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Regioselective Radical Alkene Amination Strategies by Using Phosphite-Mediated Deoxygenation

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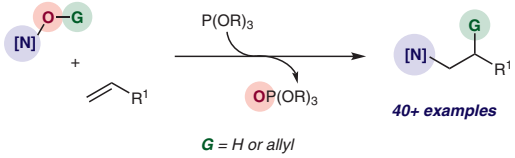

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Abstract Nitrogen-containing compounds are an essential motif in all disciplines of chemistry and the efficient synthesis of these frameworks is a highly sought-after goal. Presented here is a summary of recent efforts conducted by our group to develop radical-mediated amination strategies for the formal synthesis of primary amines from alkenes with exclusive anti-Markovnikov regioselectivity. We have found that *N*-hydroxyphthalimide is an effective reagent capable of supplying both the N and H atoms for alkene hydroamination in a group transfer radical addition-type mechanism. Furthermore, allyl-oxyphthalimide derivatives are similarly capable of radical group transfers and allow for the aminoallylation of an external alkene.

Key words radicals, polarity effects, aminoallylation, hydroamination, phosphite, O-atom transfer

Introduction

The use of radical-mediated processes to selectively introduce carbon- and heteroatom-based functionality is robust and continues to inspire new developments in synthetic methodology. Atom transfer radical additions (ATRA), also known as the Kharasch reaction, were first reported in the 1940s where halogenated methanes added across carbon–carbon double bonds, initiated thermally or with light (Scheme 1A).[1] Introduction of transition-metal complexes (based on Cu, Fe, Ru, Ni) as catalysts has greatly expanded the scope and efficiency of ATRA.[2] The development of atom transfer radical polymerization (ATRP) by Sawamoto[3] and Matyjszewski[4] further cemented the utility of this approach for macromolecule synthesis.[5]

Samuel W. Lardy grew up in Edina, Minnesota, USA and obtained a Bachelor's degree in chemistry from Loyola Marymount University in 2016. He performed research under the supervision of Dr. Jeremy McCallum as an undergraduate and started his graduate studies at the University of California, San Diego in 2017 under the leadership of Prof. Valerie A. Schmidt. His research focus is on phosphorous(III)-mediated atom- and group-transfer methodology development.
Valerie A. Schmidt earned her undergraduate degree in chemistry from Towson University. She then pursued graduate studies under the supervision of Prof. Erik J. Alexanian at the University of North Carolina at Chapel Hill as a Burroughs-Wellcome Fellow. She then performed postdoctoral studies with Prof. Paul Chirik at Princeton University as a Ruth L. Kirschstein National Institutes of Health Postdoctroal Fellow developing Fe- and Co-based catalytic systems for hydrocarbon functionalization enabled by redox-active chelates. In 2016, she began her independent career at the University of California, San Diego. Her main interests are the development of new chemical processes by harnessing the unique reactivities of open-shell intermediates.

Kamigata developed a desulfonylative ATRA transformation using trifluoromethanesulfonyl chloride and a Ru catalyst that delivers trifluoromethyl and chloro groups across an alkene, demonstrating that the atoms/groups delivered need not be directly bonded to one another to participate in alkene addition (Scheme 1B).[6]

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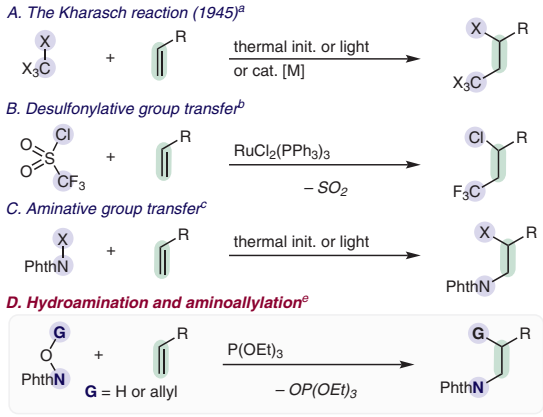


Scheme 1 Historical context of radical-mediated atom and group transfer. [a] See ref 1. [b] See ref 6. [c] See ref 12. [d] See refs 16 and 19.

These methods are excellent ways to add halogens and halogenated alkyl groups across olefinic bonds. The installation of other heteroatomic functionality is similarly of great interest with high potential synthetic utility.

Nitrogen atom functionalities are crucial components of biopolymers (DNA and proteins), bioactive small molecules, natural products, materials, and agrochemicals. Installation of N-based groups by using open-shell radical intermediates is particularly promising because of the typically high compatibility of radicals with various polar functional groups. Generating N-centered radicals has traditionally been accomplished through homolytic cleavage of weak N–X bonds which can be achieved photochemically or thermally, such as in the Hoffman–Löffler–Freytag reaction.[7] Similarly, amines covalently attached to redox-active groups can, upon single electron oxidation or reduction, cleave the N–leaving group bond to form N-centered radicals to achieve aryl and alkene functionalizations.[8] The addition of N-centered radicals to olefins is an intriguing pathway to synthesize amines because it would provide access to the more elusive anti-Markovnikov regioisomeric products.

Considerable efforts have led to the development of a variety of alkene hydroamination methods that achieve high levels of selectivity for the anti-Markovnikov regioisomeric products.[9] Despite these advances, the use of ammonia as an aminating reagent, while maintaining high levels of regioselectivity, remains an unmet challenge. The direct use of ammonia as a N-atom source for alkene hydroaminations is hindered by several practical and design considerations: (a) ammonia itself is a corrosive gas and its use requires specific safety and handling procedures; (b) direct, polar, or acid-promoted pathways are sluggish and would favor the Markovnikov addition isomer, and (c) transition-metal-catalyzed strategies are hampered by the propensity to form catalytically inactive Werner-type complexes with ammonia.[10]

Phthalimidyl radicals generated from N–X homolytic bond cleavage have been used previously for the amination of arenes[11] as well as for the aminohalogenation of alkenes (Scheme 1C).[12] Installation of a phthalimidyl group is of great interest as it can easily be hydrolyzed to furnish the corresponding primary amine, thereby serving as an ammonia surrogate.[13] While aminohalogenation using PhthN• precursors proceeds through an ATRA pathway, regioselectivity is difficult to control because of the simultaneous formation of PhthN• and X• through homolysis. Additionally, current PhthN• precursors preclude an ATRA-type hydroamination because of the lack of transferable H atoms. While this challenge could be overcome by the addition of an external H-atom source, this opens up chemoselectivity concerns which may detract from desired reactivity.

N-Hydroxyphthalimide (NHPI) has well-established uses in numerous oxidative radical methodologies, serving as the precursor to PhthNO•.[14] NHPI is an excellent reagent because of its commercial availability, low cost, and long-term stability towards air and moisture. Owing to the weak O–H (89 kcal mol^{-1}) and N–O (~65 kcal mol^{-1}) bonds of NHPI,[15] we envisioned that under deoxygenative conditions it could be used as a source of PhthN• as well as H• for the development of a formal ammonia ATRA-mediated alkene hydroamination with high fidelity for anti-Markovnikov regioisomers. Similarly, we hypothesized that this strategy could achieve alkene difunctionalization by using O-functionalized NHPI derivatives to transfer groups beyond a hydrogen atom (Scheme 1D).[16]

Reaction Development

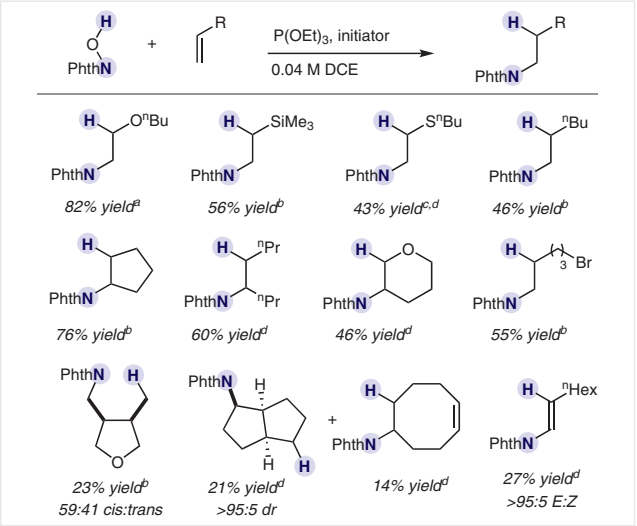
We began by attempting to perform the hydroamination of *n*-butyl vinyl ether (NBVE) using NHPI in the presence of a thermal radical initiator and triethyl phosphite as an O-atom acceptor.

Phosphorus(III) reagents such as triethyl phosphite have been shown to reduce N–O functionalities[17] and we envisioned that the thermodynamic driving force for the exchange of a weak N–O bond (~55–65 kcal mol^{-1})[18] for a strong phosphoranyl unit (148 kcal mol^{-1} for **OP**$(OEt)_3$) would allow for the generation of the desired phthalimidyl radical.

Our first attempts involved heating a mixture of NHPI (1 equiv), NBVE (10 equiv), 2,2′-azobis(2-methylpropionitrile) (AIBN) (0.25 equiv), and triethyl phosphite (1.5 equiv) in benzene to 90 °C. After 12 hours, NHPI had been fully consumed, with the major product isolated arising from the polar O addition of NHPI to NBVE (30% yield) and the desired hydroamination product only detected in small amounts (<10% yield). In an attempt to improve reaction efficiency and decrease the undesired production of acetal, a variety of radical initiators and solvents were screened. While common initiators such as *tert*-butylhydroperoxide,

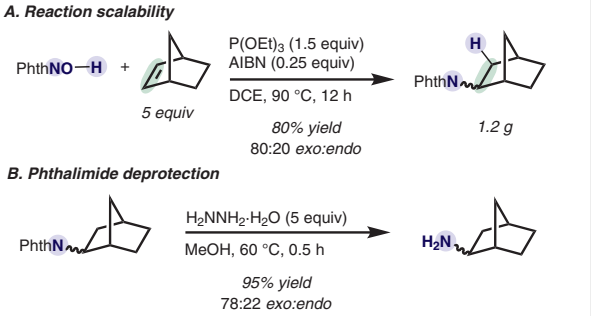
di-*tert*-butyl peroxide, and benzoyl peroxide resulted in very poor reaction performance, dilauroyl peroxide [(undecyl$(CO_2)_2$] at 90 °C and di-*tert*-butyl hyponitrite [(*t*-BuON)$_2$] at 35 °C proved particularly effective at promoting exclusively the desired hydroamination process. Similarly, reaction efficiency was found to be optimal when using 1,2-dichloroethane (DCE), whereas many other common solvents such as benzene, toluene, or ethyl acetate resulted in poor reaction efficiency.

Scheme 2 depicts a selection of alkenes we found amenable to this hydroamination procedure. Electronically rich vinyl ethers, silanes, and sulfides were well tolerated, as were unactivated alkenes such as 1-hexene. Internal alkenes similarly underwent this transformation in good yields and exclusive anti-Markovnikov regioselectivity. Notably, a primary bromide was retained indicating that hydroamination outperformed potential Arbuzov-type side reactivity. Compounds containing multiple alkenes capable of cyclization such as diallyl ether and 1,5-cyclooctadiene also took part in this reaction. While it was observed that diallyl ether exclusively underwent a 5-*exo* cyclization, the reaction with 1,5-cyclooctadiene resulted in a separable mixture of bicyclic and monocyclic hydroamination products. Notably, 1-octyne underwent hydroamination in modest yield to deliver exclusively the *trans*-vinylphthalimide.



Scheme 2 Selected hydroamination substrate scope. *Reagents and conditions*: All reactions carried out by using NHPI (1 equiv) and alkene (10 equiv) with the specified initiator and temperature. [a] Carried out by using (*t*-BuON)$_2$ (0.25 equiv) at 35 °C. [b] Carried out by using (undecyl-$CO_2)_2$ (1 equiv) at 110 °C. [c] 5 equiv of alkene used. [d] Carried out by using (*t*-BuON)$_2$ (0.25 equiv) at 50 °C.

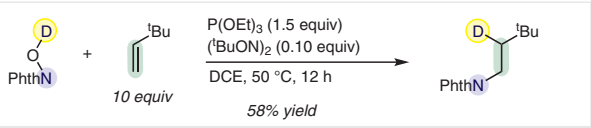
The scalability of this method was demonstrated by the hydroamination of norbornene on a gram scale (Scheme 3A). The desired phthalimidyl product was easily obtained in 80% yield with no significant decrease in efficiency because of reaction scale. Furthermore, the phthalimidyl group was easily removed by using aqueous hydrazine in methanol to reveal the corresponding primary amine in only 0.5 hours (Scheme 3B).



Scheme 3 Hydroamination scalability and utility

Mechanistic Investigation

In order to determine whether or not this radical-mediated hydroamination was truly an ATRA process in which NHPI supplied both the N and the H atoms for the overall hydroamination, we prepared d_1-NHPI and subjected it to our standard reaction conditions with *tert*-butyl ethylene (Scheme 4). The corresponding 3,3-dimethylbutan-2-*d*-1-phthalimide was isolated in 58% yield with deuteration observed exclusively at the C2 position. This supports our proposed ATRA-mediated pathway of hydroamination.



Scheme 4 Isotopic labeling

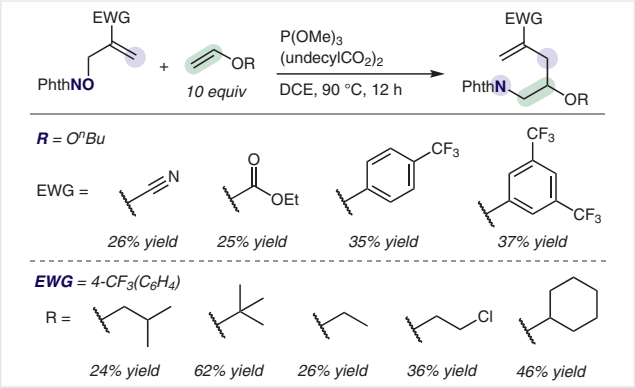
Expansion to GTRA

Having demonstrated NHPI was able to carry-out deoxygenative ATRA alkene hydroamination, we hypothesized that O-modified NHPI derivatives could be used as reagents for alkene difunctionalization. Previous work from Tanko and co-workers showed that *O*-allyl oxyphthalimides can undergo β-fragmentation in the presence of nucleophilic benzylic radicals, serving as an allylation reagent and producing PhthNO$^{\bullet}$ as a by-product. With this in mind, we turned our attention to *O*-allyl oxyphthalimides as potential GTRA reagents for alkene aminoallylation.

We began by subjecting an allyl oxypthalimide derivative bearing a cyano group to the standard reaction conditions used for the hydroamination procedure and 10 equivalents of NBVE.[19] Under these conditions, the corresponding aminoallylation product was obtained in 34% yield with the main product being *N*-(*O*-ethyl)hydroxypthalimide re-

sulting from a polar S_N2' Arbuzov-type reaction. Through a series of exhaustive optimization studies we were able to improve reaction efficiency to 45% by switching to trimethyl phosphite as this decreased the Arbuzov side reactivity.

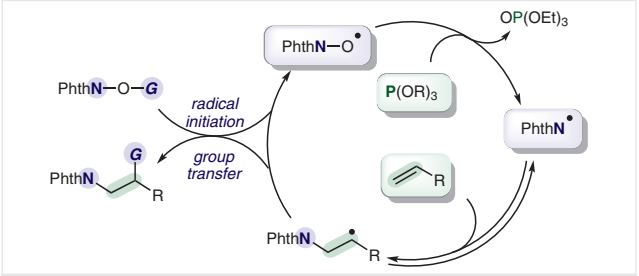
While pursuing the scope of allyl oxyphthalimide substrates amenable to this transformation, we observed significant electronic effects (Scheme 5). For instance, we found that electron-withdrawing groups such as nitrile, ethyl ester, and fluorinated electron-deficient arenes were tolerated vinyl substituents partnering with NBVE. However, less electronically biased substrates such as the unsubstituted *O*-allyl parent, or derivatives bearing a vinyl sulfide, amide, sulfoxide, or phenyl group did not result in aminoallylation. Similarly, electronic effects were crucial with regard to the external alkene component used. Productive reactivity was observed only when the external alkene contained an ether substituent. Less biased alkenes such as vinyl silanes, sulfides, and acetates were not tolerated and lead solely to *O*-allyl oxyphthalimide reagent decomposition.



Scheme 5 Aminoallylation scope. *Reagents and conditions*: All reactions carried out by using the corresponding allyl oxyphthalimide (1 equiv), trimethyl phosphite (1.5 equiv), and undecyl$(CO_2)_2$ (0.1 equiv) in 1,2-dichloroethane (0.40 M) at 90 °C for 12 h.

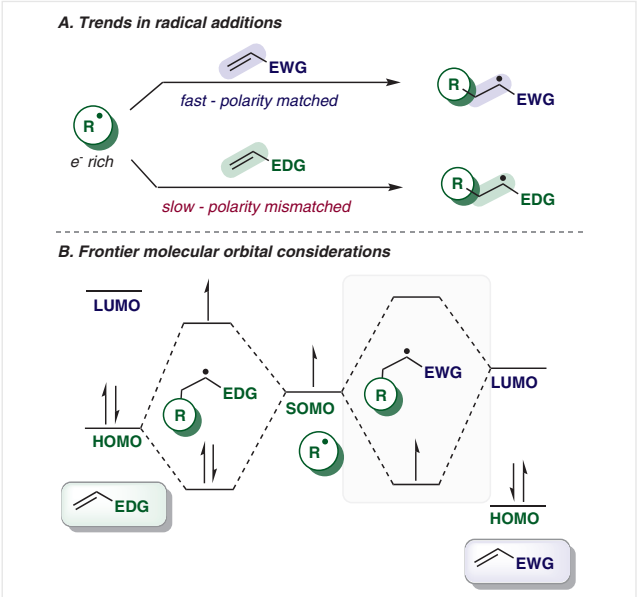
A mechanistic hypothesis consistent with our data is outlined in Scheme 6. Radical initiation generates an electrophilic imidoxyl radical which undergoes O-atom transfer with the trialkylphosphite, exchanging the weak N–O bond for a strong P–O bond, to generate PhthN•. Phthalimidyl radical is then poised to add to the external, electron-rich olefin preferentially generating a nucleophilic C-centered radical intermediate. Intermolecular group transfer from another equivalent of either NHPI or an allyl derivative produces the functionalized alkene product and regenerates PhthNO•.

We postulate that the stark electronic effects, most pronounced in our aminoallylation studies, are a result of proper radical polarity matching. Significant effort has been expended to understand the polarity effects of radical reactions.[20]



Scheme 6 Mechanistic proposal

Typically, these effects manifest as relative rates of reactivity. For instance, nucleophilic radicals add to electron-deficient alkenes at much faster rates than electron-rich alkenes, with the opposite being true for electrophilic radicals (Scheme 7A). These preferences can be understood through frontier molecular orbital (FMO) interactions (Scheme 7B) in which the singly occupied molecular orbital (SOMO) of a nucleophilic radical preferentially engages the low-lying lowest-unoccupied-molecular-orbital (LUMO) of an electron-deficient alkene over the relatively high energy highest-occupied-molecular-orbital (HOMO) of an electron-rich alkene so as to minimize the energy of the subsequent intermediate.



Scheme 7 Polarity matching effects

In our system, the electrophilic phthalimidyl radical generated from deoxygenation with phosphite preferentially adds to the electron-rich external alkene to furnish a new, nucleophilic C-centered radical that selectively adds to the electronically deficient alkene of the *O*-allyl oxyphthalimide. The FMO energy considerations of each radical

intermediate formed throughout this process explains why the process is so well controlled, and also rationalizes the inability of unbiased alkenes to participate.

Future Outlook

We have developed a deoxygenative strategy to achieve alkene aminations using *N*-hydroxyphthalimide derivatives and trialkylphosphites. Current efforts in our group involve expanding the scope of *N*-hydroxy-containing functionalities capable of serving as N-centered radical precursors to engage in a wider range of synthetically useful processes.

Funding Information

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