of O-/S-/ N-containing heteroaryls, such as benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, oxazolyl, and thiazolyl, readily migrate in the reactions. Mechanistic studies reveal that the heteroaryl migration prefers a five-membered cyclic intermediate. Moreover, the transformation features broad functional group tolerance and good regioselectivity. This protocol offers an ingenious approach for selective functionalization of inert C(sp<sup>3</sup>)-H bonds.

# Conflicts of interest

There are no conflicts to declare.

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