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Digest paper

Radical-mediated difunctionalization of unactivated alkenes through distal migration of functional groups

Xinxin Wu[a], Shuo Wu[a], Chen Zhu[a,b,*]

[a] Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, 199 Ren-Ai Road, Suzhou, Jiangsu 215123, China
[b] Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

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ABSTRACT

Radical-mediated controllable difunctionalization of alkenes provides a powerful tool for the manipulation of olefins and has become a hot topic recently. In general, however, the scope of alkene is largely restricted to the activated alkenes. The development of a general strategy for the functionalization of unactivated alkenes is desired, yet remains challenging. In this review, we have summarized the recent advances in the strategy of intramolecularly distal migration of functional groups which has been efficiently applied in the radical-mediated difunctionalization of unactivated alkenes. A portfolio of functionalities including aryl, cyano, heteroaryl, imino, carbonyl, alkynyl, and alkenyl groups showcase the migratory aptitude.

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Introduction

Alkenes are abundant synthetic feedstocks widely used in organic synthesis. Radical-mediated concomitant incorporation of two different functional groups into alkenes, namely radical difunctionalization of alkenes, renders an efficient and step-economic tactic for alkene manipulation. The reaction is highly dependent upon the electronic character of alkenes; the electronically activated alkenes are, in general, favored substrates for such transformation.[1] Mechanistically, the nascent *C*-centered radical engendered by addition of external radical to alkene is mainly stabilized by the proximal group or heteroatom via p-π conjugation, which facilitates the introduction of the second functional group. However, the radical difunctionalization of non-activated alkenes remains challenging.

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* Corresponding author at: Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, 199 Ren-Ai Road, Suzhou, Jiangsu 215123, China.

E-mail address: chzhu@suda.edu.cn (C. Zhu).

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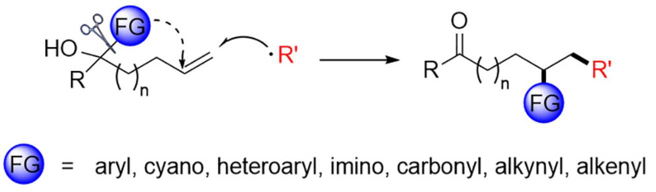


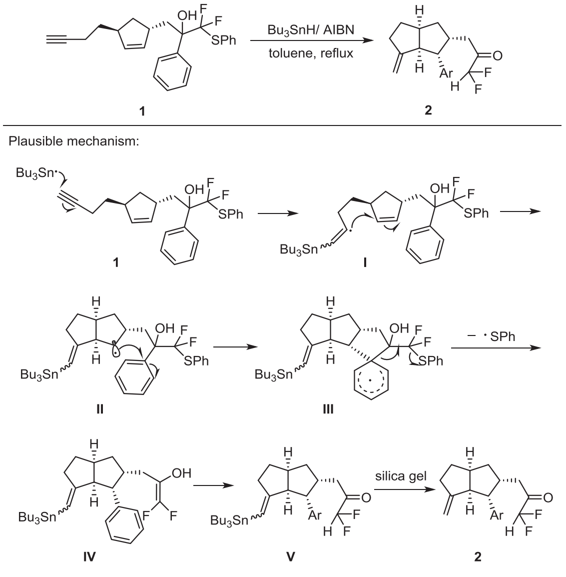
Scheme 1. Difunctionalization of unactivated olefins by means of distal functional group migration.

The radical-promoted intramolecular functional group migration has been proven to be privileged strategy for radical difunctionalization of unactivated alkenes.[2] Over the past decades, 1,2-aryl migration became prevalent in the arylfunctionalization of alkenes.[3] Moreover, examples of distal aryl migration have also been disclosed.[4] Nevertheless, the migration of functional groups other than aryl has been greatly underexplored. It was not until 2016 that the distal cyano migration was developed by Zhu and coworkers for the cyanation of unactivated olefins for the first time.[5] Thereafter, a portfolio of functionalities including heteroaryl, aryl, imino, carbonyl, alkynyl, and alkenyl groups have been investigated to showcase the migratory aptitude. So far, this has been an emerging active research field. This Digest will give a brief introduction on these newly developed distal migration reactions (Scheme 1).

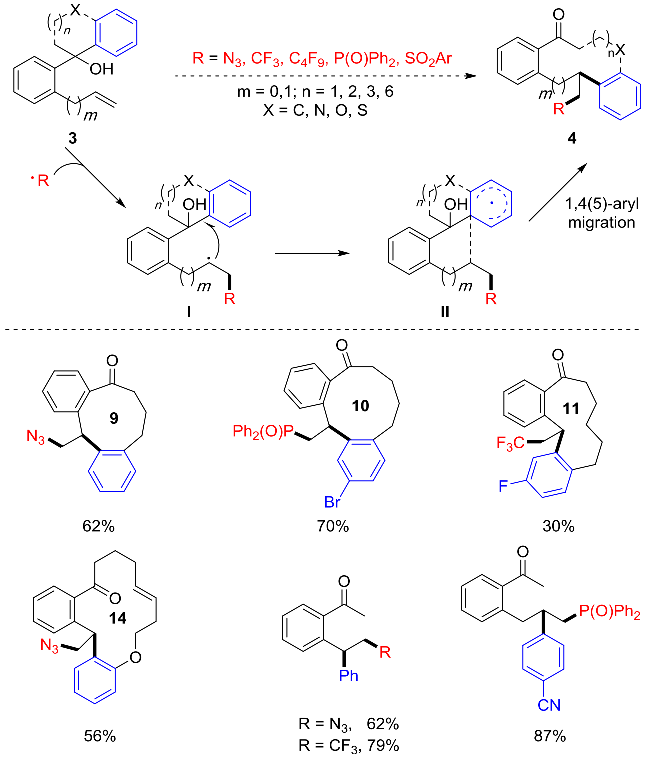
Aryl migration

In 2014, Pohmakotr et al. disclosed an approach to synthesize 3,3-difluoro-2-propanoylbicyclo-[3.3.0]octane **2** from the aryl-substituted tertiary alcohol **1**, which involved an intramolecular radical cyclization and *ipso*-1,4-aryl migration cascade (Scheme 2).[4b] In the process, the vinylic radical **I**, which was resulted from the addition of a tributylstannyl radical to the alkyne, initiated the tandem *exo*-mode cyclization to form the bicyclic radical **III**. The subsequent *ipso*-1,4-phenyl migration and elimination of the phenylsulfanyl group led to the intermediate **V** that afforded the final product **2** after protodestannylation.

Based on the aryl migration strategy, very recently Liu et al. reported an efficient approach for the synthesis of benzannulated carbon- and heteroatom-containing cyclic and acyclic ketones (Scheme 3).[4g,h] This protocol involved the 1,4 or 1,5-aryl migration triggered by the addition of various external radicals (e.g., N_3, C_nF_{2n+1}, $P(O)Ph_2$, $ArSO_2$ etc.) to the aryl-substituted tertiary alcohols **3**. Similarly, cyclization of the nascent alkyl radical **I** gave rise to the bicyclic radical **II**. The fragmentation of **II** and the resultant ring opening (expansion) finally generated the product **4**. This method provided a new tactic for the construction of medium-sized and macrocyclic ring scaffolds.



Scheme 2. Radical cyclization/*ipso*-1,4-aryl migration cascade.



Scheme 3. Remote aryl migration for the synthesis of cyclic and acyclic ketones.

Several examples of the radical-mediated Smiles-type rearrangement were developed by Nevado and coworkers.[4c–f] The well-designed *N*-(arylsulfonyl)acrylamides were employed as starting materials. In this domino radical transformation, the addition of an external radical to the activated alkene triggered the distal aryl migration. Because the difunctionalization of activated alkenes was involved, this work will not be presented in this review.

Cyano migration

The synthesis of alkyl nitriles is of significance as alkyl nitriles often serve as the precursors of amines, amides, carboxylic acids, and other useful chemical products. Radical-mediated cyanation of alkenes offers a shortcut to incorporation of cyano group into organic molecules and production of alkyl nitriles. However, the radical cyanofunctionalization of unactivated alkenes has been rarely reported.[6]

In 2016, Zhu et al. disclosed the first azidocyanation of unactivated alkenes by using the strategy of distal cyano migration (Scheme 4).[5] The azido radical to trigger the migration was generated from the mixture of PIDA and $TMSN_3$. The reaction demonstrated a broad tolerance of functional groups. Aryl, heteroaryl, and alkyl substituted cyanohydrins were suitable substrates. Both electron-rich and deficient cyanohydrins delivered comparable high yields. Positional change of substituents did not have much