Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest Paper

Recent developments in sulfur- and selenium-catalyzed oxidative and isohypsic functionalization reactions of alkenes

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ARTICLE INFO

Article history:
Received 31 December 2014
Revised 27 March 2015
Accepted 9 April 2015
Available online xxxx

Keywords:
Organocatalysis
Alkenes
Radicals
Oxidations
Asymmetric reactions

ABSTRACT

This digest manuscript delineates recent developments in the context of sulfur- and selenium-catalyzed oxidative and isohypsic functionalization reactions of simple alkenes. The discussion also includes considerations of mechanistic modes of reactant and/or reagent activation exhibited by sulfur and selenium in the context of various transformations, such as electrophilic aminations, sulfenylations, selenenylations, oxygen-transfer reactions, and radical reactions. Furthermore, current applications of thiocatalytic methods in the realm of complex natural product synthesis are discussed.

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Introduction

The forthright oxidative or isohypsic manipulation of simple, unactivated alkenes is a fundamental and privileged strategy for the step-economic[1] construction of functionalized hydrocarbon architectures. In this context, numerous investigations throughout the last six decades have dealt with the development of new methods for the selective derivatization of non-polarized C–C double bonds, particularly involving the use of electrophilic organochalcogen compounds (chalcogen = S, Se).[2] Due to their pronounced carbophilicity, organosulfur- and organoselenium electrophiles have been employed in a diverse array of consecutive olefin derivatization protocols, such as hydroamidations,[3] allylic etherification,[4]

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http://dx.doi.org/10.1016/j.tetlet.2015.04.045
0040-4039/

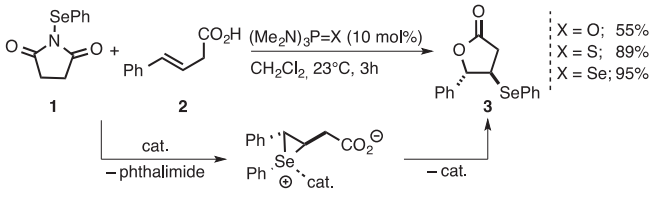
allylic alkylations,[2a] enyne couplings,[5] and addition reactions of enolates across C–C double bonds.[6] An additional important methodological facet of heavier organochalcogens in the context of olefin derivatization reactions is their rich radical chemistry. Both thiyl-[7] and selenyl radicals[8] have been used in a variety of transformations to construct carbon–carbon and carbon–element bonds. Considering the aforementioned utile chemical features of organic sulfur- and selenium compounds, including the fact that many of these reagents are generally easy-to-handle and insensitive to air, organochalcogens are also very attractive candidates for organocatalytic applications. Early examples of oxidative selenium-catalyzed alkene derivatizations, namely allylic halogenations, have initially been reported in the late 1970s.[9] In the ensuing decades many research groups have developed a plethora of sulfur- and selenium-catalyzed halofunctionalizations of unsaturated hydrocarbons.[10] The body of investigations on this topic has been thoroughly portrayed in several recent reviews.[10] Consequently, the purpose of the current article is to delineate recent methodological developments in the realm of catalytic oxidative and isohypsic manipulations of non-polarized and polarized alkenes facilitated by organochalcogen catalysts with an exclusive focus on bond forming processes other than halogenation reactions including discussions on reaction mechanisms. Furthermore, contemporary applications of these methods in synthetic campaigns toward complex natural products will be described.

Oxidative non-radical alkene functionalizations

Sulfur- and selenium-catalyzed sulfenylations and selenenylations of non-polarized alkenes

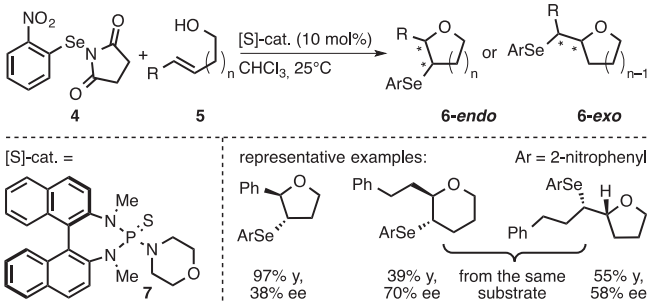
Organosulfur- and organoselenium compounds play an imperative role in various scientific disciplines such as synthetic organic methodology,[11] catalysis,[12] natural product research,[13] and medicinal chemistry.[14] Among the multitude of operations available for the incorporation of sulfur- and selenium entities into carbon frameworks, catalytic olefin functionalizations constitute a viable strategy. Due to the reactivity profiles of non-polarized alkenes, which are generally orthogonal to those of polar functional groups, high degrees of chemoselectivity can be obtained by this strategy. In general, reactions of such alkenes with sulfur- and selenium electrophiles are believed to proceed by a common mechanistic scheme involving the transient formation of chalcogeniranium ions that are eventually attacked by nucleophiles in a stereospecific manner. Given the established cognizance[15] on this type of reactions it is surprising that even to this date there is only a very limited number of asymmetric catalytic methods available for the direct sulfenylation and selenenylation of simple alkenes.

In 2007, Denmark and coworkers reported a seminal example of a chalcogen-catalyzed olefin selenenylation.[16] The authors demonstrated that facile activation of selenium electrophiles, such as *N*-phenylselenylsuccinimide (**1**), was possible by means of Lewis-base catalysis. A key aspect regarding the catalytic potency of the investigated Lewis-bases was the polarizability of the corresponding Lewis-basic donor groups. In a comparative study hexamethylphosphoric triamide (HMPA), hexamethylthiophosphoric triamide (HMPA(S)), and hexamethylselenophosphoric triamide (HMPA(Se)) were used as catalysts in the selenolactonization of (*E*)-4-phenylbut-3-enoic acid (**2**) (Scheme 1). It was shown that the heavier homologs of HMPA exhibited a significantly highecatalytic activity compared to the parent system, which was rationalized on the basis of strong sulfur–sulfur and sulfur–selenium interactions between the reactant and the respective catalyst.



Scheme 1. Organochalcogen-catalyzed selenolactonization.[16]

On the basis of these initial findings the same research group developed an enantioselective protocol for the selenofunctionalization of non-polarized alkenes (Scheme 2).[17,18] In the context of a thorough mechanistic study the transient formation of seleniranium intermediates (Scheme 1) was postulated to be the stereodetermining step.[17] However, seleniranium ions were reported to easily undergo reversible and uncatalyzed migration reactions, such as olefin-to-olefin and olefin-to-nucleophile transfer (Nu = e.g. alcohols or carboxylic acids).[17,19] Under thermal conditions such processes will eventually lead to erosion of the stereochemical information embedded in the initially formed seleniranium ions. These undesired alternative reaction pathways could be considerably curtailed by judicious choice of selenenylating reagents and reaction conditions.[17] It was found that seleniranium ions with electron deficient aryl groups attached to the selenium atom display a comparatively high configurational stability. This finding was particularly true for the *ortho*-nitrophenyl group. The benign effect of the NO_2 entity was rationalized by consideration of two factors: (1) the electron-withdrawing effect of the nitro group is believed to evoke an increased positive charge at the endocyclic carbon atoms of the seleniranium ion, thus, enhancing the proclivity for nucleophilic attack at one of these positions rather than attack at the selenium center. (2) Hypervalent interactions between the nitro group and the selenium atom ($n_O \rightarrow \sigma^*_{Se\text{-}X}$) may prevent the olefin-to-olefin transfer by blocking a requisite coordination site at the selenium center. Thus, use of *N*-(2-nitrophenylselenenyl)succinimide (**4**) in the presence of MsOH at room temperature was shown to result in er values of up to 85:15 in the intramolecular selenoetherification of alcohols **5** (Scheme 2).



Scheme 2. Sulfur-catalyzed asymmetric selenoetherification.[17]

Denmark and coworkers also investigated organochalcogen-catalyzed asymmetric sulfenylation reactions of alkenes,[20,21] a campaign that was predicated on the following mechanistic cognizance: in contrast to seleniranium ions, the corresponding sulfur homologs display a significantly diminished propensity for migratory processes between alkenes.[19a] This disparate aptitude for olefin-to-olefin transfer between sulfenium and selenenium ions was crucial for the design of highly asymmetric catalytic thiofunctionalization reactions, since the diastereospecific ring-opening of enantiomerically enriched thiiranium intermediates by nucleophiles does occur more rapidly than the unselective interchange of the sulfenium entity between alkenes. Kinetic,