

Iron-Mediated Photochemical Anti-Markovnikov Hydroazidation of Unactivated Olefins

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Cite This: *J. Am. Chem. Soc.* 2023, 145, 22347–22353



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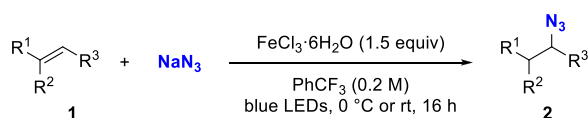


Supporting Information

ABSTRACT: Unactivated olefins are converted to alkyl azides with bench-stable NaN_3 in the presence of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ under blue-light irradiation. The products are obtained with anti-Markovnikov selectivity, and the reaction can be performed under mild ambient conditions in the presence of air and moisture. The transformation displays broad functional group tolerance, which renders it suitable for functionalization of complex molecules. Mechanistic investigations are conducted to provide insight into the hydroazidation reaction and reveal the role of water from the iron hydrate as the H atom source.

Organic azides are an integral part of an array of drug molecules, energetic materials, and chemical probes.¹ They also are valuable building blocks in the synthesis of natural products, pharmaceuticals, and agrochemicals.² As synthetic handles, azides have found widespread application in classic methods such as Staudinger reduction and ligation,³ Huisgen cycloaddition⁴ and click chemistry,⁵ as well as Schmidt⁶ and aza-Wittig reactions.⁷ More recently, azides have been utilized as nitrene precursors in transition-metal-catalyzed C–H bond aminations.⁸ Especially in the context of multistep synthesis, R– N_3 can serve as a protected amine.⁹ Herein, we report the first iron- and light-mediated anti-Markovnikov hydroazidation of unactivated olefins (Figure 1). The transformation employs NaN_3 as a bench-stable¹⁰ azide source, tolerates air and moisture, and proceeds under mild conditions allowing for a wide functional group compatibility.

✓ bench-stable reagents ✓ air tolerant ✓ broad functional group compatibility



functional groups tolerated: -Cl, -Br, -CN, -OH, -OTs, -OSiMe₂t-Bu, -NHR, -OC(O)OMe, -SPh, -CHO, -C(O)R, -CO₂R, -C(O)NR, -CF₃

structures of selected drugs, energetic materials, and probes

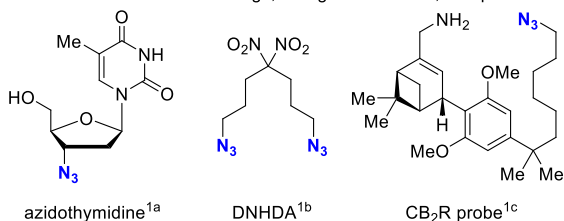


Figure 1. Iron-mediated photochemical anti-Markovnikov hydroazidation of unactivated olefins.

The widespread application of organic azides in synthetic chemistry and biology necessitates methodologies to access them directly from readily available starting materials. Traditionally, organic azides have been synthesized via nucleophilic substitution as well as diazo- and azido-transfer reactions.¹¹ In a complementary approach, direct transformations of olefins to alkyl azides have been explored. Early studies by Hassner and Kropp focused on the addition of HN_3 to alkenes, affording the corresponding Markovnikov products (Figure 2A).¹²

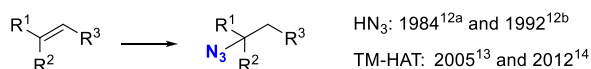
Milder and more broadly applicable conditions for the Markovnikov hydroazidation of unactivated olefins were developed in our group which employ a cobalt catalyst, silane, and TsN_3 .¹³ Boger later disclosed a Markovnikov hydroazidation that is presumed to proceed via an iron hydride species.¹⁴ To obtain anti-Markovnikov addition products, multistep sequences were required. Only recently has the direct anti-Markovnikov azidation of double bonds been reported (Figure 2B). Chiba and Gagosz have investigated a hypervalent iodine reagent (azidobenziodoxolone, ABX) for the hydroazidation of homoallylic benzyl ethers with the latter serving as intramolecular H atom donor in the reaction.¹⁵ Yu and co-workers have documented a hydroazidation reaction of unsaturated aryl amides using an Ir photocatalyst and TMSN_3 .¹⁶ Most recently, Xu and Liu independently generated the active hypervalent iodine reagent ABX *in situ* from TMSN_3 and a benziodoxolone to achieve anti-Markovnikov hydroazidation.¹⁷ Despite these important advances, convenient procedures using NaN_3 as an off-the-shelf, inexpensive azide source are lacking.

Received: August 21, 2023

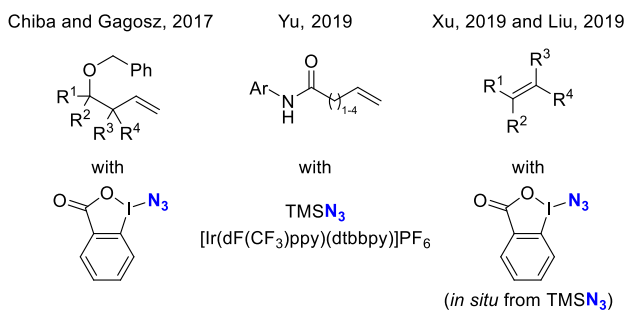
Published: October 9, 2023



A) Markovnikov hydroazidations of unactivated olefins



B) anti-Markovnikov hydroazidations of unactivated olefins



C) desired transformation

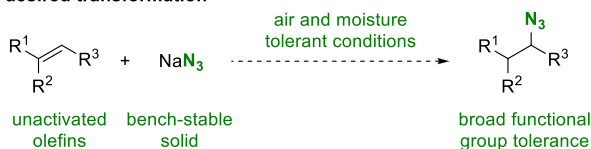


Figure 2. Approaches toward (A) Markovnikov and (B) anti-Markovnikov hydroazidation of unactivated olefins and (C) desired transformation.

Our interest in metal-mediated olefin hydroazidation reactions and, more recently, alkene functionalization and photochemical methods has led us to examine approaches to alkyl azides.^{13,18} Applications of transition-metal salts (e.g., Cu^{II}, Ti^{IV}, and Fe^{III}) under visible-light irradiation caught our attention.¹⁹ The excitation of these salts with visible light induces ligand-to-metal charge transfer (LMCT), resulting in, for example, dichlorination, diazidation, or Giese reaction.^{19c–g,20} We focused on the most abundant transition metal and hypothesized that the use of radicals generated from an iron complex under blue-light irradiation may be suitable to effect hydroazidation in a mild and selective manner. To this end, 4-phenylbutene (**1a**) was subjected to NaN₃ (3.0 equiv) and Fe(NO₃)₃·9H₂O (1.0 equiv) in dichloromethane (0.2 M) and irradiated ($\lambda_{\text{max}} = 446 \text{ nm}$, 350 W blue LED photoreactor; for technical details see the [Supporting Information](#)) for 16 h at room temperature. In this experiment, primary azide **2a** was observed in 36% yield ([Table 1](#), entry 1). Further studies revealed that FeCl₃·6H₂O in CH₂Cl₂ afforded the highest yield

Table 1. Optimization of the Reaction Conditions

entry	deviation from standard conditions	2a ^a (%)
1	Fe(NO ₃) ₃ ·9H ₂ O (1.0 equiv), CH ₂ Cl ₂ , rt	36
2	none	83
3	TMSN ₃ instead of NaN ₃	17
4	no iron salt	0
5	no light	0
6	FeCl ₃ instead of FeCl ₃ ·6H ₂ O	<5
7	40 W blue LED Kessil light, rt	80

^aYield obtained by ¹H NMR with mesitylene as internal standard.

among all investigated iron salts (for details see the [Supporting Information](#)). As azides are known to displace the chlorides in CH₂Cl₂, subsequently generating highly explosive intermediates,²¹ solvent alternatives were investigated. The use of polar solvents such as acetone, ethyl acetate, and MeCN did not yield any hydroazidation, instead giving the diazide in a range of yields (for details see the [Supporting Information](#)).^{19c,d} In contrast, employing less polar solvents such as haloarenes yielded monoazide in a good yield. Of the alternatives investigated, α,α,α -trifluorotoluene (PhCF₃) performed best. Under optimized conditions (1.5 equiv of FeCl₃·6H₂O, 3.0 equiv of NaN₃, PhCF₃ (0.2 M), 0 °C for 16 h, blue LEDs, entry 2), **2a** was formed in 83% yield.

Control experiments were performed to gain further insights into the transformation (for details including oxygen sensitivity, see the [Supporting Information](#)). When the reaction was conducted with TMSN₃ under otherwise identical conditions, **2a** was produced in 17% yield (entry 3). The reaction did not provide the product in the absence of iron salt or light, and **1a** was fully recovered (entries 4 and 5). If anhydrous FeCl₃ was used in oven-dried glassware under otherwise identical conditions, merely traces of the product were formed, indicating the necessity of water (entry 6). When using a 40 W blue LED Kessil light at 25% intensity, the best results were obtained at room temperature (entry 7; for details see the [Supporting Information](#)).

With the optimized conditions in hand, we set out to investigate the functional group tolerance of the hydroazidation reaction ([Figure 3](#)). To this end, a variety of alkyl azides were accessed in moderate to high yields from the corresponding alkenes.²² When vinyl silane **1b** was subjected to the reaction conditions, β -silyl azide **2b** was obtained in 80% yield. Alkyl azides **2c** and **2d** were isolated in yields of 73 and 80% from primary haloalkenes **1c** and **1d**. Notably, no substitution of either chloride or bromide was observed under the reaction conditions. 1-Dodecene yielded **2e** in 86% yield. A variety of electron-poor and -rich arenes were tolerated, furnishing **2f–2h** in 81–90% yield. Substrates containing protic groups, such as alcohol **1i**, tosyl amide **1j**, carbamate **1k**, and *N*-tosyl imide **1l**, were converted to the corresponding azides in 65–82% yield. Acid-labile *t*-BuMe₂Si-protected alcohol **1m** afforded **2m** in 61% yield. Methyl carbonate **1n** and thioether **1o** were competent under reaction conditions, resulting in **2n** and **2o** in 85 and 43% yield, respectively. Azides **2p–2s** were accessed in 62–75% yield. Markedly, alkenes bearing a heterocycle, such as thiophene, furan, phthalimide, oxetane, and pyridine, were also well tolerated and gave rise to products **2t–2x** in 44–86% yield. The practical aspects of the method were demonstrated by the synthesis of **2a** on a larger scale (2.0 mmol) in 75% yield. All terminal olefins underwent anti-Markovnikov hydroazidation in excellent selectivity (rr = 12:1 to >20:1; for details see the [Supporting Information](#)).

Next, the effects of the alkene substitution patterns were examined. The reaction was amenable to di-, tri-, and tetrasubstituted olefins. 1,1-Disubstituted olefins **1y** to **1aa** afforded primary azides in 73–78% yield. Substrates bearing a tosylate, malonate, acetal, or carbamate were successfully converted to products **2ab–2ae** in 40–75% yield. β -Adamantyl azide **2af** was accessed in 77% yield. Acyclic and cyclic 1,2-disubstituted alkenes were subjected to the reaction conditions, furnishing the corresponding azides **2ag–2aj** in 51–83% yield. Strained olefins, in particular norbornene and

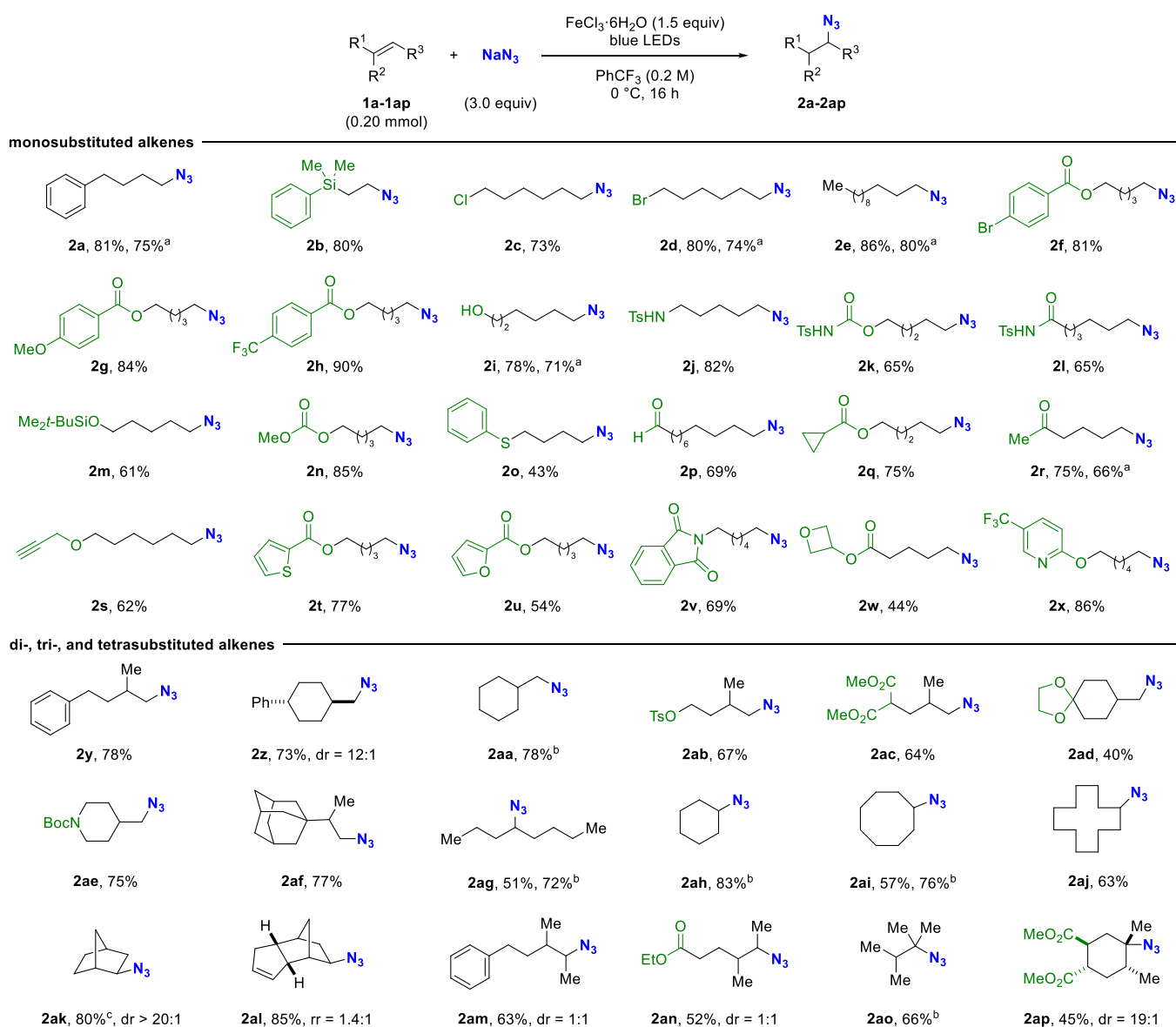


Figure 3. Substrate scope. Reaction conditions: olefin (0.20 mmol), NaN_3 (0.60 mmol), $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (0.30 mmol) in PhCF_3 (1.0 mL), irradiation in 350 W photoreactor at 0°C for 16 h. dr determined by ^1H NMR of the unpurified reaction mixture. ^aCarried out on 2.0 mmol scale with a 40 W blue LED Kessil light at rt. ^bYield obtained by ^1H NMR with mesitylene as internal standard. ^c8 h reaction time.

dicyclopentadiene, were hydroazidated in high yield (80 and 85%, respectively).²³ Trisubstituted olefins were well tolerated, giving rise to secondary azides with **2am** and **2an** isolated in 63 and 52% yield. All di- and trisubstituted olefins employed underwent anti-Markovnikov azidation in good regioselectivity (for details see the [Supporting Information](#)). Finally, tetrasubstituted alkenes **1ao** and **1ap** yielded **2ao** and **2ap** in 66 and 45% yield, respectively.

Encouraged by the broad functional group tolerance of the hydroazidation reaction, we set out to explore the generality of the protocol in a more complex setting. An array of alkenes derived from active pharmaceutical ingredients and natural products was subjected to the reaction conditions ([Figure 4](#)). To our delight, these substrates led to the formation of desired azides **4a–4u** in good yields (40–86%). In particular, molecules featuring diversely substituted arenes and heterocycles, such as oxazoles, indoles, thiazoles, β -lactams, and diazoles were well tolerated, indicating the potential of this method for late-stage application.

In order to deal with the volatility and inherent risk of low-molecular-weight azides, we examined several transformations subsequent to hydroazidation. One-pot procedures would avoid work-up, solvent evaporation, purification, isolation, and handling of the azide intermediates ([Scheme 1](#)). First, attempts to perform a Cu(I)-catalyzed azide–alkyne click reaction *in situ* were unsuccessful. We observed that the addition of NET_3 was crucial for the formation of triazole **7a** in 76% yield. When cyclooctyne was employed as a reaction partner, triazole **7b** was isolated in 54% yield from volatile azide **2ao**. Primary amine **7c** was accessed in 72% yield through Pd-catalyzed hydrogenation, and Staudinger reduction of cyclohexyl azide **2ah** with subsequent Boc-protection furnished the corresponding carbamate **7d** in 62% yield.

To gain mechanistic insights into the hydroazidation, a series of experiments was conducted ([Figure 5](#)). Initial investigations focused on determining whether radical species are involved in the reaction. The addition of 2.0 equiv TEMPO as radical scavenger²⁴ under standard conditions suppressed

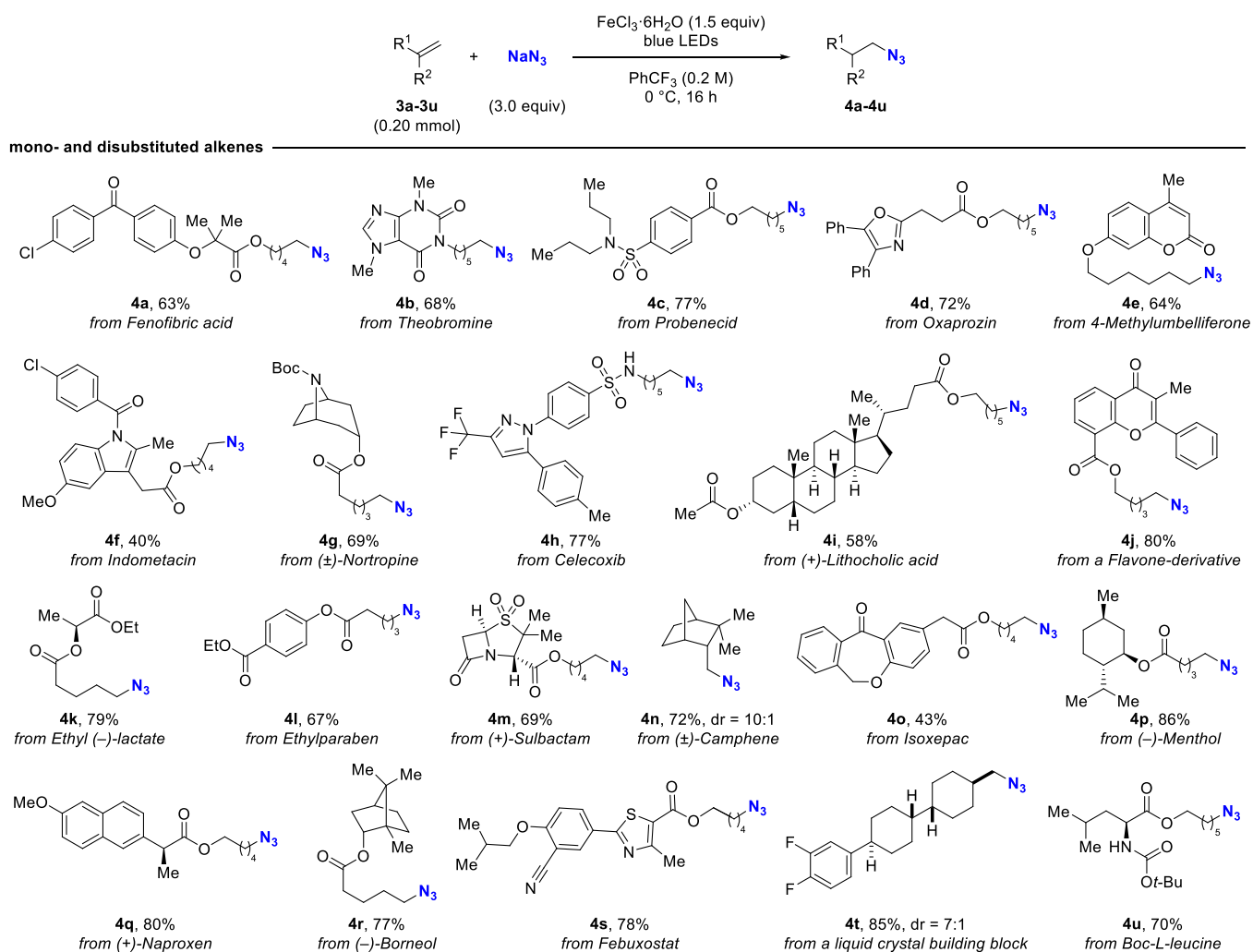


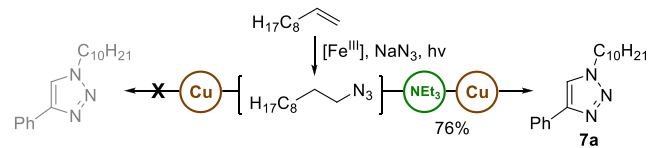
Figure 4. Substrate scope for olefins derived from natural products and drugs. dr determined by ^1H NMR of the unpurified reaction mixture.

the reaction, and no hydroazidation product could be detected by either ^1H NMR or HRMS. Instead, alkene starting material was recovered.

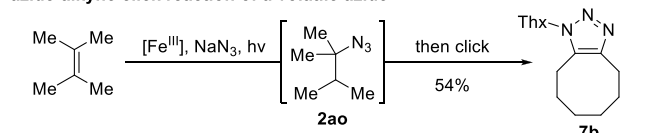
In the context of our examination of the substrate scope, when aldehyde **8** was subjected to the standard reaction conditions, we observed 1-azido-4-methylpentane (**9**) as the

Scheme 1. Sequential One-Pot Transformations

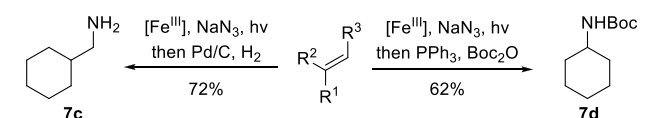
NEt_3 -addition enables a hydroazidation–Cu-click procedure



azide-alkyne click reaction of a volatile azide



hydroamination procedures to avoid azide isolation



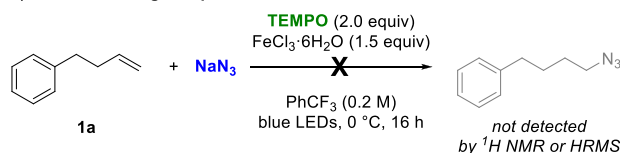
sole product (Figure 5B). This is consistent with the formation of a secondary carbon-centered radical from the olefin followed by a 1,5-radical hydrogen atom abstraction from the aldehyde. Decarbonylation affords the more stable tertiary radical which is quenched.²⁵

This result prompted us to examine substrates **10a** and **10b** which could undergo 5-exo-trig cyclization reactions (Figure 5C). *N*-Tosyl diallyl amine furnished pyrrolidine **11a** in 55% yield, and diethyl diallylmalonate delivered the corresponding cyclopentyl product **11b** in 79% yield. For both substrates, only cyclization products were isolated, suggesting that quenching is slower than cyclization for **10a** and **10b**.²⁶

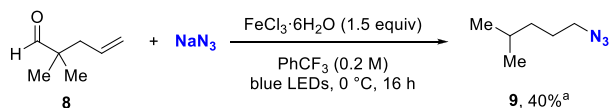
It has been proposed in the literature that under visible-light irradiation Fe(III) azides generate Fe(II) salts along with azidyl radicals.^{19c,d} Based on these reports, in the system we describe the azidyl radical can then add (anti-Markovnikov) to the olefin to provide a reactive carbon-centered radical.²⁷ This intermediate is ultimately quenched by an H atom donor. Accordingly, we set out to identify the origin of the hydrogen atom involved in the quenching.

It has previously been observed that hydrates of boron ($\text{Me}_3\text{B} \cdot \text{OH}_2$) and titanium ($\text{Cp}_2\text{Ti} \cdot \text{OH}_2$) serve as H atom donors in radical reactions.²⁸ Consequently, we hypothesized that the iron-bound water in $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ might be involved as an H atom source. In an experiment in oven-dried glassware

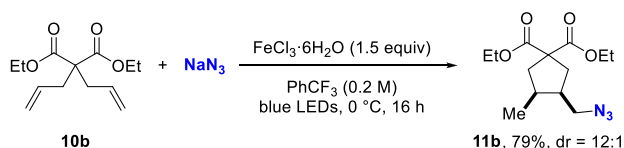
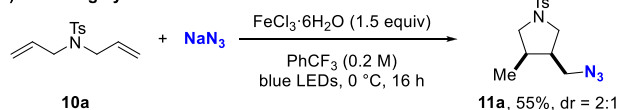
A) radical scavenger experiment



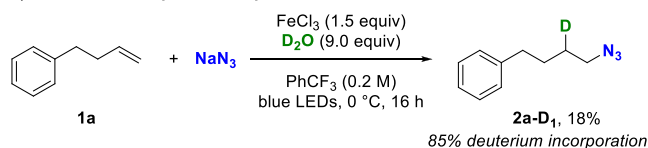
B) 1,5-hydrogen atom abstraction



C) 5-exo-trig cyclizations



D) deuterium incorporation experiment



E) proposed mechanism

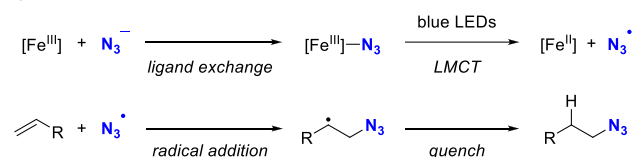


Figure 5. Mechanistic investigations and the proposal of a plausible mechanistic construct. dr determined by $^1\text{H NMR}$ of the unpurified reaction mixture. ^aYield obtained by $^1\text{H NMR}$ with mesitylene as internal standard.

under a nitrogen atmosphere, D_2O was added to anhydrous FeCl_3 followed by addition of $\text{PhCF}_3/\text{NaN}_3/4$ -phenylbutene (Figure 5D). After being stirred for 16 h under blue-light irradiation, azidodeuterated product **2a-D₁** was isolated in 18% yield. In parallel experiments using H_2O under otherwise identical conditions, product **2a** was obtained in 77% yield. The difference in yield between the two experiments suggests a strong primary kinetic isotope effect ($k_{\text{H}}/k_{\text{D}} \gg 1$; for details see the Supporting Information). These data support water as the terminal H atom source and indicate that the H atom transfer to the secondary carbon-centered radical likely is the rate-limiting step of the transformation.^{17a,29} Although free water is not known to be an H atom source ($H_{\text{BDE}}(\text{HO-H}) = 118 \text{ kcal/mol}$), its coordination to iron dramatically decreases the bond-dissociation energy ($H_{\text{BDE}}(\text{Fe}^{\text{II}}(\text{H}_2\text{O})_5(\text{HO-H})) = 77 \text{ kcal/mol}$).^{30,31} Our observation of solvent effects described in the optimization reactions suggests that the nature of the solvent affects speciation of Fe(III) complexes in the presence of azide and chloride counterions as well as water. Further mechanistic studies to understand the nature of Fe complexes formed, including μ_2 -bridged dimers, are clearly necessary as they may provide additional avenues for the development of new transformations.³²

In conclusion, we have developed a photochemical anti-Markovnikov hydroazidation of unactivated alkenes with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$. The transformation shows broad functional group tolerance and was amenable to terminal as well as highly substituted olefins. Salient features of the reaction are its tolerance to air and moisture and the successful use of NaN_3 as a bench-stable, low-cost, and easy-to-handle azide source. We demonstrated that the simplicity and generality of this method make it ideally positioned for late-stage applications, allowing for the efficient and versatile synthesis of diverse organic azides featuring biologically active motifs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c09122>.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 2295827 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by the European Research Council (OLECAT, Grant ID 833540). We are grateful to Dr. M.-O. Ebert, R. Frankenstein, S. Burkhardt, and R. Arnold for support with NMR experiments, Dr. N. Trapp and M. Solar for X-ray crystallographic analysis, and C. A. Bärtschi, C. Marro, and H. Benz for the maintenance and construction of the photoreactor (all ETH Zürich). W.M.A. is grateful for partial support with funding from the SSCI (Scholarship Fund of the Swiss Chemical Industry).

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