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Direct Intermolecular Anti-Markovnikov Hydroazidation of Unactivated Olefins

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Abstract

We herein report a direct intermolecular anti-Markovnikov hydroazidation method for unactivated olefins, which is promoted by a catalytic amount of bench-stable benziodoxole at ambient temperature. This method facilitates previously difficult, direct addition of hydrazoic acid across a wide variety of unactivated olefins in both complex molecules and unfunctionalized commodity chemicals. It conveniently fills a synthetic chemistry gap of existing olefin hydroazidation procedures, and thereby provides a valuable tool for azido-group labeling in organic synthesis and chemical biology studies.

Graphical Abstract

INTRODUCTION

Olefin hydroazidation, the nitrogen atom transfer process that involves direct or formal addition of hydrazoic acid (HN_3) across an unactivated alkene, is valuable for synthetic chemistry. Not only does this reaction introduce the azido-group to a variety of complex molecules for organic synthesis¹ and chemical biology studies,² it can also complement olefin hydroamination methods^{3,4} that rapidly convert unfunctionalized olefins to high-value

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ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, characterization data for all new compounds, and selected NMR spectra (PDF) X-ray crystallographic data for S1, a derivative of 8 (CIF)

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nitrogen-containing building blocks. The direct acid-catalyzed Markovnikov addition of HN_3 across a list of activated or strained olefins is known,⁵ presumably through the intermediacy of stabilized tertiary and benzylic carbocations.⁵ Markovnikov hydroazidation of unactivated olefins has also been developed. Carreira⁶ and Boger⁷ independently reported metal hydride-catalyzed or -mediated Markovnikov olefin hydroazidation methods (Scheme 1a).

However, direct anti-Markovnikov hydroazidation methods for unactivated olefins have been under-developed, and direct addition of HN_3 across an unactivated alkene remains difficult. As a result, a hydroboration–oxidation–mesylation–azidation procedure is often used for indirect anti-Markovnikov olefin hydroazidation (Scheme 1b).^{1c} As a significant advance, Renaud^{8a} reported a two-step hydroazidation procedure that involves anti-Markovnikov olefin hydroboration using a stoichiometric amount of catecholborane and subsequent azidation with benzenesulfonyl azide (Scheme 1b). A stereo-selective variant tailored for an array of trisubstituted olefins was recently developed by the same group through asymmetric olefin hydroboration using (+)- IpcBH_2 .^{8b} As a specific tandem reaction, metal-catalyzed formal hydroazidation of homoallylic benzyl ethers was also achieved through an olefin azidation–intramolecular 1,5-H-atom transfer–oxidative debenzylation cascade.^{9a}

These multi-step, indirect methods are synthetically enabling; however, stoichiometric amounts of both oxidants and reductants are often used in these formal HN_3 addition reactions. Therefore, a general method of direct anti-Markovnikov addition of HN_3 across a wide variety of unactivated olefins is yet to be developed that will fill the gap of existing hydroazidation approaches and thereby minimize the generation of a stoichiometric amount of byproducts. Herein, we report a direct anti-Markovnikov olefin hydroazidation that is promoted by a catalytic amount of benziodoxole (Scheme 1c). This room-temperature reaction directly adds HN_3 across a broad range of unactivated olefins in both unfunctionalized and complex molecules, many of which are incompatible with the existing anti-Markovnikov hydroazidation procedures. Our preliminary mechanistic studies suggest a unique reaction pathway that is distinct from the known olefin hydroazidation reactions.

RESULTS AND DISCUSSION

We selected 1-dodecene **1**, a prototypical unactivated olefin, as a model substrate for reaction discovery (Table 1). Through numerous explorations, we discovered that a catalytic amount of benziodoxole **2a**, a bench-stable oxidant as the precursor for an array of hypervalent iodine reagents^{10,11} effectively promotes dodecene hydroazidation in the presence of TMSN_3 and H_2O at ambient temperature, affording terminal azide **3** with excellent anti-Markovnikov selectivity (Table 1, 90% yield). Since **2a** is almost insoluble in CH_2Cl_2 , the reaction mixture is initially heterogeneous, and it becomes homogeneous upon completion of the reaction. Notably, **2a** is converted to TMS *o*-iodobenzoate at the end of the reaction.

There are several key observations that are mechanistically important. First, benziodoxole **2a** is crucial for the observed reactivity: there is no dodecene hydroazidation and **1** is fully recovered in the absence of **2a** (Table 1, entry 1). Notably, replacement of **2a** with a range of

peroxides rendered this method ineffective (entry 2). Next, TMSN_3 with the Lewis-acidic silicon group is indispensable: attempts to replace TMSN_3 with other ionic azides, including NaN_3 and $^t\text{Bu}_4\text{NN}_3$, shut down the reaction (entry 3). Furthermore, a stoichiometric amount of H_2O (1.0 equiv) is advantageous for the hydroazidation while the $\text{TMSN}_3/\text{H}_2\text{O}$ (1:1) mixture is completely ineffective (entries 4 and 5). We also noted that lower loading of promoter **2a** (from 0.1 equiv to 0.07 equiv) leads to an incomplete reaction (entry 6). To develop a more efficient hydroazidation procedure with lower promoter loading, we evaluated an array of Brønsted acid additives (entries 7 and 8). Surprisingly, a catalytic amount of $\text{CF}_3\text{CO}_2\text{H}$ (0.2 equiv) proves uniquely effective, and it cooperatively promotes high-yielding dodecene hydroazidation with **2a** (entry 8, 0.07 equiv).¹²

With two optimal procedures in hand, we explored this newly discovered anti-Markovnikov hydroazidation with a variety of unactivated olefins. First, we evaluated an array of unfunctionalized olefins, including monosubstituted and 1,1-disubstituted, as well as *trans*- and *cis*-disubstituted olefins (Table 2, entries 1–7). They are generally excellent substrates and readily converted to organic azides **3–9** in good yields within 2 h. Notably, the hydroazidation of terminal olefins exclusively affords anti-Markovnikov addition products **3** and **4** (entries 1 and 2), while the reaction with dissymmetric *trans*-disubstituted olefins tends to furnish both internal azides **6a/6b** (entry 4). We also noted that the hydroazidation of strained norbornene affords 2-*exo*-azidobicyclo[2.2.1]heptane **7** as a single diastereomer (entry 5)¹³ and that (+)-camphene hydroazidation furnishes the *exo*-hydroazidation product **8** with excellent *dr* (entry 6, *dr*: 10:1).¹³ Additionally, both procedures are effective for hydroazidation of unstrained cyclooctene (entry 7).

Next, we focused on the olefins with allylic functional groups, including allylbenzene, allylsilanes, and allylic esters and carbamates (entries 8–14). The 1,3-difunctionalized anti-Markovnikov addition products from these olefins are synthetically valuable;¹⁴ however, *the direct hydroazidation of these substrates has not been reported*. We observed that almost all of them are less reactive than unfunctionalized olefins; therefore, an increased loading of promoter **2a** (0.3 equiv) is often necessary for full conversion.¹⁵ We suspect that the lack of reactivity may not be simply attributed to an olefin's electronic effect since allyl silane (entry 9) and allyl benzoate (entry 10) demonstrate essentially the same reactivity. Prenyl benzoate, a trisubstituted allylic ester, is compatible with this reaction, which affords a secondary organic azide **13** in good yield and excellent anti-Markovnikov selectivity (entry 11). We also noted that the hydroazidation of *N*-Troc-allyl carbamate furnishes both a terminal and an internal azide (**14a** and **14b**, 57 and 10%, respectively, entry 12). To improve the anti-Markovnikov selectivity, two *N,N'*-disubstituted allyl carbamates were evaluated (entries 13 and 14), both of which can exclusively undergo anti-Markovnikov hydroazidation with good to excellent yields. Interestingly, homoallylic benzoate and phthalimide are excellent substrates, and they are readily converted to terminal azides **17** and **18** with good yields (entries 15 and 16).

Furthermore, we evaluated unactivated olefins within the substrates that have reactive functional groups (entries 17–23). *These more functionalized substrates have not been explored using the existing anti-Markovnikov hydroazidation procedures*. We noted that carboxylic acids and primary alcohols are tolerated by this reaction and they can undergo

high-yielding hydroazidation in the absence of H₂O or CF₃CO₂H (entries 17 and 18). However, Brønsted acid additives are still required in hydroazidation of tertiary allylic alcohols (entry 19). Interestingly, electrophilic aldehyde and ketone groups, as well as reactive primary alkyl bromides and chlorides, are all compatible with this method, and the corresponding terminal azides **22–25** were isolated in good to excellent yields (entries 20–23).

Low-molecular-weight organic azides may present potential safety concerns for their handling;¹⁶ however, our recent process safety assessment of the iron-catalyzed olefin diazidation suggests that most organic azides with C/N ratio greater than 1.5 are thermal stable at room temperature and that they are generally impact insensitive.¹⁷ Encouraged by this study, we explored the hydroazidation–reduction procedure for dodecene and norbornene on a large scale, in order to demonstrate the potential practicality of this reaction (Scheme 2). Notably, we improved the original workup procedure, such that purification of organic azides is no longer needed prior to reduction, and the *N*-Boc carbamate products **26** and **28** can be directly isolated.¹⁸ To our pleasure, both hydroazidation–reduction procedures can be consistently scaled up to gram scale with good product yield and low promoter loading.

We felt that this hydroazidation method could be particularly valuable for azido-group labeling of complex molecules; therefore, we evaluated the reactivity of densely functionalized complex molecules and small-molecule probes of biological relevance (Scheme 2). First, we observed that hydroazidation of *O*-acyl quinine **29** exclusively affords terminal azide **30** in good yield. Notably, higher loading of CF₃CO₂H and promoter **2a** is required for a high-yielding reaction, presumably due to the presence of basic quinuclidine and quinoline nitrogen groups. Next, allyl dihydrocarbazol-1-one **31** can also be directly converted to terminal azide **32** in good yield using this method. This discovery is synthetically appealing since an analogous multi-step hydroazidation procedure was used during the synthesis of a family of monoterpene indole alkaloids, including mersicarpine, leuconodines, and rhazinilam.^{1b,c} Additionally, functionalized saccharides **33/35** with an olefin appendage are also compatible with this method, which opens up the opportunity for facile azido-group labeling of complex glycans for biological target identification.^{2c}

Notably, this method is ineffective for hydroazidation of electron-rich and activated alkenes, including styrenes, indene, 1,3-dienes, enol ethers, and enamides, all of which are largely recovered under the reaction conditions (Figure 1).¹⁹

The underlying mechanism of this anti-Markovnikov olefin hydroazidation is intriguing. Since HN₃ can be readily generated by TMSN₃ and H₂O or TFA, the mechanistic detail of direct addition of HN₃ across an unactivated olefin is particularly interesting. To formulate a plausible mechanistic working hypothesis, we carried out an array of control experiments to gain more insights into both the C–N₃ and C–H bond forming steps (Scheme 3).

First, hydroazidation of diethyl diallylmalonate **37** readily affords a *cis*-disubstituted cyclopentane **38** in excellent yield (Scheme 3, eq 1). Interestingly, hydroazidation of 1,6-heptadiene **39** followed by reduction–acylation provides both a *cis*-disubstituted

cyclopentane **40** and a dicarbamate **41** (Scheme 3, eq 2).²⁰ Next, we observed that a TEMPO-addition product **42** was exclusively formed when TEMPO radical was introduced in dodecene hydroazidation (Scheme 3, eq 3). Surprisingly, styrene **43**, which is unreactive under the standard hydroazidation condition, was readily converted to its azido-oxygenation product **44** in the presence of TEMPO (Scheme 3, eq 4).²¹ These results suggest that azido radical is likely involved in the C–N₃ bond forming step and that the C–H bond forming step is possibly rate-limiting in olefin hydroazidation.

Next, we evaluated a (*Z*)-olefin **45** for the hydroazidation and observed a significant amount of an isomerized (*E*)-olefin **46** in 15 min (Scheme 3, eq 5). Notably, both **45** and **46** were converted to organic azides **47a/47b** in 2 h (eq 5). These observations suggest that the C–N₃ bond-forming step is likely reversible.

Furthermore, we observed the dodecene deuteroazidation with D₂O and TMSN₃ (Scheme 3, eq 6). Surprisingly, a much lower conversion (35%) and diminished anti-Markovnikov selectivity (48a/48b 6.7:1) were observed.²² These experiments suggest that HN₃ is involved in the rate-limiting C–H bond-forming step and that H-atom transfer from HN₃ to the transient β -azido carbo-radical intermediate is likely both rate- and regio-selectivity determining.

Built upon these insights, we further probed the decomposition mechanism of **2a**. It is known that **2a** can be reversibly activated by TMSN₃ to generate the azido-radical,¹¹ yet **2a** is kinetically stable toward TMSN₃ in the absence of other additives (Scheme 3, eq 7). We also noted that **2a** is kinetically stable toward HN₃ (eq 7). However, **2a** rapidly decomposed to TMS *o*-iodobenzoate in the presence of both TMSN₃ (3.0 equiv) and H₂O (1.0 equiv) (Scheme 3, eq 8). This result suggests that TMSN₃ and HN₃ may cooperatively facilitate the decomposition of **2a** (Scheme 4). Interestingly, azidoiodinane **2b** is also a viable promoter under the standard olefin hydroazidation condition (Scheme 3, eq 9); however, **2b** is unable to promote the reaction with HN₃ in the absence of TMSN₃ (eq 9). These results corroborate that azidoiodinane **2b** may be a viable reactive intermediate and that TMSN₃ is necessary to activate **2b** to promote the reaction.

Based upon an array of mechanistic evidence presented in Scheme 3, a plausible working hypothesis for this anti-Markovnikov olefin hydroazidation is described in Scheme 4. First, TMSN₃ may reversibly convert otherwise insoluble benziodoxole **2a** to azidoiodinane **2b**, and then to a transient iodine(III)—diazide species **2c**, from which an azido-radical species can be reversibly generated. Next, the azido-radical may reversibly add to an unactivated olefin **49**, affording a β -azido carbo-radical species **50**. Subsequently, rate-limiting and irreversible H-atom transfer^{23a} may occur from the in situ generated HN₃ to **50**, which will readily furnish the hydroazidation product **51** and regenerate the azido-radical. Notably, the observed regio-chemistry profile from dodecene deuteroazidation (Scheme 3, eq 6) suggests that the observed anti-Markovnikov selectivity is determined during the H-atom transfer step.

CONCLUSION

In summary, we have reported a direct anti-Markovnikov hydroazidation method for unactivated olefins at ambient temperature. This method facilitates the previously difficult, direct addition of hydrazoic acid across a broad range of unactivated olefins in both unfunctionalized and complex molecules. It effectively fills a synthetic chemistry gap of existing olefin hydroazidation methods—and thereby provides azido-group labeling as a valuable tool for organic synthesis and chemical biology studies. The preliminary mechanistic studies suggest a unique hydroazidation pathway that is distinct from the known hydroazidation reactions, and our current effort focuses on the mechanistic understanding and synthetic applications of this new reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Representative electron-rich and activated alkenes that are unreactive in the olefin hydroazidation.

a) Markovnikov olefin hydroazidation mediated by metal hydrides

b) existing methods for indirect anti-Markovnikov olefin hydroazidation

c) this research: direct anti-Markovnikov hydroazidation of unactivated olefins

Scheme 1.

Existing and Currently Reported Hydroazidation Methods for Unactivated Olefins

Scheme 2.

Large-Scale Anti-Markovnikov Olefin Hydroazidation—Reduction and Anti-Markovnikov Hydroazidation of Complex Molecules

Scheme 3.
Mechanistic Control Experiments to Probe for a Possible Mechanism

Scheme 4.
Mechanistic Working Hypothesis for the Direct Anti-Markovnikov Olefin Hydroazidation
Promoted by 2a

Table 1.

Reaction Discovery of the Direct Anti-Markovnikov Dodecene Hydroazidation

entry ^a	variation from the standard conditions	conversion (%)	yield (%) ^b
1	in the absence of 2a	<5	NA
2	replace 2a with TBHP, benzoyl peroxide, or <i>t</i> BuOOBz	<5	NA ^c
3	replace TMSN ₃ with NaN ₃ or ⁿ Bu ₄ NN ₃	<5	NA
4	in the absence of H ₂ O	10	7
5	TMSN ₃ (1.0 equiv) + H ₂ O (1.0 equiv)	<5	NA
6	2a (0.07 equiv) instead of 0.1 equiv	78	71
7	2a (0.07 equiv), H ₂ O (0.8 equiv) TsOH, MsOH, or AcOH (0.2 equiv)	55–75	48–69
8	2a (0.07 equiv), H ₂ O (0.8 equiv) CF ₃ CO ₂ H (0.2 equiv)	>95	91
9	2a (0.05 equiv), H ₂ O (0.8 equiv) CF ₃ CO ₂ H (0.2 equiv)	85	79

^aReactions were carried out under N₂ at 22 °C on 1 mmol scale in CH₂Cl₂ (0.2 mL) unless stated otherwise. Reactions were quenched with saturated NaHCO₃ solution. TMS-*o*-iodobenzoate was identified at the end of the reaction.

^bIsolated yield.

^cAIBN and benzoyl peroxide promote low-yielding (<10%) hydroazidation at elevated temperatures. See SI.

Table 2.

Substrate Scope of the Direct Anti-Markovnikov Olefin Hydroazidation

$ \begin{array}{c} \text{R}^1 \text{---} \text{C}=\text{C} \text{---} \text{R}^2 \\ \text{R}^3 \end{array} + \text{TMSN}_3 \xrightarrow[\text{CH}_2\text{Cl}_2, 22^\circ\text{C}, 2-4\text{ h}]{\begin{array}{c} \text{2a (0.1-0.2 equiv)} \\ \text{H}_2\text{O (1.0 equiv) or} \\ \text{H}_2\text{O (0.8 equiv), TFA (0.2 equiv)} \end{array}} \begin{array}{c} \text{R}^1 \text{---} \text{C} \text{---} \text{C} \text{---} \text{R}^2 \\ \quad \\ \text{H} \quad \text{N}_3 \end{array} $			
entry ^a	olefins	organic azide products	yield ^b
1			90%
2			88%
3			71%
4			73%
5			70%
6			88%
7			68%
8 ^{c,d}			70%
9 ^e			72%
10 ^f			61%
11 ^e			77%
12 ^{e,g}			67%
13 ^e			73%
14 ^e			63%
15			87%
16			86%
17 ^f			83%
18 ^f			80%
19 ^f			74%
20 ^f			71%
21			76%
22			90%
23 ^e			81%

^aReactions were carried out under N₂ at 22 °C and were quenched with saturated NaHCO₃ solution. ^bIsolated yield. ^c2a (0.3 equiv). ^dA regio-isomeric internal azide was isolated in 4% yield. ^eTFA (0.6 equiv), H₂O (0.6 equiv). ^fNo external proton donor was added.