Communication

Intermolecular Radical Mediated Anti-Markovnikov Alkene Hydroamination using *N*-Hydroxyphthalimide

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Intermolecular Radical Mediated Anti-Markovnikov Alkene Hydroamination using *N*-Hydroxyphthalimide

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Supporting Information Placeholder

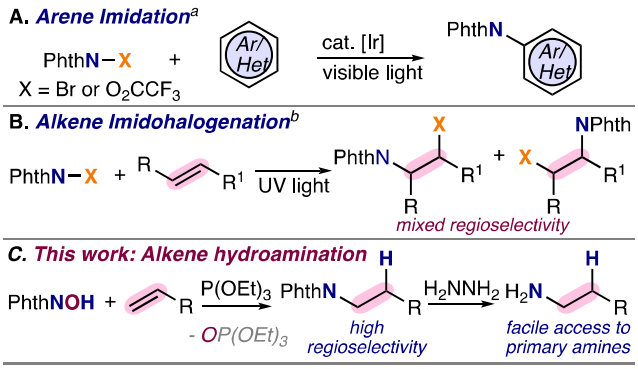
ABSTRACT: An intermolecular anti-Markovnikov hydroamination of alkenes has been developed using triethyl phosphite and *N*-hydroxyphthalimide. The process tolerates a wide range of alkenes, including vinyl ethers, silanes, and sulfides as well as electronically unbiased terminal and internal alkenes. The resultant *N*-alkylphthalimides can readily be transformed to the corresponding primary amines. Mechanistic probes indicate that the process is mediated via a phosphite promoted radical deoxygenation of *N*-hydroxyphthalimide to access phthalimidyl radicals.

Nitrogen-atom functionalities are essential motifs that appear in a wide range of pharmaceutical agents, agrochemicals, and natural products. The construction of C-N bonds for use in these contexts continues to serve as a strong motivating force for the development of new synthetic methods. Olefin hydroamination has received considerable attention in this area as direct addition of N-H across a C-C double bond is a conceptually attractive approach to alkyl amine synthesis. Many catalytic alkene hydroamination protocols proceed with Markovnikov regioselectivity[1] and while examples that deliver anti-Markovnikov regioisomers are more limited, significant advancements have been made using transition metal[2] and photoredox catalysis.[3]

Many of these successful methods use substituted amine substrates such that hydroamination products are unreactive towards additional hydroamination. As a result, the use of ammonia, or practical ammonia surrogates as substrates while maintaining high levels of anti-Markovnikov regioselectivity remains a largely unmet synthetic challenge.[4]

We became interested in phthalimidyl radicals (PhthN•) for use in alkene hydroamination because the addition of N-centered radicals to alkenes would predictably deliver anti-Markovnikov adducts[3a-d,5] and phthalimide groups can be readily removed under mild conditions to reveal primary aliphatic amines[6] providing a practical solution to directly using ammonia as a substrate for alkene hydroamination.

Scheme 1. PhthN• addition to unsaturations.



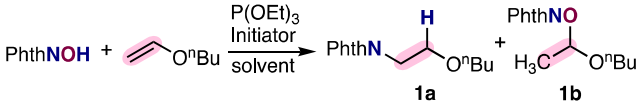
[a]See ref. 8. [b]See ref. 9.

Phthalimidyl radicals[7] have previously been used in arene amination (Scheme 1A)[8] and alkene aminohalogenation (Scheme 1B)[9] by taking advantage of the photochemical lability of the N-X bonds of the PhthN• precursors. Despite the intense interest in selective C-N bond formation via olefin hydroamination, phthalimidyl radicals have not previously been used in this context. This may be due to a lack of suitable precursors as the general pathway to PhthN• is via N-X bond homolysis where the X-group lacks transferrable H-atoms and the addition of a stoichiometric H-atom source would likely shunt the desired radical chain process.[10]

N-Hydroxyphthalimide (NHPI) is an inexpensive, commercially available reagent with long term benchtop stability at ambient temperatures that is well known as a precursor to PhthNO• used with great success in the mild, aerobic oxidation of aliphatic C-H bonds.[11] Despite the use of NHPI in radical mediated processes, its use has been limited to that of an O-radical precursor. We envisioned that NHPI could serve as a low-cost source of PhthN• if a suitable deoxygenative procedure was developed. We elected to investigate phosphites as O-atom transfer reagents due to the wide availability of many inexpensive phosphites and their demonstrated

ability to reduce oxygen functionality.[12-14] Additionally, we envisioned that deoxygenation of NHPI would be thermodynamically favored by the exchange of a weak N-O bond (~55-65 kcal/mol) to form a strong phosphoryl unit (148 kcal/mol for **OP**$(OEt)_3$).[15]

Table 1. n-Butyl Vinyl Ether Optimization.[a]

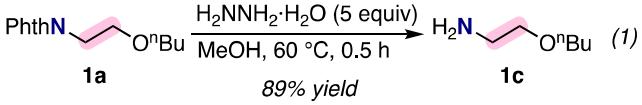


Entry	Initiator	Solvent	Ratio **1a**:**1b**[b]	Yield[c]
1	AIBN	PhH	23 : 77	9% + 30% **1b**
2	AIBN	MeCN	93 : 7	67%[b]
3	AIBN	DCE	75 : 25	79%
4	*None*	DCE	<2 : 98	81% **1b**
5	$(BzO)_2$	DCE	38 : 62	30%[b]
6	$(^tBuO)_2$	DCE	7 : 93	8%[b]
7	$(dodecylCO_2)_2$	DCE	94 : 6	79%
8[d]	$(^tBuON)_2$	DCE	98 : 2	82%
9[d,e]	$(^tBuON)_2$	DCE	<2 : 98	47% **1b**

[a]Reactions carried out with NHPI (1 equiv), *n*-butyl vinyl ether (5 equiv), triethyl phosphite (1.5 equiv), and radical initiator (0.25 equiv) in the specified solvent (0.04M) at 90 °C; Bz=benzoyl. [b]Determined by gas chromatography using mesitylene as an internal standard. [c]Isolated yield of **1a** following purification on silica gel. [d]Reaction temperature 35 °C. [e]No triethyl phosphite added.

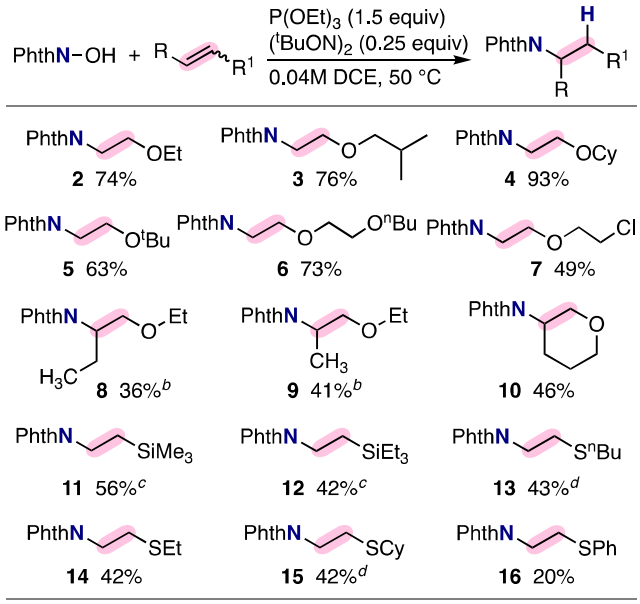
To test this hypothesis, we examined the hydroamination of *n*-butyl vinyl ether using NHPI, triethyl phosphite, and thermal radical initiators. We chose to begin our investigations using *n*-butyl vinyl ether as a model alkene due to its expected favorable electronic match with the electrophilic PhthN•. As shown in Table 1, entry 1, a mixture of NHPI and *n*-butyl vinyl ether with 2,2'-azobis(2-methylpropionitrile) (AIBN) in benzene resulted in full consumption of NHPI in 12 hours at 90 °C. Desired hydroaminated product **1a** was isolated in only 9% yield, while acetal **1b** was isolated in 30% yield. Presumably **1b** formed via polar addition of the hydroxyl group of NHPI to the electron rich vinyl ether. Using acetonitrile (MeCN) or 1,2-dichloroethane (DCE) as the reaction solvent (entries 2 and 3) resulted in formation of desired amine **1a**, with lesser amounts of **1b**. Acetonitrile led to higher selectivity for **1a** (93:7 **1a**:**1b**), while DCE afforded an overall more efficient reaction (79% isolated yield of **1a**) albeit with slightly diminished selectivity (75:25 **1a**:**1b**). A control experiment omitting any radical initiator resulted in formation of **1b** only, suggesting that hydroamination is indeed a radical mediated process (entry 4).

The relative rates of the radical process leading to **1a**, and the polar pathway leading to **1b**, should be adjustable through judicious choice of reaction temperature and radical initiator, which prompted an investigation of other commonly used thermal initiators. Benzoyl peroxide (entry 5), and di-*tert*-butylperoxide (entry 6) produced only small amounts of **1a**, but dilauroyl peroxide (entry 7) resulted in nearly exclusive hydroamination of *n*-butyl vinyl ether (94:6 **1a**:**1b**) producing **1a** in 79% yield at 90 °C in 20 minutes. To eliminate the undesired polar addition leading to **1b** which is likely increased at higher reaction temperatures, we tested *tert*-butyl hyponitrite which fragments at much lower temperatures compared to AIBN, benzoyl peroxide, di-*tert*-butylperoxide, or dilauroyl peroxide.[16,17] Using *tert*-butyl hyponitrite at 35 °C resulted in clean conversion to **1a** in 82% yield (entry 8). A control reaction shows that **1a** is not formed in the absence of triethyl phosphite (entry 9). This confirms the vital role of phosphite in the radical hydroamination process. We also found that treatment of **1a** with aqueous hydrazine rapidly produced the corresponding primary amine **1c** in 89% yield (eq 1), highlighting the role of NHPI to serve as an ammonia surrogate in this hydroamination.



With optimized conditions in hand, we next explored the scope of electron-rich alkenes amenable to this regioselective hydroamination process. Terminal and 1,2-disubstituted vinyl ethers react efficiently to produce the anti-Markovnikov hydroaminated products in good to excellent yields (Scheme 2, compounds **2-6**). Although these reactions take place at 35 °C, we found that increasing the temperature to 50 °C generally increased the reaction efficiency for a broader range of alkenes. The 12 hour reaction time was chosen to standardize the protocol, although many substrates showed full consumption of NHPI within 6 hours. Notably, a primary alkyl chloride remains undisturbed under these hydroamination conditions (product **7**). Vinyl ethers containing internal alkenes were hydroaminated in lower yields compared to α-olefin analogs, likely due to a decreased rate of PhthN• addition (compounds **8**, **9** and **10**). Vinyl sulfides and vinyl silanes were also well tolerated, producing the corresponding amino-sulfide and amino-silane adducts in moderate to good yields (products **11-16**). Also noteworthy, unlike many conventional reductive radical transformations that require rigorous exclusion of air or moisture, we found that oxygen removal through a series of freeze-pump-thaw cycles did not improve reaction efficiencies and reagents and solvents used did not require purification beyond received commercial grade.

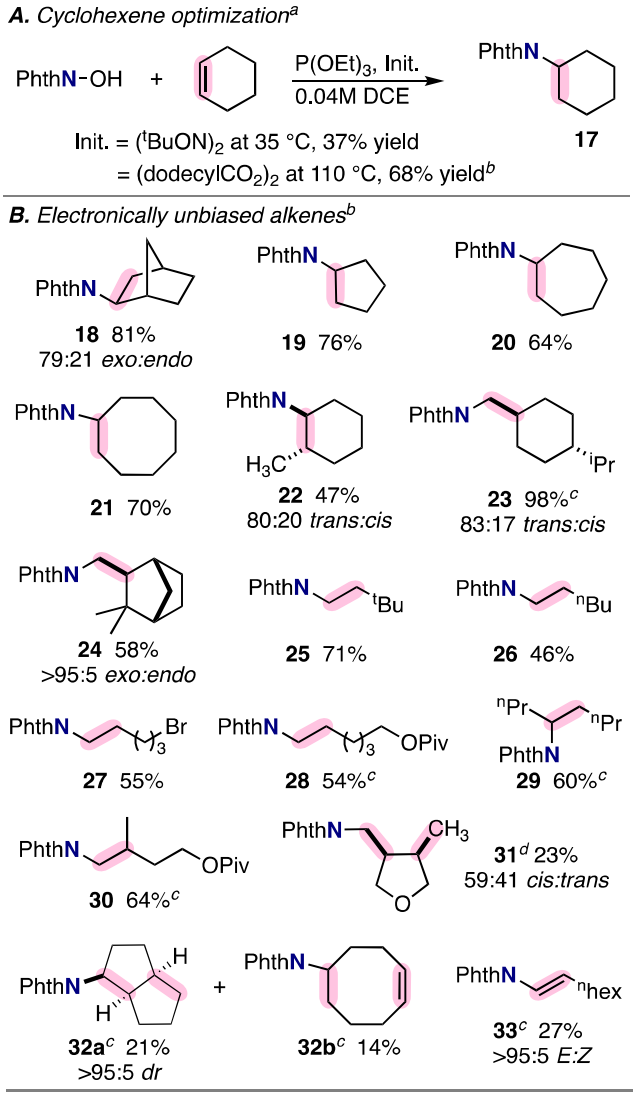
Scheme 2. Hydroamination of functionalized alkenes.[a]



[a]All reactions carried out using $P(OEt)_3$ (1.5 equiv), ($^tBuNO)_2$) (0.25 equiv), alkene (10 equiv) in DCE (0.04M) at 50 °C for 12 h; yields are for isolated material following chromatography on silica gel; >20:1 Regioselectivity for isomer shown. [b]Carried out using 5 equiv alkene, dilauroyl peroxide (0.5 equiv) at 90 °C. [c]Carried out using dilauroyl peroxide (1 equiv) at 110 °C. [d]5 equiv alkene used.

We further investigated the viability of electronically unbiased alkenes to undergo hydroamination (Scheme 3). Cyclohexene was successfully hydroaminated using *tert*-butyl hyponitrite at 35 °C, albeit with a suboptimal 26% yield of **17** and required 24 hours to reach completion. We hypothesized that the reaction time could be decreased and reaction efficiency improved by increasing the temperature and using an alternative initiator. Using 1 equivalent of dilauroyl peroxide at 110 °C resulted in a 68% yield of **17** in only 12 hours.[18] Norbornene and other cyclic alkenes such as cyclopentene, cycloheptene, and cyclooctene all readily underwent efficient hydroamination using these conditions (products **18**-**21**). In the case of 1-methylcyclohexene where regioisomeric products are possible, hydroamination proceeded with exclusive anti-Markovnikov selectivity and moderate 80:20 diastereoselectivity favoring the *trans*-1,2-disubstituted cyclohexane adduct **22**. Exomethylene containing 1-isopropyl-4-methylenecyclohexane and camphene were both hydroaminated successfully to produce **23** and **24**, respectively, in good yields. The bicyclic camphene product **24** was formed as a single diastereoisomer while the less bulky **23** was formed as a 83:17 *trans*:*cis* mixture. Electronically unbiased terminal alkenes, *tert*-butyl ethylene and 1-hexene, also underwent efficient anti-Markovnikov selective hydroamination (products **25** and **26**). Primary bromide containing 5-bromo-1-pentene cleanly converted to **27** in good yield, with no evidence of Arbuzov-type reactivity of the primary bromide with triethyl phosphite.

Scheme 3. Hydroamination of unactivated alkenes.



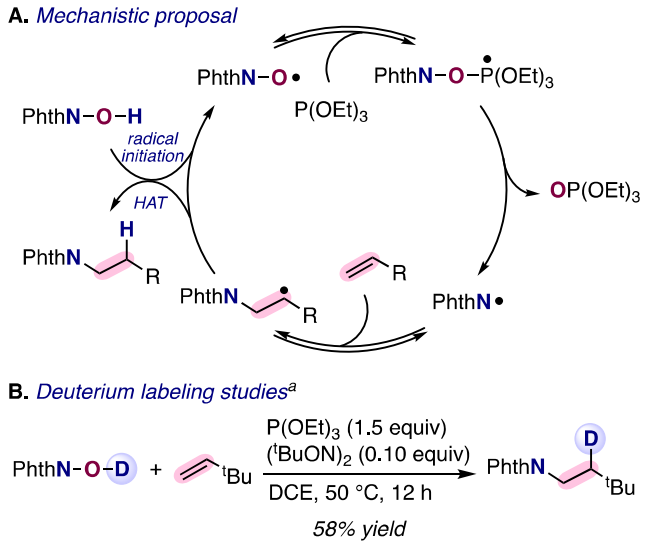
[a]All reactions carried out with $P(OEt)_3$ (1.5 equiv), specified initiator (0.25 equiv), alkene (10 equiv) in DCE (0.04M) at the specified temperature for 12 h; yields shown were determined by gas chromatography using mesitylene as an internal standard. [b]Carried out using dilauroyl peroxide (1 equiv) at 110 °C for 12 h; yields are for isolated material following chromatography on silica gel; >20:1 Regioselectivity for isomer shown. [c]Carried out using ($^tBuON)_2$ (0.25 equiv) at 50 °C for 12 h. [d]Carried out using dilauroyl peroxide (0.20 equiv).

5-Hexenyl pivalate was converted to **28** in 54% yield as a single regioisomer. Acyclic and unactivated *trans*-4-octene and 3-methylbut-3-enyl pivalate were both cleanly hydroaminated to produce **29** and **30** in good yields. Diallyl ether was transformed to **31**, inserting a 5-*exo*-trig cyclization during the hydroamination process. Hydroamination of only one alkene of diallyl ether without

cyclization was not detected suggesting that the rate of cyclization (~$9x10^6$ s^{-1})[19] is faster than terminal H-atom transfer. We also investigated 1,5-*cis*-*cis*-cyclooctadiene as an additional substrate capable of cyclization during the hydroamination process. We found that a mixture of bicyclic hydroaminated product **32a** and monocyclic hydroaminated product **32b** were formed in a 1.5:1 ratio (21% yield **32a**, 14% yield **32b**). This product mixture suggests that the slower 5-*exo*-trig cyclization rate (~$1x10^5$ s^{-1})[19] of this substrate is competitive with product forming H-atom abstraction. The hydroamination of 1-octyne resulted in the formation of the corresponding substituted *N*-vinyl phthalimide **33** in moderate yield exclusively as the *E* isomer.

A plausible mechanism for this hydroamination is outlined in Scheme 4. Thermal radical initiation is followed by H-atom abstraction from NHPI to produce PhthNO• which then undergoes reversible addition to triethyl phosphite.[13d] The PhthNO-phosphite adduct can then undergo β-scission of the relatively weak N-O bond to form triethyl phosphate and PhthN• which adds to the alkene to preferentially produce the more substituted C-centered radical. This alkene addition product is now poised to perform a thermodynamically favorable H-atom abstraction from another equivalent of NHPI (2° C-H bond formed ~93-98 kcal/mol[15] versus 88 kcal/mol O-H bond broken[20]) to afford the hydroaminated product and regenerate PhthNO•. Formally, NHPI supplies both the required N- and H-atoms for alkene hydroamination.

Scheme 4. Hydroamination mechanistic proposal.

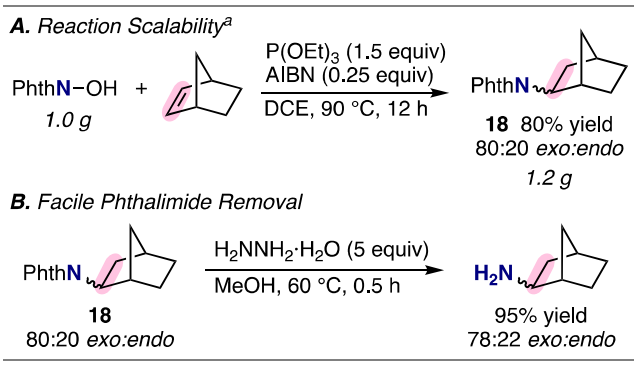


[a]10 equiv alkene used.

To support this mechanistic hypothesis, we prepared NHPI-d_1 and subjected it to an excess of *tert*-butyl ethylene and 10 mol % *tert*-butyl hyponitrite at 50 °C for 12 hours. Product **25**-d_1 was isolated in 58% yield with deuterium incorporation exclusively at the C-2 position adjacent to the phthalimido group, consistent with the proposed mechanism.

To demonstrate the scalability and practicality of our intermolecular anti-Markovnikov alkene hydroamination, we carried out the hydroamination of norbornene on a 1.0 g scale of NHPI (Scheme 5A). We found no significant decrease in reaction efficiency at this scale, affording **18** in 80% yield in 12 hours. As anticipated, the removal of the phthalimido group was easily achieved using a small excess of aqueous hydrazine in methanol at 60 °C for 30 minutes to deliver 2-aminonorbornane in 95% yield (Scheme 5B).

Scheme 5. Hydroamination scale-up and phthalimide deprotection.



[a]5 equiv alkene used.

In conclusion, we describe an anti-Markovnikov selective hydroamination of a variety of alkene substrates achieved via a phosphite promoted O-atom transfer process. This work uses inexpensive reagents, triethyl phosphite and NHPI, to access PhthN•.[21] Our anti-Markovnikov hydroamination method addresses limitations of prior work generating PhthN• as it excludes further functionalization of NHPI, negates the use of UV irradiation, and circumvents expensive photocatalysts. The direct introduction of a phthalimido group is particularly attractive as simple deprotection procedures can be used to reveal versatile primary amines.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental details; characterization data including NMR spectra of novel compounds; methods and results (PDF)

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Notes

The authors declare no competing financial interest.

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(21) $P(OEt)_3$ can be purchased from Sigma Aldrich for $0.04/g and NHPI can be purchased from Acros Organics for $0.17/g. Prices current as of June 2018.

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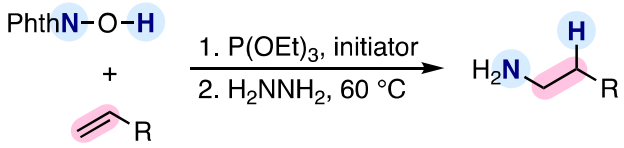

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