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Chemo- and Regioselective Distal Heteroaryl *ipso*-Migration: A General Protocol for Heteroarylation of Unactivated Alkenes

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Supporting Information

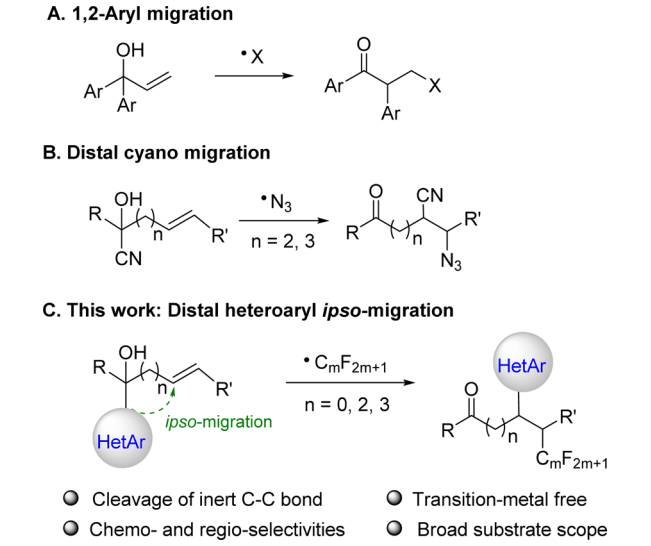
ABSTRACT: Herein we report a novel, general protocol for distal heteroaryl *ipso*-migration and its application to the elusive heteroarylation of unactivated alkenes. A set of nitrogen-containing heteroaryl groups showcase the migratory aptitude. This reaction provides a variety of fluoroalkyl functionalized heteroarenes under mild reaction conditions. This is the first report of a difunctionalization of unactivated alkenes with distal heteroaryl migration.

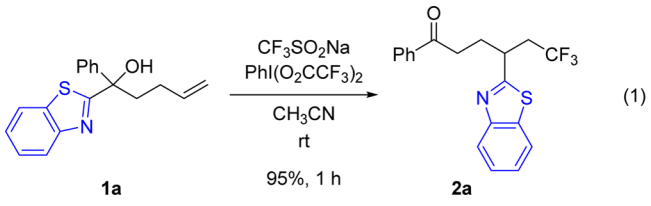
Radical-mediated, controlled difunctionalization of alkenes is a powerful tool for the manipulation of olefins.[1] Despite progress in the past decade, the scope of alkenes is largely restricted to activated olefins, in which the presence of an adjacent aryl, carbonyl, or heteroatom is required to stabilize the transient radical intermediate by p−π conjugation.[2] Without the stabilization of the radical intermediate, the reaction typically proceeds with poor yield and/or regioselectivity. Therefore, radical difunctionalization of unactivated alkenes still remains challenging.

Difunctionalization of alkenes with concomitant functional group migration is a highly useful but underdeveloped synthetic method.[3] Particularly, the scope of this reaction was mainly limited to 1,2-migration of an aryl group (Scheme 1A).[4] There are also a few cases of distal aryl migration dependent upon certain substrates.[5] Recently, we have disclosed the first example of distal cyano migration with azidation of unactivated alkenes (Scheme 1B).[6] We now expand the scope of distal migration to include heteroaryl groups that are frequently used in drug development and present in almost half of the top 200 pharmaceuticals.[7] A set of useful nitrogen-containing heteroaryl groups showcase the migratory aptitude. Additionally, we show that distal migration can be induced by radical fluoroalkylation of alkenes under mild reaction conditions with good chemo- and regioselectivities (Scheme 1C). The resultant products can serve as versatile building blocks to construct complex heteroarenes and natural products.[8]

We used benzothiazole-substituted tertiary alcohol **1a** as the standard substrate to identify the optimal reaction conditions. Oxidation of Langlois' reagent (CF_3SO_2Na) with phenyliodine bis(trifluoroacetate) (PIFA) generated a trifluoromethyl radical[9] that added rapidly to **1a** at room temperature and induced the migration of the benzothiazolyl group to provide **2a** with no phenyl migration product (eq 1; for detailed optimization of reaction conditions, see SI).[10,11]

Scheme 1. Combinational Strategy of Functional Group Migration and Olefin Difunctionalization





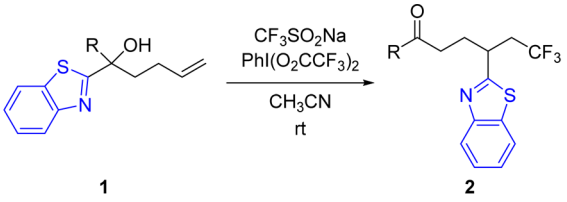
(1)

With the optimized reaction conditions in hand, we set about examining the generality of this protocol. The benzothiazolyl group migrated chemoselectively in preference to the aryl group regardless of its electronic and steric characters (**2a**−**l**) (Scheme 2). Notably, halides, in particular bromide (**2i**), were tolerated in this radical reaction, providing a platform for further manipulation of products by cross couplings. The aryl group is not requisite for this reaction and can be replaced by either a linear or cyclic alkyl group (**2m** and **2n**). Increasing the steric hindrance around the hydroxyl group of **1** led to slightly decreased yield (**2o**). It seems that so far the control of the stereochemistry in this radical process remains difficult as both two isomers of **1p** delivered the products with similar yields and diastereomer ratios (**2p**). The example of **2q** was remarkable

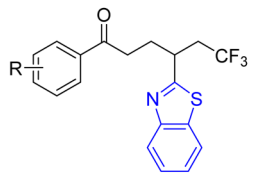
Received: October 28, 2016
Published: January 18, 2017

DOI: 10.1021/jacs.6b11234
J. Am. Chem. Soc. 2017, 139, 1388−1391

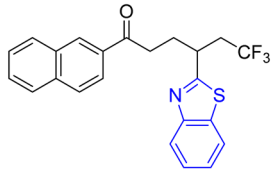
Scheme 2. Scope of Benzothiazole-Substituted Tertiary Bishomoallylic Alcohols[a,b]



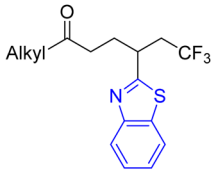
1 2



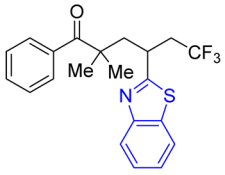
2a: R = H, 95%, 1 h
2b: R = 4-Ph, 70%, 3 h
2c: R = 4-OMe, 76%, 3 h
2d: R = 4-Me, 81%, 1 h
2e: R = 3-Me, 81%, 1 h
2f: R = 2-Me, 79%, 2 h
2g: R = 4-F, 81%, 1 h
2h: R = 4-Cl, 80%, 1 h
2i: R = 4-Br, 90%, 1 h
2j: R = 4-OCF_3, 85%, 1 h
2k: R = 4-CF_3, 73%, 1 h



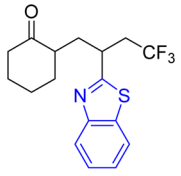
2l (57%, 3 h)



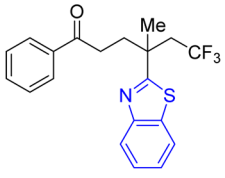
2m: Alkyl = *n*-pent, 83%, 3 h
2n: Alkyl = *c*-hex, 76%, 1 h



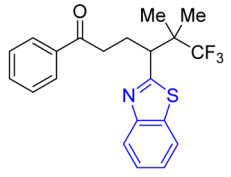
2o (62%, 3 h)



2p
from **1p**: 65%, *dr* = 1.3:1, 1 h (isomer a)
56%, *dr* = 1:1, 1 h (isomer b)

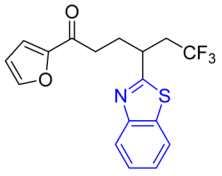


2q (65%, 1 h)

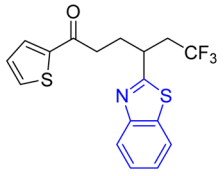


2r (30%, 3 h)

Discrimination of two heteroaryls



2s (55%, 3 h)



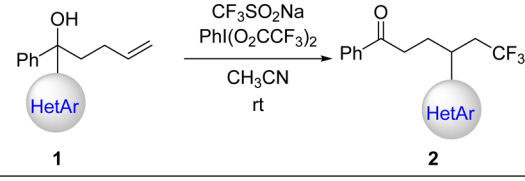
2t (53%, 3 h)

[a]Reaction conditions: **1** (0.20 mmol, 1.0 equiv), CF_3SO_2Na (0.40 mmol, 2.0 equiv), and PIFA (0.40 mmol, 2.0 equiv) in CH_3CN (1.5 mL) at rt under N_2. [b]Yields of isolated products.

that the reaction readily built up a new quaternary carbon center regardless of the steric congestion. The internal alkene is rarely recruited as substrate in radical difunctionalization of alkenes, because there is no regioselectivity at the initial radical addition step. Accordingly, low yield of **2r** was obtained along with an appreciable amount of unidentified byproducts. The migration could differentiate *N*-containing heteroaryls from other heteroaryls such as furyl and thienyl, affording the chemoselectively migrated products (**2s** and **2t**).

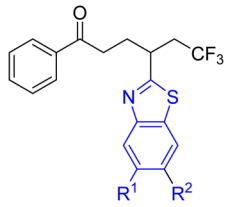
Subsequently, we evaluated the migration of heteroaryl groups other than benzothiazole (Scheme 3). In addition to

Scheme 3. Generality of Heteroaryl Groups[a,b,c]

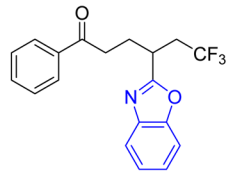


1 2

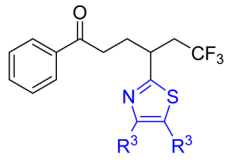
Five-membered heteroaryls



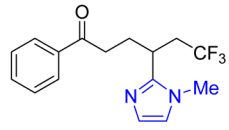
2u: R^1 = Cl, R^2 = H, 81%, 1 h
2v: R^1 = H, R^2 = OMe, 54%, 4 h



2w (65%, 1 h)[c]

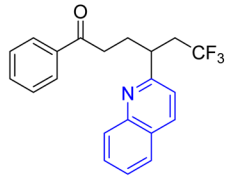


2x: R^3 = Me, 87%, 4 h
2y: R^3 = H, 93%, 1 h

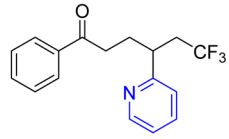


2z (75%, 2 h)

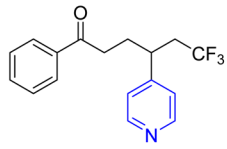
Six-membered heteroaryls



2aa (80%, 3 h)



2ab (60%, 1 h)



2ac (77%, 2 h)

[a]Reaction conditions: **1** (0.20 mmol, 1.0 equiv), CF_3SO_2Na (0.40 mmol, 2.0 equiv), and PIFA (0.40 mmol, 2.0 equiv) in CH_3CN (1.5 mL) at rt under N_2. [b]Yields of isolated products. [c]By using 10 mol % CuI and 1.5 equiv of Togni reagent II.

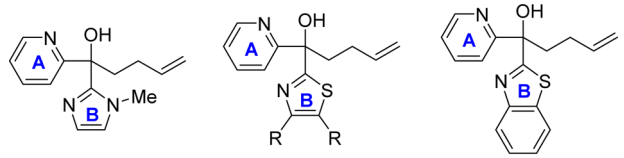
substituted benzothiazoles (**2u** and **2v**), thiazoles and imidazoles also migrated smoothly (**2x**–**2z**). The benzoxazolyl group was susceptible to the current reaction conditions; however, the migration of benzoxazole could be induced by generating CF_3 radical from the Togni reagent II (**2w**). It is worth mentioning that the examples of **2u**–**2z** cover a portfolio of *N*,*S*-, *N*,*O*-, and *N*,*N*-containing heteroaryls that represent the vast majority of five-membered heteroaryls. Additionally, six-membered heteroaryls are also able to participate in the migration process. For instance, the migration of 2-quinolyl, 2-pyridyl, and 4-pyridyl took place smoothly to generate the corresponding products in satisfactory yields (**2aa**–**2ac**). The

DOI: 10.1021/jacs.6b11234
J. Am. Chem. Soc. 2017, 139, 1388–1391

migration of other functionalized six-membered *N*-containing heteroaryls can also be anticipated.

We have also compared the relatively migratory aptitude of different *N*-containing heteroaryl groups (Scheme 4). We

Scheme 4. Selectivity between Different Heteroaryls



1ad
standard conditions
51%, **B**/ **A** > 19:1

1ae: R = Me
standard conditions
50%, **B**/ **A** = 14:1

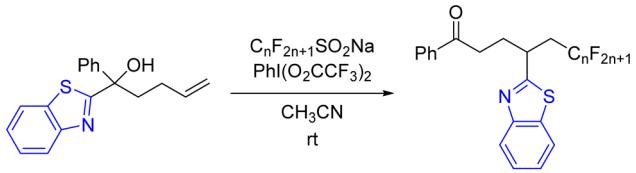
1af: R = H
CH_2Cl_2, -60 °C,
61%, **B**/ **A** = 10:1

1ag
CH_2Cl_2, -40 °C,
66%, **B**/ **A** > 19:1

found that the migration of five-membered heteroaryls (e.g., imidazolyl, thiazolyl, and benzothiazolyl) superseded six-membered heteroaryls (e.g., pyridyl). The migration selectivity with **1af** or **1ag** under the standard reaction conditions was low, but it could be significantly improved by reducing the reaction temperature.

This protocol was further applied to the perfluoroalkylation of unactivated alkenes by simply replacing the Langlois' reagent with analogous $C_nF_{2n+1}SO_2Na$. The corresponding perfluoroalkylated products **3a** and **3b** were furnished in synthetically useful yields at room temperature (Scheme 5).

Scheme 5. Perfluoroalkylation-Heteroarylation of Unactivated Olefin[a,b]



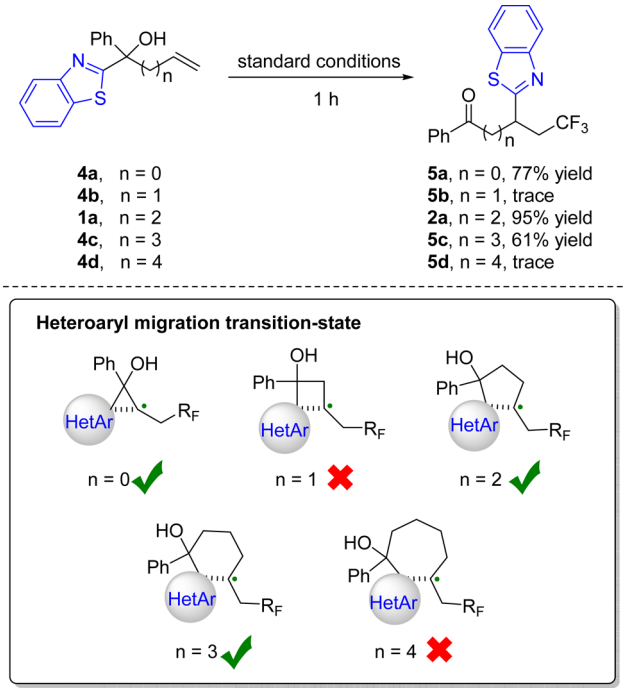
1a

3a, n = 6, 66%, 1 h
3b, n = 8, 82%, 4 h

[a]Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), $C_nF_{2n+1}SO_2Na$ (0.40 mmol, 2.0 equiv), and PIFA (0.40 mmol, 2.0 equiv) in CH_3CN (1.5 mL) at RT under N_2. [b]Yields of isolated products.

To gain insight into the migration pathway, a set of benzothiazole-substituted tertiary alcohols (**1a** and **4a**–**4d**) were examined under the standard reaction conditions (Scheme 6). We found that only the allylic (**4a**, n = 0), bishomoallylic (**1a**, n = 2), and trishomoallylic alcohol (**4c**, n = 3) afforded the corresponding heteroaryl-migrated products **5a**, **2a**, and **5c**, respectively. These results might suggest that the migration proceeded via possible cyclic transition states in which three-, five-, and six-membered cyclic transition states are thermodynamically favored (n = 0, 2, 3), whereas four- and seven-membered cyclic transition states are disfavored (n = 1, 4). In the reaction of **4a**, interestingly, the migration of the heteroaryl occurred in preference to the phenyl group, which also has a strong potential for 1,2-migration.[4] Moreover, we did not detect crossover products in the reaction with a mixture of **1d** and **1v** (see SI). This experiment supports the hypothesis that the heteroaryl migration proceeds in an intramolecular manner.

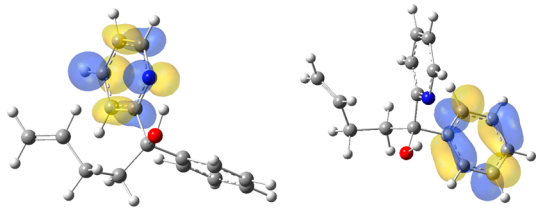
Scheme 6. Transition States of Migration Reaction



4a, n = 0
4b, n = 1
1a, n = 2
4c, n = 3
4d, n = 4

5a, n = 0, 77% yield
5b, n = 1, trace
2a, n = 2, 95% yield
5c, n = 3, 61% yield
5d, n = 4, trace

Computational studies were carried out to shed light on the origin of chemoselectivity. Take substrate **1ab** for example: the energy barrier for addition of alkyl radical to pyridyl moiety is about 3.3 kcal/mol lower than that to phenyl moiety, suggesting that the former pathway is more favorable than the latter (see SI). Frontier molecular orbital analysis indicates that the LUMO of **1ab** is essentially the LUMO of pyridyl moiety (Figure 1a). The LUMO of phenyl moiety (Figure 1b:



a: LUMO **b: LUMO+2**

Figure 1. LUMO and $LUMO_{+2}$ of **1ab**.

$LUMO_{+2}$ in **1ab**), however, is higher in energy than that of pyridyl moiety. Therefore, the pyridyl moiety is more ready to accept the nucleophilic alkyl radical, which is consistent with experimental results.

Based on the experimental and computational data, a plausible mechanism is outlined in Figure 2. Initially, the mixture of CF_3SO_2Na and PIFA generated a CF_3 radical. Addition of CF_3 radical to **1** gave alkyl radical **I** that added intramolecularly to the heteroaryl group to generate radical **II**. Subsequently, homolysis of C–C σ-bond in **II** presumably enabled by ring strain provided a more stable hydroxyalkyl radical **III**. Oxidation of radical **III** by hypervalent iodine yielded the cationic intermediate **IV**. Finally, loss of a proton from **IV** furnished product **2**.

In summary, we have developed a novel, general method for difunctionalization of unactivated alkenes with distal heteroaryl *ipso*-migration. A variety of five- and six-membered heteroaryl

DOI: 10.1021/jacs.6b11234
J. Am. Chem. Soc. 2017, 139, 1388–1391

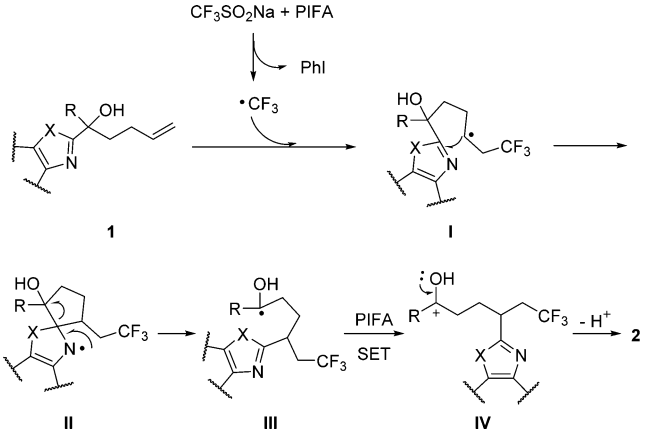


Figure 2. Plausible mechanism.

groups on tertiary alcohol migrate selectively in the presence of an aryl or alkyl group. This migration reaction can be induced by fluoroalkylation under mild reaction conditions, readily affording a variety of fluoroalkyl functionalized heteroarenes. This is the first report of a difunctionalization of unactivated alkenes with distal heteroaryl migration.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11234.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

C.Z. is grateful for the financial support from Soochow University, the National Natural Science Foundation of China (Grant no. 21402134), the Natural Science Foundation of Jiangsu Province (Grant no. BK20140306), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD). We thank Prof. Xiaoguang Bao of Soochow University for the help with computational studies.

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DOI: 10.1021/jacs.6b11234
J. Am. Chem. Soc. 2017, 139, 1388−1391