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Journal

European Journal of Organic Chemistry, 2019(40)

ISSN

1434-193X

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Publication Date

2019-10-31

DOI

10.1002/ejoc.201901071

Peer reviewed

Intermolecular Aminoallylation of Alkenes Using Allyl-oxyphthalimide Derivatives: A Case Study in Radical Polarity Effects

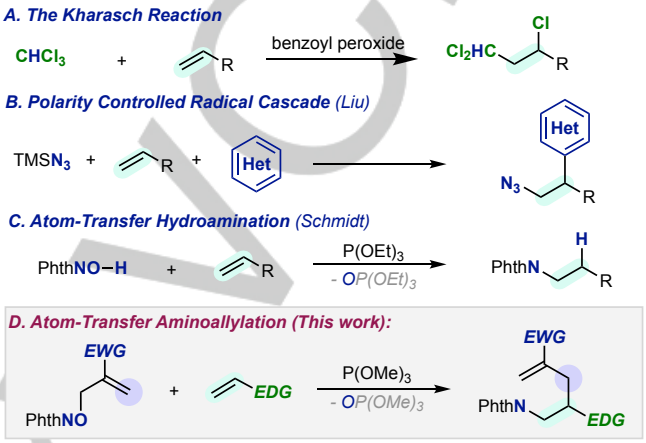
Samuel W. Lardy[a] and Valerie A. Schmidt*[a]

Abstract: A case study on the polarity effects of radical mediated intermolecular alkene aminoallylation is presented herein. This radical group transfer method pairs vinyl ethers with electronically deficient allyl-oxyphthalimide derivatives to give difunctionalized products while illustrating the guiding effects of polarity on this radical reactivity.

Introduction

Methods that achieve the difunctionalization of alkenes are particularly powerful as they rapidly introduce molecular complexity from abundant olefin starting materials in a single synthetic step.[1-13] Seminal work by Kharasch and co-workers demonstrated the difunctionalization of unactivated alkenes via atom transfer radical addition (ATRA) using simple halogenated reagents (Scheme 1A).[14] This work paved the way for the subsequent development of a sophisticated class of radical-mediated alkene difunctionalization methodologies invoking ATRA.[15-18] Group transfer radical additions (GTRA) allow the transfer of more complex functionalities to alkenes, with particularly useful applications in polymer synthesis.[19-25] Despite these advances, the majority of ATRA and GTRA systems require transition metal catalysts and are limited by the redox potential of the reagents used which corresponds to the atoms/groups that are transferable.

Understanding the effects of radical polarity is an important design consideration in radical-mediated transformations.[26-28] Polarity effects of radicals that facilitate hydrogen-atom transfer processes[29-31] or undergo addition to π-systems[32-33] play a crucial role in determining the expected reactivities. While these effects are typically manifested in relative rates – where proper electronic matching of reactants results in more efficient processes as compared to electronically mismatched pairs – they can also exhibit a pronounced impact on chemoselectivity. A prime example of this is the polarity controlled, three component Minisci-type reaction reported by Liu and co-workers wherein an electrophilic azidyl radical adds to an electron-rich alkene, generating a nucleophilic carbon-centered radical intermediate that is then trapped by an electron-poor heterocycle



Scheme 1. Prior radical atom/group transfer processes to incorporate N-atom functionality

(Scheme 1B).[34]

We recently reported an ATRA O-atom transfer strategy that achieved intermolecular alkene hydroamination using *N*-hydroxyphthalimide (NHPI) as a PhthN• and H-atom source, with triethyl phosphite as an O-atom acceptor (Scheme 1C).[35] The electrophilic character of the imidyl radical generated in this process led us to believe that we could trap the nucleophilic carbon centered radical formed following PhthN• addition with a second, electron-deficient alkene. Allyl-oxyphthalimide derivatives have been used as allyl traps of C-radicals while generating phthalimide N-oxyl radical which serves as the H-atom abstractor.[36] We hypothesized that an allyl-oxyphthalimide derivative could achieve an intermolecular alkene aminoallylation by supplying the second, electron-deficient alkene (Scheme 1D).

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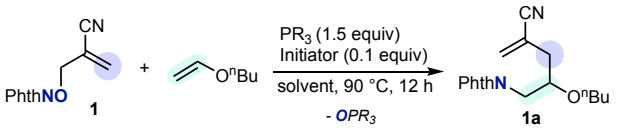
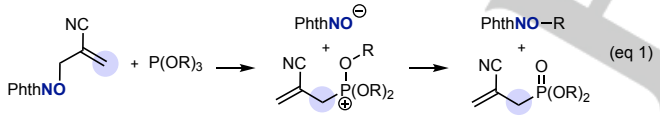
Results and Discussion



Entry	PR_3	Initiator	Solvent	Yield of 1a[b]
1	$P(OEt)_3$	$(undecylCO_2)_2$	DCE	34%
2	$P(O^tBu)_3$	$(undecylCO_2)_2$	DCE	<5%
3	$P(O^iPr)_3$	$(undecylCO_2)_2$	DCE	20%
4	**$P(OMe)_3$**	**$(undecylCO_2)_2$**	**DCE**	**45%[c]**
5	$P(OMe)_3$	AIBN	DCE	21%
6	$P(OMe)_3$	$(BzO)_2$	DCE	<5%
7	$P(OMe)_3$	$(undecylCO_2)_2$	MeCN	36%
8	$P(OMe)_3$	$(undecylCO_2)_2$	PhH	<5%
9	None	$(undecylCO_2)_2$	DCE	<5%
10	$P(OMe)_3$	*None*	DCE	<5%

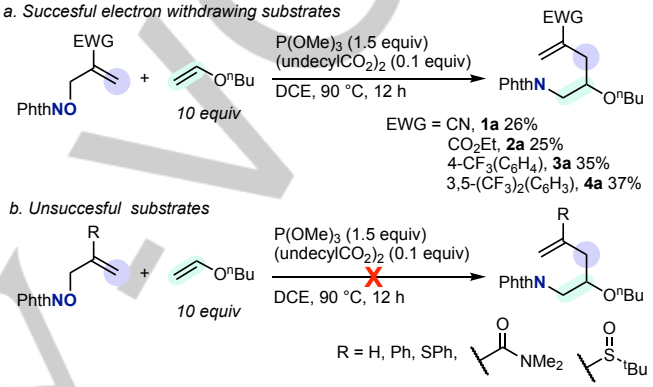
Table 1. Reaction optimization. All reactions carried out with **1** (1 equiv) and n-butyl vinyl ether (10 equiv) in the specified solvent (0.04M) unless otherwise noted. [b]Determined by gas chromatography using mesitylene as an internal standard. [c]Isolated yield of 26% following purification on silica gel.

We began by subjecting allyl-oxyphthalimide derivative **1**, bearing a vinyl cyano-group, to a small excess of triethyl phosphite (1.5 equiv), dilauroyl peroxide ($(undecylCO_2)_2$, 0.1 equiv), and 10 equiv of n-butyl vinyl ether (NBVE) in 1,2-dichloroethane (DCE) at 90 °C (Table 1, entry 1). While aminoallylation product **1a** was detected in 34% yield as determined by gas chromatography, the major product, isolated in 42% yield, was *N*-(*O*-ethyl) hydroxyphthalimide. We attribute the formation of this by-product to a polar, S_N2' Arbuzov-type pathway producing diethyl (2-cyanoallyl)phosphonate and *N*-(*O*-ethyl) hydroxyphthalimide (eq 1). In order to prevent this unwanted reactivity, we investigated other alkyl phosphites as



O-atom acceptors. Using tri-*tert*-butyl phosphite, which should be less prone to nucleophilic attack at the tertiary center, we no longer observed the corresponding O-alkylated oxyphthalimide, however the aminoallylation reaction efficiency fell to only trace formation of **1a** (<5% yield, entry 2). We ascribe this observation to a decreased rate of O-atom transfer to the more sterically encumbered phosphorus center. The more accessible triisopropyl phosphite again proved successful in minimizing the formation of the O-alkylated oxyphthalimide by-product, but only improved aminoallylation reaction efficiency to 20% yield (entry 3).

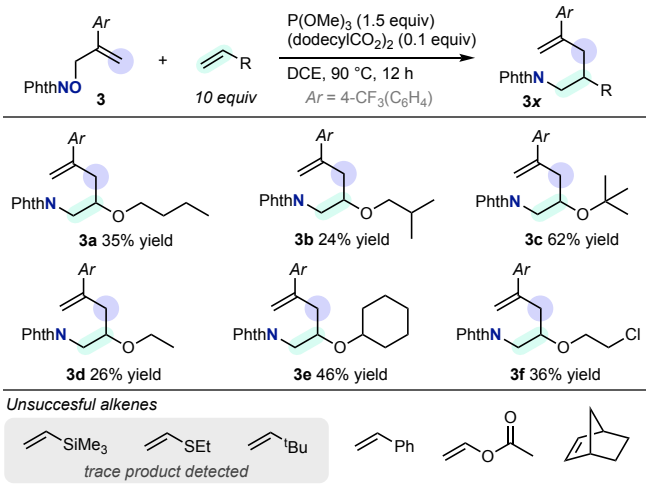
Contrary to our initial hypothesis, the use of the smallest, primary alkyl phosphite, trimethyl phosphite, was found to be the most successful at promoting aminoallylation, improving the yield of **1a** to 45%, while minimizing the amount of O-alkylation (entry 4). The mass balance is attributed to non-selective decomposition of **1a** as unreacted starting material was not recovered after 12 h. While it has been demonstrated that the rate of O-atom transfer from peroxyl radicals to trimethyl phosphite is slower than to triethyl or triisopropyl phosphite,[37] our data suggests that in the present aminoallylation, O-atom transfer occurs with trimethyl phosphite while the polar Arbuzov-type pathway does not.[38] Other thermal radical initiators such as 2,2′-azobis(2-methylpropionitrile) (AIBN) or benzoyl peroxide ($(BzO)_2$) in place of dilauroyl peroxide uniformly resulted in decreased reaction efficiency (Table 1, entries 5 and 6), as did changing solvent from DCE to acetonitrile (MeCN) or benzene (entries 7 and 8). The necessity of phosphite and initiator was confirmed, as experiments that excluded either did not result in the formation of **1a** (entries 9 and 10).



Scheme 2. Electronic requirements of the transferring allyl group

We found that allyl-oxyphthalimide derivatives bearing electron withdrawing substituents such as esters, nitriles, or electron deficient arenes were the most successful at undergoing this aminoallylation process (compounds **1a**, **2a**, **3a**, and **4a**, Scheme 2a). Less electronically deficient substrates bearing sulfoxides or amides lead only to decomposition (Scheme 2b),[39] while precursors containing a sulfide or phenyl substituent, as well as the parent, unsubstituted allyl group resulted only in the recovery of starting material. These results highlight the importance of the allyl-oxyphthalimide olefin polarity.

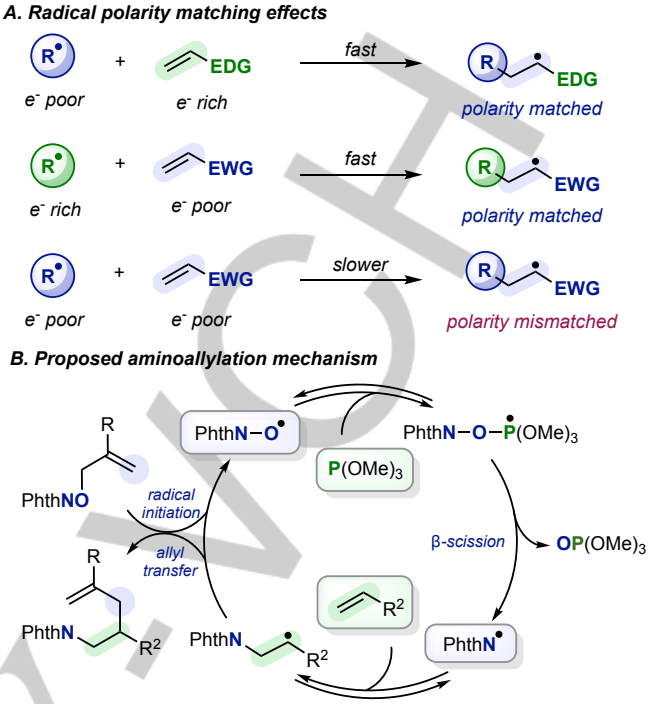
Noting the importance of the electronic properties of the allyl-oxyphthalimide reagents, we became interested in the external alkenes that would participate in this transformation. While an array of electron rich vinyl ethers were successfully functionalized (compounds **3a** – **3f**, Scheme 3), vinyl sulfides and vinyl silanes resulted in only trace amounts of desired products. Internal vinyl ethers were similarly unsuccessful, which we attribute to decreased rates of radical addition. Less electronically unbiased alkenes such as 1-hexene and styrene did not participate, further emphasizing the importance of polarity effects for this transformation. It's relevant to note that alkene hydroamination was not observed in this study irrespective of the external alkene or allyl-oxyphthalimide reagent used.



Scheme 3. Alkene scope. Yields given of purified material following silica gel chromatography.

As was the case for both the allyl-oxyphthalimide derivatives and the external alkenes amenable to this reaction, substrate electronics played a major role in reaction efficiency, and only when electronically deficient allyl-oxyphthalimides were paired with electron rich alkenes was productive reactivity observed. We propose that these electronic effects are a result of the need for proper polarity matching of each radical formed. It is well known that polarity has a strong influence on the rates of radical-mediated processes, and that the rate of addition of electrophilic radicals to electron-rich alkenes is more rapid than to electron deficient alkenes, whereas electron-rich, nucleophilic radicals are biased to add to electronically deficient alkenes (Scheme 4A). For the radical mediated aminoallylation reaction presented herein, proper polarity matching was indeed essential for product formation.

We propose that aminoallylation initiates by addition of the primary alkyl radical generated from dilauroyl peroxide thermolysis to the allyl-oxyphthalimide (Scheme 4B). This generates PhthNO• which adds to trimethyl phosphite generating an intermediate now setup to cleave the weak N-O bond via β-scission. This step is driven by the formation of the strong phosphoranyl unit while simultaneously producing PhthN•. This electrophilic N-centered radical is now poised to selectively add to the electron-rich alkene substrate in preference to the allyl-oxyphthalimide reagent bearing an electron-deficient alkene. The result is a nucleophilic C-centered radical intermediate that is now electronically matched to add to the allyl-oxyphthalimide substrate to form the aminoallylated product and regenerate PhthNO•. This mechanism is consistent with the pronounced electronic effects observed in our study.



Scheme 4. Mechanistic proposal.

Conclusions

In summary, we report a radical-mediated aminoallylation of alkenes using allyl-oxyphthalimides that further cements our mechanistic proposal that both groups connected to the central O-atom of NHPI or allyl-oxyphthalimides transfer with predictable regioselectivity to alkenes. The pairing of an electron deficient allyl-oxyphthalimide substrate with an external electron-rich alkene was found to be essential for productive reactivity, emphasizing the importance of polarity matching. While somewhat limited in scope, this serves as an excellent example of radical polarity effects, specifically with respect to how this dictates reactivity.

Experimental Section

General aminoallylation procedure: To a 1-dram vial charged with a magnetic stir bar was added the respective allyl-PINO derivative (20 mg), dilauroyl peroxide (0.10 equiv), triethyl phosphite (1.5 equiv), olefin (10 equiv), and 1,2-dichloroethane (3 mL). The vial was capped and heated to 90 °C. Upon consumption of the *N*-(*O*-allyl)hydroxyphthalimide derivative as judged by TLC (25% EtOAc in hexanes), the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (10% EtOAc in hexanes).

Acknowledgments

Financial support was provided by start-up funds from the University of California San Diego. We would also like to thank Angel Mendoza and Kathleen Gundran for assistance in substrate preparation during our preliminary studies.

Keywords: radical chemistry • polarity effects • aminoallylation • O-atom transfer • phosphite

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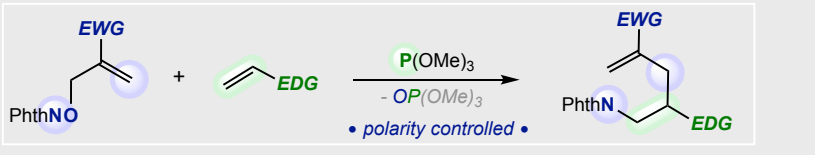

Radicals reactions, amination*

*Samuel W. Lardy, Valerie A. Schmidt**

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Intermolecular Aminoallylation of Alkenes Using Allyl-oxyphthalimide Derivatives: A Case Study in Radical Polarity Effects

This work describes the essential radical polarity effects manifested in pursuit of a group transfer radical addition to achieve alkene aminoallylation. Each open shell intermediate along the proposed mechanistic pathway is steered to preferentially react with only one reagent.

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