Radical Additions to Nitrogen Radicals to Allenes: Versatile Syntheses of Amines and Heterocycles

The addition of $N$-centered radicals to allenes with high and predictable levels of chemo-, site-, and stereoselectivity represents a potentially powerful strategy for the efficient construction of $N$-heterocycles that occur frequently in pharmaceuticals, agrochemicals, and bioactive natural products. While additions of nitrogen radicals to allenes and alkynes have been well-studied, the analogous chemistry with allenes has been far less explored, despite unique features that offer: 1) three potential sites for amidation that might be tuned by proper selection of the allene, radical source, and catalyst, 2) the potential for transfer of axial-to-point chirality or use of asymmetric catalysis to secure enantioenriched amines, and 3) the possibility of trapping vinyl or allyl radical intermediates with diverse acceptors to expand the product scope (Scheme 1B).

Nitrogen-centered radicals come in a variety of 'flavors', with their reactivities broadly categorized as electrophilic, ambiphilic, or nucleophilic (Scheme 1A). Our long-term goals are to use experimental and computational studies to understand how the substitution pattern, the tether length between the $N$-radical and the allene, the electronic features of both the $N$-radical and allene, and method of generating the reactive radical species impacts reaction outcome. To better inform our future studies, we undertook the preparation of a comprehensive review article covering the literature from 1950 onwards that pertains to the addition of radicals to allenes. A revised version of this manuscript was just submitted to *Chemical Reviews*, taking into consideration helpful comments from five experts in the field. It became quickly apparent while preparing this review that the rules for predictable tuning of the selectivity of radical additions to allenes, including nitrogen radicals, are not well-established and differ from those observed for allenes and alkynes.

We developed general approaches to install three types of $N$-centered radicals (amidyl, iminyl, and aminyl) into allenes; in addition to the type of radical precursor, the tether length and the allene substitution pattern could be easily varied. After some optimization, we found that irradiation of 1 with a 40 W Kessil LED in the presence of a base ($K_2CO_3$) and the H-atom donor 1,4-cyclohexadiene (CHD) in acetone furnishes 85% yield of 2 in a $3.2:1\ E:Z$ ratio. Interestingly, no photocatalyst was required, in contrast to additions of similar radicals to allenes. This unexpected result suggests irradiation at 440 nm alone is sufficient to directly excite 1 to promote either direct homolysis of the N-O bond or a SET event that initiates formation of the amidyl...
Results and insights gained during these preliminary studies have stimulated our ongoing explorations into regioselective radical cascade that functionalizes all three unsaturated allene to trap with an oxygen radical will generate an enol ether or acceptors under investigation to form new C-C bonds include phosphonates partners, including trimethylphosphite to give the α-aminated vinyl species arising from reaction of We have also successfully trapped the intermediate vinyl radical and pyridines (Scheme 1B).

We are in the process of exploring whether radical stabilizing groups, including aryl and electron-withdrawing groups, such as –SO2Ph, -P(O)Ar2, -CO2Et and –CN, will retard 5-exo attack and accelerate the 6-endo pathway to provide access to six-membered rings. Computational studies have indicated other allene substitution patterns that are predicted to favor attack on the β allene carbon and these will be examined. Efforts to compare and contrast the behavior of iminyl and aminyl radicals to amidyl radicals in additions to allenes are also currently under active investigation in efforts to prepare pyrrolines, pyrroles, 2-azadienes, and pyridines (Scheme 1B).

We have also successfully trapped the intermediate vinyl radical species arising from reaction of 1 with a variety of coupling partners, including trimethylphosphite to give the α-aminated vinyl phosphonates 9 (Scheme 3), with NCS to furnish vinyl chloride 10, using diethyl bromomalonate to give 11 (NBS reacts with the allene directly), and a Se atom donor to yield 12. Other potential acceptors under investigation to form new C-C bonds include conjugate acceptors and electron-rich aromatics, while the ability to trap with an oxygen radical will generate an enol ether or enolate that may add to another electrophile; in this manner, a radical cascade that functionalizes all three unsaturated allene carbons in a single pot can be envisaged. Accompanying our experimental work with computational studies is key to gaining a better understanding and ability to predict reactivity patterns.

Results and insights gained during these preliminary studies have stimulated our ongoing explorations into regioselective intermolecular additions of nitrogen radicals to allenes, which has been aided by the increasing availability of synthetic methods to access allenes of diverse substitution patterns. Finally, we are intrigued by applying modern methods of generating radicals, including metal-catalyzed visible light photocatalysis, to assess how the redox potential of the photocatalytic or the electrochemical potential might be tuned to control regio-, chemo-, and stereoselectivity in additions of not just nitrogen radicals, but a broad range of radicals to allenes.

Students involved in this research have learned standard experimental techniques for handling both air-stable and air-sensitive organic compounds, been introduced to the principles underlying visible-light photochemistry and photocatalysis, learned to measure reaction kinetics using various spectroscopic techniques, and carry out computational modeling of species with unpaired electrons.