

# Radical-Mediated Distal Ipso-Migration of O/S-Containing Heteroaryls and DFT Studies for Migratory Aptitude

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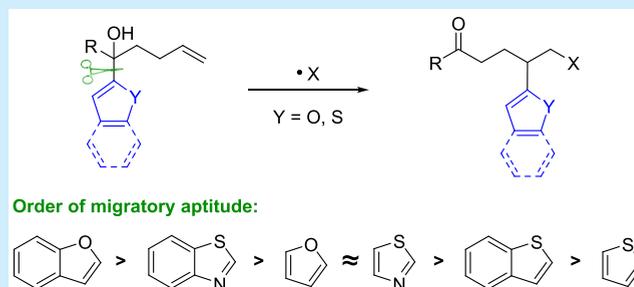


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Supporting Information

**ABSTRACT:** Herein we describe an efficient distal ipso-migration of O- and S-containing heteroaryls and the radical heteroarylation of unactivated alkenes. The migration is triggered by various fluoroalkyl radicals, leading to valuable multifunctionalized ketones. The comparisons of migratory aptitude for O-/S-containing heteroaryls are comprehensively investigated. The origin of the chemoselective migration could be partially attributed to the discrepancy in the energy level of the LUMO of each heteroaryl group.



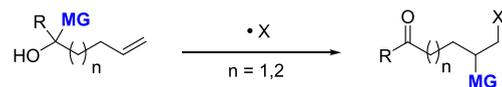
Simultaneous incorporation of two different functional groups to alkenes supplies an effective utilization technique of alkenes. Upon consideration of the broad availability of alkenes, the radical-mediated difunctionalization of alkenes is of highly synthetic importance, which has attracted extensive attention.<sup>1</sup> Despite the great progress over the past few decades, the reaction substrates are largely limited to activated alkenes, in which the olefinic moiety is adjacent to  $\pi$ -conjugated system, e.g., aryl, carbonyl, or heteroatom. As a consequence, the transient alkyl radical intermediate can be stabilized by p- $\pi$  conjugation, thus allowing the subsequent functionalization to proceed readily due to increased lifetime. In contrast, unactivated alkenes are commonly regarded as challenging substrates in this transformation due to the absence of such stabilizing effect.

Recently, remote functional group migration (FGM) has proven to be a robust tactic for elusive radical-mediated difunctionalization of unactivated alkenes.<sup>2</sup> In this context, a portfolio of groups including (hetero)aryl,<sup>3,4</sup> cyano,<sup>5</sup> oximino,<sup>4e,6</sup> carbonyl,<sup>6a,7</sup> alkynyl,<sup>8</sup> and alkenyl<sup>9</sup> have displayed migratory aptitude (Scheme 1A), leading to various synthetically useful functionalization of unactivated alkenes.

In 2017, we disclosed the radical-mediated heteroarylation of unactivated alkenes by means of remote heteroaryl migration for the first time.<sup>4a</sup> The utility of this protocol has been comprehensively explored in the later accomplishments.<sup>4b-1</sup> Among these efforts, N-containing heteroaryls (e.g., benzothiazolyl, benzoxazolyl, benzimidazolyl, pyridyl, quinolyl, etc.) were mostly engaged in the radical-induced migration. However, little attention has been paid to migration of O- or S-containing heteroaryls, which are also a class of important structural motifs widely found in nature and play key roles in numerous bioactive compounds. If the migration of O- or S-containing heteroaryls could take place, it could lead to a

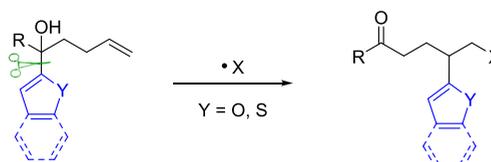
## Scheme 1. Distal Functional Group Migration for Radical Difunctionalization of Unactivated Alkenes

### A. Previous work

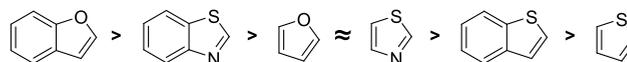


MG (migratory group) = N-containing heteroaryl, aryl, oximino, carbonyl, alkynyl, alkenyl

### B. This work: O/ S-containing heteroaryl migration (underexplored)



Order of migratory aptitude:



novel alkene difunctionalization. Herein, we provide concrete support for the hypothesis (Scheme 1B). A set of O- or S-containing heteroaryls such as benzofuryl, benzothienyl, furyl, and thienyl readily migrate under mild conditions. The distal migration is triggered by fluoroalkyl radicals (CF<sub>3</sub>, CF<sub>2</sub>R,

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CHFR), affording a vast array of multifunctionalized ketones. The comparison of migratory aptitude is comprehensively studied between O-, S-, or N-containing heteroaryls, offering a significant complement to the current knowledge of heteroaryl migration. DFT studies provide insight into the driving force of the radical-mediated heteroaryl migration and the origin of the chemoselectivity.

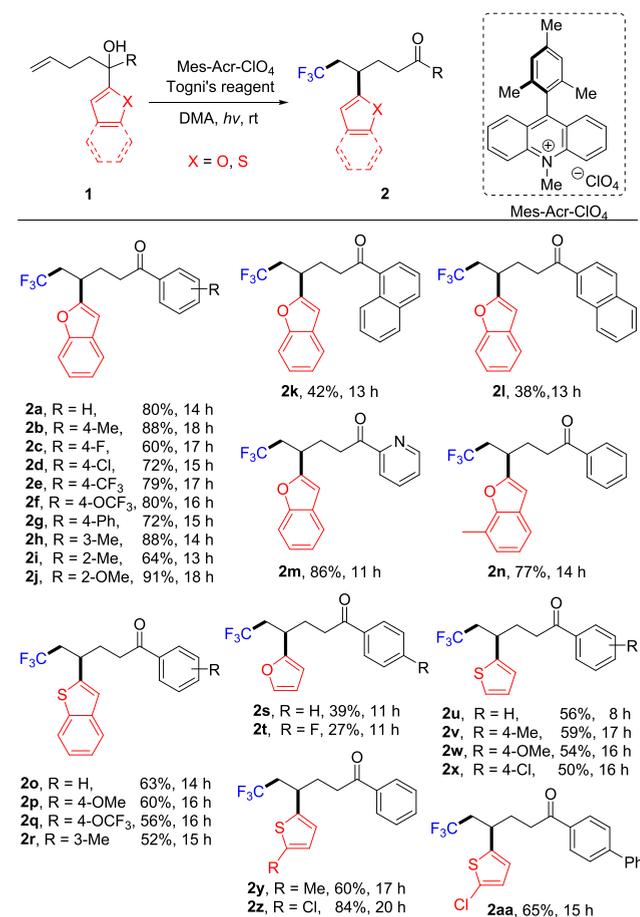
The presence of a fluoroalkyl group in biologically active molecules usually leads to significant improvement in metabolic stability, lipophilicity, and selectivity.<sup>10</sup> Simultaneous incorporation of a fluoroalkyl and a heteroaryl group holding pharmaceutical values provides an efficient approach to the diverse synthesis of fluorine-containing compounds. The trifluoromethylheteroarylation of unactivated alkenes via the distal migration of O/S-containing heteroaryls was implemented by using the benzofuryl-substituted tertiary alcohol **1** as model substrate and the Togni's reagent II as trifluoromethylating reagent under visible-light irradiation.<sup>11</sup> A set of photosensitizers were examined, indicating that Mes-Acr-ClO<sub>4</sub> (9-mesityl-10-methylacridinium perchlorate) offered the best catalytic efficiency under 14 W blue LED irradiation (see Table S1). Solvent screening revealed that the highest yield of desired product was delivered by using DMA (*N,N*-dimethylacetamide) as solvent. Control experiments demonstrated that the use of photocatalyst was indispensable to the reaction, which also did not proceed without photoirradiation.

With the optimized reaction conditions in hand, we set about assessing the generality of the method and defining the substrate scope (Scheme 2). The transformation displayed a good functional group tolerance; a variety of electron-rich and deficient groups were compatible with the mild conditions. The positional change of the ortho-, meta-, or para-substituents on benzene did not have much impact on the reaction outcome. The 1,4-migration of the benzofuryl group occurred exclusively in the presence of phenyl or naphthyl groups (**2a**–**2l**) and was even preferential over other migratory group such as pyridyl (**2m**). In addition to benzofuryl, other O-/S-containing heteroaryls such as benzothienyl, furyl, and thienyl also exhibited good migratory aptitude, affording the corresponding heteroaryl-migrated products with unique chemo- and regioselectivity (**2n**–**2aa**). Remarkably, the reaction of **1a** could be performed on a 1.5 mmol scale without compromising the outcome, affording **2a** with 73% yield (see SI).

In order to gain deeper insight into the migratory aptitude, the comparison of migration rate between different heteroaryls was systematically performed (Scheme 3). Because it has been proven that migration of the five-membered N-containing heteroaryls (benzothiazolyl, benzoxazolyl, and benzimidazolyl) was prior to the six-membered ones (pyridyl, quinolyl),<sup>4a</sup> the competitive experiments herein were focused on the favorable five-membered heteroaryl migration. The cases of **1ab**–**1af** explicitly illustrated that the migration rate of benzofuryl was superior to others. The following comparisons in **1ag**–**1an** were carried out in the same manner. Finally, the order of migratory aptitude was in line with benzofuryl > benzothiazolyl > furyl ≈ thiazolyl > benzothienyl > thienyl.

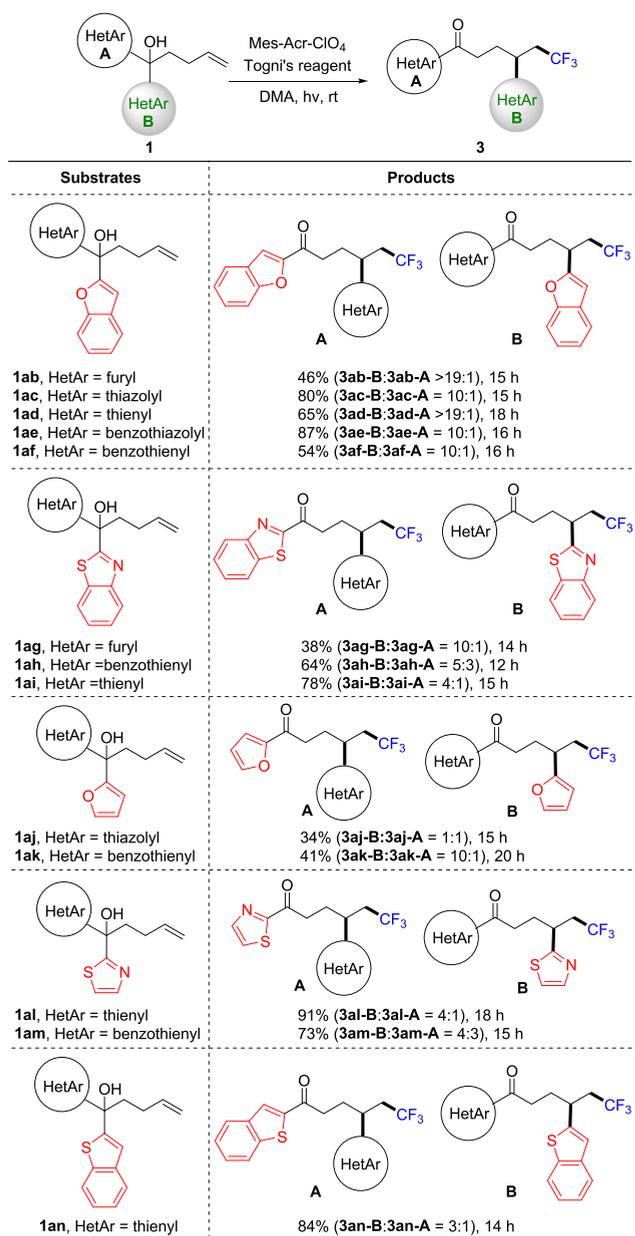
Computational studies<sup>12</sup> were performed to shed light on the migratory activity for these O-/S-containing heteroaryls. First, the comparisons between benzoannelated heteroaryls and their parent aryls were carried out. Take **1ab**, for example; the generated CF<sub>3</sub> radical is ready to attack the terminal carbon (C<sup>1</sup>) of alkenyl moiety to afford intermediate **1ab-INT1**.

## Scheme 2. Scope of Benzofuryl-, Furyl-, Benzothienyl-, and Thienyl-Substituted Tertiary Bishomoallylic Alcohols<sup>a</sup>



<sup>a</sup>Reaction conditions: **1** (0.2 mmol, 1.0 equiv), Togni's reagent (**II**) (0.4 mmol, 2.0 equiv), and Mes-Acr-ClO<sub>4</sub> (0.008 mmol, 4 mol %) in DMA (3.0 mL) at rt, 14 W blue LED irradiation. Yields of isolated products are given.

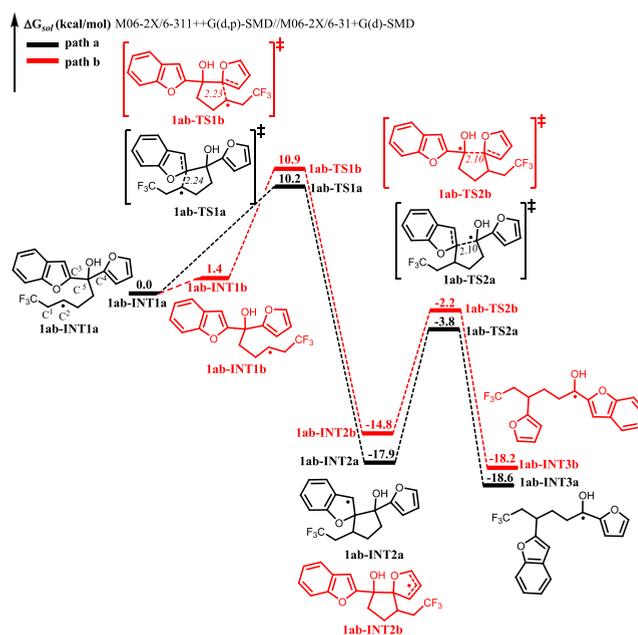
Subsequently, the formed alkyl radical (spin density mainly locates on C<sup>2</sup>) could undergo radical addition to either C<sup>3</sup> of benzofuryl (path a) or C<sup>4</sup> of furyl (path b), leading to **1ab-INT2a** and **1ab-INT2b**, respectively. Computational results show that the free energy barriers for path a and path b are 10.2 and 10.9 kcal/mol, respectively, indicating that the intramolecular radical addition to C<sup>3</sup> of benzofuryl is more favorable than to C<sup>4</sup> of furyl moiety (Figure 1). It should be noted that the spin density of the formed **1ab-INT2a** is more delocalized than **1ab-INT2b** due to the presence of the annelated benzo group (Figure S1). Therefore, the formed **1ab-INT2a** is thermodynamically more stable than **1ab-INT2b**. In addition, frontier molecular orbital (FMO) analysis can provide an insight into the discrepancy in the energy level for the two heteroaryls in **1ab**. The LUMO of **1ab**<sup>13</sup> is essentially the same as the LUMO of benzofuryl group, while the LUMO+1 of **1ab** mainly locates in the furyl group (Figure 2). The radical addition is more likely to occur with LUMO and consequently C<sup>3</sup> of benzofuryl is more facile to be attacked than C<sup>4</sup> of furyl in **1ab**. Next, the yielded radical intermediate **1ab-INT2a** could undergo C<sup>3</sup>–C<sup>5</sup> bond cleavage to afford the benzofuryl migration intermediate **1ab-INT3a**. It is noteworthy that the generated **1ab-INT3a** is thermodynamically more stable than **1ab-INT2a**. Due to the connection of both

Scheme 3. Comparison of Migratory Aptitude between Different Heteroaryls<sup>a</sup>

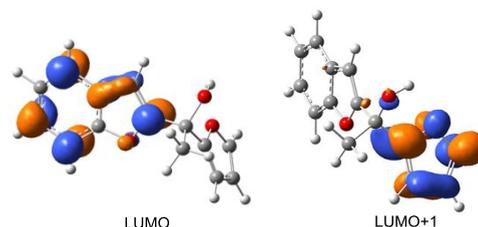
<sup>a</sup>Reaction conditions: **1** (0.2 mmol, 1.0 equiv), Togni's reagent (**II**) (0.4 mmol, 2.0 equiv), and Mes-Acr-ClO<sub>4</sub> (0.008 mmol, 4 mol %) in DMA (3.0 mL) at rt, 14 W blue LED irradiation. Yields of isolated products are given.

furyl and hydroxyl groups for C<sup>5</sup>, the formed radical intermediate **1ab-INT3a** is well stabilized. The calculated energy profile shows that transformation from **1ab-INT1** to **1ab-INT3a** is downhill, which is the driving force for the migration of heteroaryls and could be rationalized by the relative stability of the formed radical intermediates. Similarly, it is not difficult to deduce that the benzothieryl group is more ready to migrate than the thienyl group (Figure S2).

Second, the order of migratory activity for benzofuryl, benzothiazolyl, and benzothieryl was investigated (Figures S3 and S4). Computational studies for the substrate **1ae** demonstrate that the generated alkyl radical is more ready to attack C<sup>3</sup> of benzofuryl, indicating that benzofuryl group is



**Figure 1.** Energy profile (in kcal/mol) for the migration of heterocycles of **1ab**. Bond lengths are shown in angstroms.



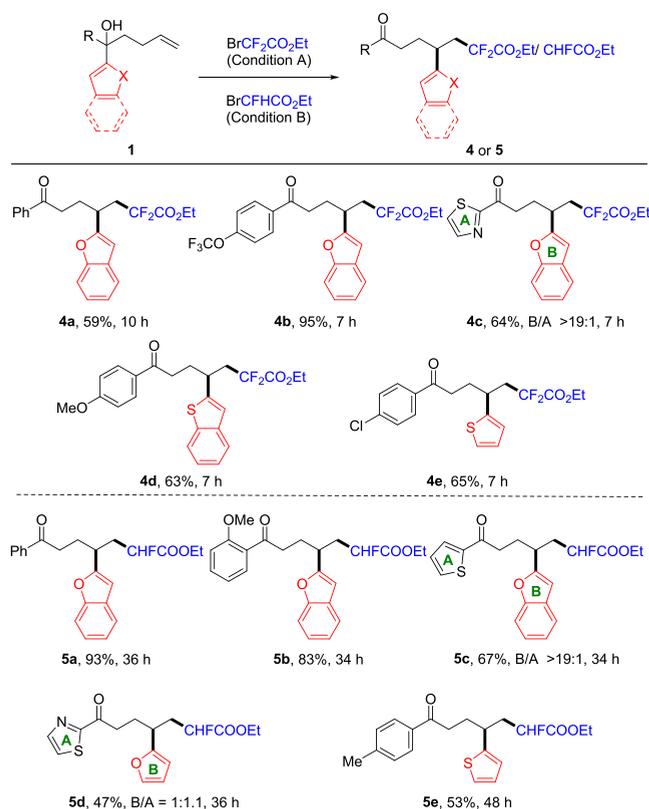
**Figure 2.** LUMO and LUMO+1 of **1ab'**.

more ready to migrate than benzothiazolyl group. Likewise, the substrate **1ah** was studied computationally, suggesting that the benzothieryl group is more favorable to migrate than benzothienyl group. Therefore, the order of migratory activity is benzofuryl > benzothiazolyl > benzothieryl. Similarly, the order of migratory activity for the parent heteroaryls is also obtained computationally, which is furyl ≈ thiazolyl > thienyl (Figures S5 and S6). Third, the migratory activities between benzothiazolyl and furyl and between thiazolyl and benzothieryl were examined. Computational studies for the substrate **1ag** show that the migration of benzothiazolyl is easier than that of furyl group (Figure S7). For substrate **1am**, computational results suggest that the migration of thiazolyl is more favorable than that of benzothieryl group (Figure S8). Overall, the order of migratory ability can be concluded as benzofuryl > benzothiazolyl > furyl ≈ thiazolyl > benzothieryl > thienyl, which is consistent with the experimental results well. Additionally, the calculated  $\Delta\Delta G^\ddagger$  values for the two chemoselective pathways are qualitatively consistent with the experimental ratios of migrated products (see Table S2).

Then we focused attention toward incorporating di- and monofluoroalkyl into unactivated alkenes through the aforementioned olefin difunctionalization approach. Di-/monofluoromethylheteroarylation both readily proceeded with the similar visible-light photoredox catalysis via cascade radical addition. First, the desired products (**4a–4e**) of difluoroalkyl-heteroarylation were furnished in moderate to excellent yields,

regardless of the electronic characteristics of substrates (Scheme 4, top). The monofluoroalkylation also generated

#### Scheme 4. Di-/Monofluoromethylheteroarylation of Unactivated Alkenes<sup>a</sup>



<sup>a</sup>Reaction conditions A: **1** (0.2 mmol, 1.0 equiv), BrCF<sub>2</sub>CO<sub>2</sub>Et (0.4 mmol, 2.0 equiv), and *fac*-Ir(ppy)<sub>3</sub> (0.008 mmol, 4 mol %) in DMF (2 mL) at rt, 14 W blue LED irradiation. Reaction conditions B: **1** (0.2 mmol, 1.0 equiv), BrCFHCO<sub>2</sub>Et (0.3 mmol, 1.5 equiv), *fac*-Ir(ppy)<sub>3</sub> (0.006 mmol, 3 mol %), and K<sub>2</sub>HPO<sub>4</sub> (0.3 mmol, 1.5 equiv) in EtOAc (2 mL) at rt, 30 W blue LED irradiation. Yields of isolated products are given.

the products in useful yields and good selectivities (Scheme 4, bottom). The example of **4c** and **5c** also indicated that the migration of benzofuryl was prior to other heteroaryls in the reaction. The example of **5d** again verified the similar migration rate between furyl and thiazolyl groups. Remarkably, the addition of electrophilic fluoroalkyl radicals to the electron-rich O-/S-containing heteroaryls was not detected, manifesting the exclusive chemoselectivity.

In summary, we have disclosed the radical-mediated heteroarylfunctionalization of unactivated alkenes via the distal migration of O-/S-containing heteroaryls. In this protocol, benzofuryl, furyl, benzthienyl, and thienyl showcase the remote migratory aptitude for the first time, complementary to the current knowledge of heteroaryl migration mainly involving N-containing heteroaryls. Fluoroalkyl radicals, such as CF<sub>3</sub>, CF<sub>2</sub>COOEt, and CHF COOEt, trigger the migration process and are readily incorporated into alkenes alongside the construction of C–C bonds. The transformation features good chemo-/regioselectivities, mild reaction conditions, and broad functional group compatibility. DFT studies shed light on the driving force for the radical-mediated migration of heteroaryls, which could be rationalized by the thermodynam-

ical stability of the sequentially formed radical intermediates. In addition, the discrepancy in the energy level of the LUMO of each heteroaryl might partially account for the origin of the chemoselective migration. After the formation of alkyl radical via an external radical addition, the following intramolecular radical cyclization prefers to attack the heteroaryl with LUMO in lower energy level, subsequently leading to the chemoselective migration of the attacked heteroaryl group. The comprehensive comparisons of the migration rates between different heteroaryls and mechanistic insights may provide a guide for subsequent efforts in the design of selective migrations.

#### ■ ASSOCIATED CONTENT

##### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c02030>.

Experimental details, compound characterization data, NMR spectra (PDF), DFT studies, and mechanism studies (PDF)

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##### Notes

The authors declare no competing financial interest.

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(12) See the SI for computational details.

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