Aminoxyl-Catalyzed Electrochemical Diazidation of Alkenes Mediated by a Metastable Charge-Transfer Complex

Juno C. Siu[‡], **Joseph B. Parry**[‡], and **Song Lin**[*]

Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853, United States

Abstract

We report the development of a new aminoxyl radical catalyst, CHAMPO, for the electrochemical diazidation of alkenes. Mediated by an anodically generated charge-transfer complex in the form of CHAMPO–N_3, radical diazidation was achieved across a broad scope of alkenes without the need for a transition metal catalyst or a chemical oxidant. Mechanistic data support a dual catalytic role for the aminoxyl serving as both a single-electron oxidant and a radical group transfer agent.

The discovery of reactions mediated by organic radicals continues to provide solutions to challenging synthetic problems in traditional two-electron chemistry.[1] In this context, design and implementation of new catalytic strategies have both expanded the toolbox available for accessing new synthetic targets and transformed the fundamental understanding of reactions involving open-shell pathways.[2] For example, persistent aminoxyl radicals [e.g., (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)] have been extensively explored in catalytic oxidation reactions with both conventional chemical[3] and electrochemical techniques,[4] which has given rise to synthetically useful processes for small-molecule and polymer syntheses.

Despite significant advances, we contend that the scope of TEMPO chemistry remains to be fully explored. TEMPO and related *N*-oxyl radicals can undergo one-electron redox processes, granting access to three discrete oxidation states.[4] This feature distinguishes these radicals from common organic compounds and likens them to many transition metal complexes. In this fashion, TEMPO has been shown to enable single-electron oxidation events in an inner-sphere manner via the formation of metastable closed-shell intermediates. [5,6] Nevertheless, the systematic use of the "metallic" character of *N*-oxyls in catalyst development remains meager.[7] To date, reactions catalyzed by *N*-oxyls are largely confined to oxidations of alcohols,[8] aldehydes,[9] amines,[10] (thio)amides,[11] and peroxyl radicals.[12] In

these transformations, the persistent radical is used primarily in two capacities: as a single/two-electron oxidant or an H atom abstractor. In this report, we expand the scope of *N*-oxyl catalysis in the development of metal-free electrochemical diazidation of alkenes.

We previously reported a first-generation electrochemical protocol for the diazidation of alkenes catalyzed by Mn (Scheme 1A, eq 1).[13] This work was built on foundational contributions by Minisci,[14] Magnus,[15] Snider,[16] Xu,[17] and others[18] in alkene diazidation using conventional chemical methods. These reactions provide 1,2-diazides in a single step from common alkenes, giving access to vicinally dinitrogenated structures that are highly prevalent in biomedically and synthetically relevant molecules.[19] Nevertheless, all methods reported to date require the use of a transition metal or a chemical oxidant, or both. These reactive species often lead to environmentally deleterious wastes and present an explosion hazard when used alongside N_3^-. Although our electro-chemical protocol[13] circumvents the use of strong chemical oxidants, the need for a metal catalyst and a Brønsted acid (HOAc) as the sacrificial oxidant remains undesirable from a safety perspective.

While studying the electrochemical alkene diazidation, we discovered a new electrochemical method for the azidooxygenation of alkenes mediated by TEMPO (Scheme 1A, eq 2).[20] Detailed mechanistic investigation showed that TEMPO plays two roles in this reaction. Aside from being a radical trap, TEMPO also promotes the single-electron oxidation of N_3^- to $N_3^{\bullet}$.[21] This process is mediated by a metastable charge-transfer complex (CTC) formed between anodically generated TEMPO$^+$ and N_3^-. Upon azidyl addition to the alkene, the nascent carbon-centered radical **I** rapidly combines with TEMPO to deliver the masked vicinal aminoalcohol (Scheme 1B, red pathway).

We envisioned that the TEMPO-*consuming* azidooxygenation reaction could be engineered into a TEMPO-*catalyzed* alkene diazidation if intermediate **I** was terminated by an $N_3^{\bullet}$ equivalent instead of directly by TEMPO (Scheme 1B, blue pathway). Specifically, we hypothesize that the TEMPO–N_3 adduct may behave as an azidyl group transfer agent akin to the function of a redox-active transition metal complex (e.g., [Mn^{III}]–N_3). This operation will furnish the desired vicinal diazide while returning the aminoxyl from an oxoammonium ion to a neutral radical oxidation state.

We investigated the plausibility of *N*-oxyl-catalyzed electrochemical diazidation (Table 1). In our alkene azidooxygenation, diazidation products were occasionally observed in small quantities when sterically encumbered alkenes were used. The diazide formation was more pronounced at a higher applied voltage and using less TEMPO. Under these conditions, the [TEMPO$^+$]/[TEMPO] ratio is maximized to favor the formation of the CTC and mitigate the undesired azidooxygenation. For example, the electrolysis of alkene **1a**, NaN$_3$, and 1 equiv TEMPO in MeCN/H$_2$O at a cell voltage of 2.7 V[22] yielded 36% 1,2-diazide **2a** in addition to 45% **3a** (entry 1). Decreasing TEMPO loading to a catalytic amount still provided encouragingly 11% **2a** alongside 7% **3a** (entry 2). However, the catalyst was unproductively consumed in the azidooxygenation pathway, which was also indicated by the color change of the reaction medium. Upon starting electrolysis, the solution turned dark red, which is characteristic of the TEMPO–N_3 CTC. This color disappeared after a mere 10 min as a

result of TEMPO depletion. This visual indicator thus provided a convenient readout for reaction optimization.

We reasoned that heating the reaction would promote homolysis of the C–O bond in byproduct 3a, thus returning both TEMPO and the carbon-centered radical to the catalytic cycle.[23] Counterintuitively, this operation led to rapid decomposition of the CTC and suppressed diazidation. Instead, cooling the reaction improved the yield to 46% at 0 °C and 61% at −10 °C (entries 3 and 4). However, the color of the CTC decayed after 2 h with concomitant formation of 3a (ca. 5%).

Studies by Bobbitt,[8k] Minteer/Sigman,[24] and Stahl[25] showed that the distal C4 substituent of the aminoxyl has a profound influence on its reactivity in alcohol oxidation. Accordingly, we surveyed various catalysts[26] and found that 4-acetamido-TEMPO (ACT) proved the most promising, furnishing 71% **2a** and <5% **3a** (entry 5). However, the CTC decayed after ca. 3 h. We hypothesized that catalyst degradation could also occur via β-H$^+$ elimination of the corresponding oxoammonium ion[27] in a manner akin to the Hofmann elimination.

We reasoned that increasing the steric encumbrance about the *N*-oxyl center should disfavor catalyst consumption via azidooxygenation[28] and β-elimination.[29] Accordingly, we synthesized cyclohexane-substituted (4-acetamidopiperidin-1-yl)oxyl (CHAMPO).[27,30] With CHAMPO as the electrocatalyst, the lifetime of the CTC significantly improved and the color of the solution persisted upon full conversion of the alkene (4 h).[31] Diazide **2a** was obtained in 97% isolated yield with complete elimination of the *N*-oxyl trapping product (entry 6). Importantly, exclusion of catalyst led to olefin consumption but negligible diazide formation (entry 7).[32] In addition, common single-electron oxidants in lieu of electricity did not provide appreciable diazide.[33] We observed the same catalyst trend using trisubstituted alkene **1b**: from TEMPO to ACT to CHAMPO, improvement in product yield and catalyst stability was evident (entries 8–10).

We subsequently explored the scope of this new electrochemical diazidation (Table 2). A broad range of alkenes with diverse structures and electronic properties underwent the desired transformation with high efficiency (**2a, c–p**). Unactivated monosubstituted alkenes were less reactive toward N$_3$$^\bullet$ addition and more prone to azidooxygenation due to reduced steric hindrance.[20a,34] Therefore, 15 mol % CHAMPO was used to ensure synthetically useful yields (**2c, d**).

Alkenes with a catalog of labile functional groups underwent electrochemical diazidation smoothly (**2b, q–y**). For example, electrophiles prone to nucleophilic displacement by N$_3$$^-$, such as alkyl bromide and epoxide groups, remained intact. Oxidatively sensitive functionalities, such as enolizable ketone, aldehyde, sulfide, and ferrocene groups, also were tolerated. Intriguingly, a primary alcohol-derived alkene was converted to the corresponding diazide in 60% yield with traces of aldehyde byproducts. Chemoselectivity between various C=C bonds was observed with carvone or *N*-allyl-*N*-prenyltoluenesulfonamide as substrate. Owing to the electrophilic nature of N$_3$$^\bullet$, the more electron-releasing alkene was preferentially diazidated.[35]

The 1,2-diazide products can be readily reduced to the corresponding vicinal diamines using Staudinger reduction or catalytic hydrogenation. Notably, the different steric environments of the two azido groups in **2k** enabled chemoselective reduction to form β-azidoamide 5. The diazides could also be readily converted to bistriazoles or 1,2-dinitro compounds,[36] which are common structures in energetic materials.

Compared with our first-generation Mn-catalyzed alkene diazidation, the new protocol presents several practical advances. For example, replacing the transition metal catalyst with an organocatalyst and the protic acid (HOAc) with H_2O eliminates the generation of hazardous metal azides and hydrazoic acid. These features make the diazide synthesis safer and more amenable to practical applications. We conducted further experiments to exemplify the user friendliness of the protocol (Table 3). Using inexpensive Ni foam as the cathode instead of Pt only marginally decreased product yield (entry 2). Using carbon as both cathode and anode did not provide **2k** in appreciable amounts. To make the reaction system metal-free, we carried out electrolysis in a divided cell that completely separates the diazidation from the cathodic proton reduction on Pt (entry 3). The electrolysis was also successfully performed using commercial ElectraSyn 2.0[37] or AA batteries as the power source (entries 4 and 5). Electrolyte choice proved unimportant (entry 6). In fact, given the ionic nature of NaN_3, electrolysis in the absence of an additional electrolyte yielded **2k** quantitatively (entry 7). Finally, diazidation on a synthetically relevant scale resulted in a promising isolated yield of 69% (entry 8).

Aside from the radical pathway in our initial working mechanistic hypothesis (see Scheme 1B), two additional reaction pathways may be plausible to account for diazidation reactivity. Carbon-centered radical **I** may undergo single-electron oxidation, either directly on the anode or by CHAMPO[+], to generate the corresponding carbocation (**II**; Scheme 2A). The cation would subsequently react with N_3^- to form the diazide. Alternatively, azidooxygenated product 3 could be an intermediate en route to the diazide via oxidation and mesolytic cleavage[38] to form **II** (Scheme 2B).

Experimental evidence (Scheme 3) is consistent with our original mechanistic proposal in which the aminoxyl–N_3 adduct mediates the radical diazidation, whereas for certain types of substrates, carbocation pathway I also might operate. Reactions with radical clocks showed that cyclopropane 7 and bisallylamine **9/10** underwent radical-induced ring rupture or 5-*exo*-atrig cyclization, respectively. In all cases, no direct alkene diazidation was observed. In principle, upon radical ring opening or cyclization, the resultant carbon-centered radical could be further oxidized to the cation before nucleophilic azidation; however, these carbocations, either highly electron-deficient or at a primary carbon, would be rather unstable. We also carried out diazidation of amide **13**, which—if operating via a carbocation mechanism—would cyclize to furnish oxazoline **15**.[39] However, electrolysis produced diazide **14** cleanly as the only observable product. Together, these data strongly support the radical mechanism.

We further studied alkene substrates that would lead to resonance-stabilized carbocation intermediates (Scheme 3C) and observed radical-to-carbocation oxidation. For example, camphor-derived alkene **16** was converted to 11% diazide **17** in addition to 42% 1,3-

azidoalcohol **18** via carbocation rearrangement. We reasoned that the norbornyl structure selectively stabilizes carbocation (**II**) but not its radical precursor (**I**), thus favoring the oxidation of **I** to **II**. Notably, neither rearrangement-azidation (19) or direct 1,2-azidohy-droxylation products were observed. This result strongly supports the hypothesis that the alkene diazidation undergoes predominantly a radical pathway,[17b,40] whereas the azidohy-droxylation adopts a cationic pathway that triggers the rearrangement.[41] Furthermore, 4-methoxy-α-methylstyrene (**1g**) was converted to diazide **2g** (major) and azidoalcohol **20** (minor). A key finding from these experiments is that if a carbocation is formed, its capture by H_2O is inevitable. Importantly, the majority of the substrates we investigated (see Table 2) produced no appreciable amounts of azidoalcohol products. This piece of information lends further support for the radical mechanism involving N-oxyl-mediated azidyl transfer.

Finally, we conducted a control experiment using azidooxy-genated products 3g or 3k instead of the alkene as the substrate for electrolysis and observed no diazide formation. This result excluded the possibility that N-oxyl adducts are key intermediates in the alkene diazidation (see Scheme 2B).

Accordingly, we propose a CHAMPO–N_3-mediated electrocatalytic cycle (Scheme 2C). We previously showed that N-oxyl radicals trigger an inner-sphere oxidation pathway that substantially lowers the potential required for accessing $N_3^•$ from N_3^{-}[21]. In light of our new mechanistic information, we conclude that the CHAMPO–N_3 CTC plays two key roles: promoting the generation of free $N^•$ and mediating the second azidation through a putative radical group transfer event. Preliminary data suggest that the CTC is the resting state of the catalyst under a sufficient anodic potential. The first C–N_3 bond formation is slower than the second owing to the relatively slow, endergonic fragmentation of the CTC to CHAMPO and $N_3^•$. This rate difference allows the two distinct radical addition events to take place successively with high chemoselectivity toward diazidation over side pathways that unproductively consumes **I**. In this mechanistic hypothesis, the metal-like behavior of N-oxyl radicals in the alkene diazidation is particularly intriguing. Our ongoing efforts will be devoted to further evaluating the mechanistic proposal and using the knowledge to guide the discovery of other synthetically useful transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

REFERENCES

(1). (a)Renaud P; Sibi MP Radicals in Organic Synthesis; Wiley-VCH: Weinhein, 2001.(b)Yan M; Lo JC; Edwards JT; Baran PS Radicals: Reactive Intermediates with Translational Potential. J. Am. Chem. Soc 2016, 138, 12692. [PubMed: 27631602] (c)Ischay MA; Yoon TP Accessing the Synthetic Chemistry of Radical Ions. Eur. J. Org. Chem 2012, 2012, 3359.(d)Moeller KM Using Physical Organic Chemistry To Shape the Course of Electrochemical Reactions. Chem. Rev 2018, 118, 4817. [PubMed: 29498518]

(2). (a)Studer A; Curran DP Catalysis of Radical Reactions: A Radical Chemistry Perspective. Angew. Chem., Int. Ed 2016, 55, 58.(b)Skubi KL; Blum TR; Yoon TP Dual Catalysis Strategies in Photochemical Synthesis. Chem. Rev 2016, 116, 10035. [PubMed: 27109441] (c)Narayanam JMR; Stephenson CR Visible light photoredox catalysis: applications in organic synthesis. Chem. Soc. Rev 2011, 40, 102. [PubMed: 20532341] (d)Francke R; Little RD Redox catalysis in organic electrosyn-thesis: basic principles and recent developments. Chem. Soc. Rev 2014, 43, 2492. [PubMed: 24500279] (e)Yan M; Kawamata Y; Baran PS Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. Chem. Rev 2017, 117, 13230. [PubMed: 28991454] (f)Crossley SWM; Martinez RM; Obradors C; Shenvi RA Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. Chem. Rev 2016, 116, 8912. [PubMed: 27461578]

(3). (a)Bobbitt JM; Brückner C; Merbouh N Oxoammonium and Nitroxide-Catalyzed Oxidation of Alcohols. Org. React 2009, 74, 103.(b)Wertz S; Studer A Nitroxide-catalyzed transition-metal-free aerobic oxidation processes. Green Chem 2013, 15, 3116.(c)Leadbeater NE; Bobbitt JM TEMPO-Derived Oxoammonium Salts as Versatile Oxidizing Agents. Aldrichimica Acta 2014, 47, 65.

(4). Nutting JE; Rafiee MR; Stahl SS Tetramethylpiperidine N-Oxyl (TEMPO), Phthalimide N-Oxyl (PINO), and Related N-Oxyl Species: Electrochemical Properties and Their Use in Electrocatalytic Reactions. Chem. Rev 2018, 118, 4834. [PubMed: 29707945]

(5). (a)Qian X-Y; Li S-Q; Song J; Xu H-C TEMPO-Catalyzed Electrochemical C–H Thiolation: Synthesis of Benzothiazoles and Thiazolopyridines from Thioamides. ACS Catal 2017, 7, 2730. (b)Peterson BM; Lin S; Fors BP Electrochemically Controlled Cationic Polymerization of Vinyl Ethers. J. Am. Chem. Soc 2018, 140, 2076. [PubMed: 29385348] (c)Furukawa K; Shibuya M; Yamamoto Y Chemoselective Catalytic Oxidation of 1,2-Diols to a-Hydroxy Acids Controlled by TEMPO–ClO$_2$ Charge-Transfer Complex. Org. Lett 2015, 17, 2282. [PubMed: 25886211]

(6). For examples of stable TEMPO–X-type adducts formed via single-electron transfer, see: (a) Li Y.; Pouliot M; Vogler T; Renaud P; Studer A α-Aminoxylation of Ketones and β-Chloro-α-aminoxylation of Enones with TEMPO and Chlorocatecholborane. Org. Lett 2012, 14, 4474. [PubMed: 22900473] (b)Wang X; Ye Y; Zhang S; Feng J; Xu Y; Zhang Y; Wang J Copper-Catalyzed C(sp^3)–C(sp^3) Bond Formation Using a Hypervalent Iodine Reagent: An Efficient Allylic Trifluoromethylation. J. Am. Chem. Soc 2011, 133, 16410. [PubMed: 21936560]

(7). TEMPO has been used (stoichiometrically or catalytically) in lieu of transition metals for formal C−C cross coupling. See: (a) Murarka S; Studer A Transition Metal-Free TEMPO-Catalyzed Oxidative Cross- Coupling of Nitrones with Alkynyl-Grignard Reagents. Adv. Synth. Catal 2011, 353, 2708.(b)Maji MS; Murarka S; Studer A Transition-Metal-Free Sonogashira-Type Coupling of ortho-Substituted Aryl and Alkynyl Grignard Reagents by Using 2,2,6,6-Tetramethylpiperidine-N-oxyl Radical as an Oxidant. Org. Lett 2010, 12, 3878. [PubMed: 20704186]

(8). (a)For examples, see:Semmelhack MF; Chou CS; Cortes DA Nitroxyl-mediated electrooxidation of alcohols to aldehydes and ketones. J. Am. Chem. Soc 1983, 105, 4492.(b)Hoover J; Stahl S Highly Practical Copper(I)/TEMPO Catalyst System for Chemo-selective Aerobic Oxidation of Primary Alcohols. J. Am. Chem. Soc 2011, 133, 16901. [PubMed: 21861488] (c)Badalyan A; Stahl SS Cooperative electrocatalytic alcohol oxidation with electron-proton-transfer mediators. Nature 2016, 535, 406–410. [PubMed: 27350245] (d)Liu R; Liang X; Dong C; Hu X Transition-Metal-Free: A Highly Efficient Catalytic Aerobic Alcohol Oxidation Process. J. Am. Chem. Soc 2004, 126, 4112. [PubMed: 15053593] (e)Shibuya M; Osada Y; Sasano Y; Tomizawa M; Iwabuchi Y Highly Efficient, Organocatalytic Aerobic Alcohol Oxidation. J. Am. Chem. Soc 2011, 133, 6497. [PubMed: 21473575] (f)Shibuya M; Doi R; Shibuta T; Uesugi S; Iwabuchi Y

Organocatalytic One-Pot Oxidative Cleavage of Terminal Diols to Dehomologated Carboxylic Acids. Org. Lett 2012, 14, 5006. [PubMed: 22991924] (g)Hickey D; McCammant M; Giroud F; Sigman M; Minteer S Hybrid Enzymatic and Organic Electrocatalytic Cascade for the Complete Oxidation of Glycerol. J. Am. Chem. Soc 2014, 136, 15917. [PubMed: 25350383] (h)Zhao M; Li J; Mano E; Song Z; Tschaen D; Grabowski E; Reider P Oxidation of Primary Alcohols to Carboxylic Acids with Sodium Chlorite Catalyzed by TEMPO and Bleach. J. Org. Chem 1999, 64, 2564.See also ref 5c. Stoichiometric oxidation: (i) Bailey WF; Bobbitt JM; Wiberg KB Mechanism of the Oxidation of Alcohols by Oxoammonium Cations. J. Org. Chem 2007, 72, 4504. [PubMed: 17488040] (j)Ganem B Biological spin labels as organic reagents. Oxidation of alcohols to carbonyl compounds using nitroxyls. J. Org. Chem 1975, 40, 1998.(k)Bobbitt JM Oxoammonium Salts. 4-Acetylamino-2,2,6,6-tetramethylpiper-idine-1-oxoammonium Perchlorate: A Stable and Convenient Reagent for the Oxidation of Alcohols. Silica Gel Catalysis. J. Org. Chem 1998, 63, 9367.

(9). For examples, see: (a) Miles K; Abrams M; Landis C; Stahl S KetoABNO/NOx Cocatalytic Aerobic Oxidation of Aldehydes to Carboxylic Acids and Access to α-Chiral Carboxylic Acids via Sequential Asymmetric Hydroformylation/Oxidation. Org. Lett 2016, 18, 3590. [PubMed: 27410397] (b)Rafiee M; Konz Z; Graaf M; Koolman H; Stahl S Electrochemical Oxidation of Alcohols and Aldehydes to Carboxylic Acids Catalyzed by 4-Acetamido-TEMPO: An Alternative to "Anelli" and "Pinnick" Oxidations. ACS Catal 2018, 8, 6738.

(10). For a review, see: (a) Bartelson A; Lambert K; Bobbitt J; Bailey W Recent Developments in the Nitroxide-Catalyzed Oxidation of Amines: Preparation of Imines and Nitriles. ChemCatChem 2016, 8, 3421–3430.For examples, see: (b) Lennox A; Goes S; Webster M; Koolman H; Djuric S; Stahl S Electrochemical Aminoxyl-Mediated α-Cyanation of Secondary Piperidines for Pharmaceutical Building Block Diversification. J. Am. Chem. Soc 2018, 140, 11227. [PubMed: 30141925] (c)Semmelhack MF; Schmid CR Nitroxyl-mediated electro-oxidation of amines to nitriles and carbonyl compounds. J. Am. Chem. Soc 1983, 105, 6732.(d)Kim J; Stahl S Cu/Nitroxyl-Catalyzed Aerobic Oxidation of Primary Amines into Nitriles at Room Temperature. ACS Catal 2013, 3, 1652. [PubMed: 24015373] (e)Sonobe T; Oisaki K; Kanai M Catalytic aerobic production of imines en route to mild, green, and concise derivatizations of amines. Chem. Sci 2012, 3, 3249.(f)Wu Y; Yi H; Lei A Electrochemical Acceptorless Dehydrogenation of N-Heterocycles Utilizing TEMPO as Organo-Electrocatalyst. ACS Catal 2018, 8, 1192. (g)Romero NA; Margrey KA; Tay NE; Nicewicz DA Site-selective arene C-H amination via photoredox catalysis. Science 2015, 349, 1326. [PubMed: 26383949] (h)Somfai P; Yu L Synthesis of α-Keto Amides by a Pyrrolidine/TEMPO-Mediated Oxidation of α-Keto Amines. Synlett 2016, 27, 2587.(i)Wertz S; Studer A Metal-Free 2,2,6,6-Tetramethylpiperidin-1-yloxy Radical (TEMPO) Catalyzed Aerobic Oxidation of Hydroxylamines and Alkoxyamines to Oximes and Oxime Ethers. Helv. Chim. Acta 2012, 95, 1758.

(11). (a)Tarantino KT; Miller DC; Callon TA; Knowles RR Bond-Weakening Catalysis: Conjugate Aminations Enabled by the Soft Homolysis of Strong N–H Bonds. J. Am. Chem. Soc 2015, 137, 6440. [PubMed: 25945955] See also refs 5a, b. Stoichiometric reaction: (b) Xu F; Zhu L; Zhu S; Yan X; Xu H-C Electrochemical Intramolecular Amino-oxygenation of Unactivated Alkenes. Chem. - Eur. J 2014, 20, 12740. [PubMed: 25145684]

(12). Griesser M; Shah R; Van Kessel TA; Zilka O; Haidasz AE; Pratt AD The Catalytic Reaction of Nitroxides with Peroxyl Radicals and Its Relevance to Their Cytoprotective Properties. J. Am. Chem. Soc 2018, 140, 3798. [PubMed: 29451786]

(13). Fu N; Sauer G; Saha A; Loo A; Lin S Metal-catalyzed electrochemical diazidation of alkenes. Science 2017, 357, 575. [PubMed: 28798126]

(14). Minisci F Free-radical additions to olefins in the presence of redox systems. Acc. Chem. Res 1975, 8, 165.

(15). (a)Magnus P; Roe MB; Hulme C New trialkylsilyl enol ether chemistry: direct 1,2-bis-azidonation of triisopropylsilyl enol ethers: an azido-radical addition process promoted by TEMPO. J. Chem. Soc., Chem. Commun 1995, 263.(b)Magnus P; Lacour J; Evans PA; Roe MB; Hulme C Hypervalent Iodine Chemistry: New Oxidation Reactions Using the Iodosylbenzene –Trimethylsilyl Azide Reagent Combination. Direct α- and β-Azido Functionalization of Triisopropylsilyl Enol Ethers. J. Am. Chem. Soc 1996, 118, 3406.

(16). Snider BB; Lin H An Improved Procedure for the Conversion of Alkenes and Glycals to 1,2-Diazides Using Mn(OAc)3· 2H2O in Acetonitrile Containing Trifluoroacetic Acid. Synth. Commun 1998, 28, 1913.

(17). (a)Yuan YA; Lu DF; Chen YR; Xu H Iron-Catalyzed Direct Diazidation for a Broad Range of Olefins. Angew. Chem., Int. Ed 2016, 55, 534.(b)Shen S-J; Zhu C-L; Lu D-F; Xu H Iron-Catalyzed Direct Olefin Diazidation via Peroxyester Activation Promoted by Nitrogen-Based Ligands. ACS Catal 2018, 8, 4473. [PubMed: 29785320]

(18). For examples, see: (a) Fumagalli G; Rabet PTG; Boyd S; Greaney MF Three-Component Azidation of Styrene-Type Double Bonds: Light-Switchable Behavior of a Copper Photoredox Catalyst. Angew. Chem., Int. Ed 2015, 54, 11481.(b)Lu M-Z; Wang C-Q; Loh T-P Copper-Catalyzed Vicinal Oxyazidation and Diazidation of Styrenes under Mild Conditions: Access to Alkyl Azides. Org. Lett 2015, 17, 6110. [PubMed: 26651361] (c)Peng H; Yuan Z; Chen P; Liu G Palladium-Catalyzed Intermolecular Oxidative Diazidation of Alkenes. Chin. J. Chem 2017, 35, 876.(d)Fristad WE; Brandvold TA; Peterson JR; Thompson SR Conversion of alkenes to 1,2-diazides and 1,2-diamines. J. Org. Chem 1985, 50, 3647.(e)Moriarty RM; Khosrowshahi JS A versatile synthesis of vicinal diazides using hypervalent iodine. Tetrahedron Lett 1986, 27, 2809.Related azidoamination: (f) Shen K; Wang Q Copper-Catalyzed Alkene Aminoazidation as a Rapid Entry to 1,2-Diamines and Installation of an Azide Reporter onto Azaheterocycles. J. Am. Chem. Soc 2017, 139, 13110. [PubMed: 28825822]

(19). (a)Lucet D; Le Gall T; Mioskowski C The Chemistry of Vicinal Diamines. Angew. Chem., Int. Ed 1998, 37, 2580.(b)Chemler SR; Fuller PH Heterocycle synthesis by copper facilitated addition of heteroatoms to alkenes, alkynes and arenes. Chem. Soc. Rev 2007, 36, 1153. [PubMed: 17576482]

(20). (a)Siu JC; Sauer GS; Saha A; Macey RL; Fu N; Chauvire T; Lancaster KL; Lin S Electrochemical Azidooxygenation of Alkenes Mediated by a TEMPO–N3 Charge-Transfer Complex. J. Am. Chem. Soc 2018, 140, 12511. [PubMed: 30160949] For related seminal work on alkene azidooxygenation using a nonelectrochemical method, see: (b) Zhang B; Studer A Stereoselective Radical Azidooxygenation of Alkenes. Org. Lett 2013, 15, 4548. [PubMed: 23930944]

(21). The potential for azidyl formation is lowered by ca. 200 mV. See ref 20a.

(22). This corresponds to ca. 0.7 V initial anodic potential ($E_{a,i}$) vs Fc/Fc$^+$ (ferrocene/ferrocenium).

(23). Studer A; Harms K; Knoop C; Müller C; Schulte T New Sterically Hindered Nitroxides for the Living Free Radical Polymerization: X-ray Structure of an a-H-Bearing Nitroxide. Macromolecules 2004, 37, 27.

(24). Hickey D; Schiedler D; Matanovic I; Doan P; Atanassov P; Minteer S; Sigman M Predicting Electrocatalytic Properties: Modeling Structure–Activity Relationships of Nitroxyl Radicals. J. Am. Chem. Soc 2015, 137, 16179. [PubMed: 26635089]

(25). (a)Gerken J; Pang Y; Lauber M; Stahl S Structural Effects on the pH-Dependent Redox Properties of Organic Nitroxyls: Pourbaix Diagrams for TEMPO, ABNO, and Three TEMPO Analogs. J. Org. Chem 2018, 83, 7323. [PubMed: 29182282] (b)Rafiee M; Miles KC; Stahl SS Electrocatalytic Alcohol Oxidation with TEMPO and Bicyclic Nitroxyl Derivatives: Driving Force Trumps Steric Effects. J. Am. Chem. Soc 2015, 137, 14751. [PubMed: 26505317]

(26). For a full list of catalysts surveyed, see SI.

(27). (a)Ma Z; Huang Q; Bobbitt JM Oxoammonium salts. 5. A new synthesis of hindered piperidines leading to unsymmetrical TEMPO-type nitroxides. Synthesis and enantioselective oxidations with chiral nitroxides and chiral oxoammonium salts. J. Org. Chem 1993, 58, 4837.(b)Moad G; Rizzardo E; Solomon DH The reaction of acyl peroxides with 2,2,6,6-tetramethylpiperidinyl-1-oxy. Tetrahedron Lett 1981, 22, 1165.

(28). This strategy has been employed in nitroxide-mediated polymerization (NMP) to reverse N-oxyl trapping and thus decrease the temperature needed to maintain chain growth. See ref 23.

(29). In addition to increased steric encumbrance, CHAMPO also has fewer β-H's. The cyclohexane motifs could also stabilize the CHAMPO$^+$ ion through hyperconjugation. See ref 27a.

(30). Haugland M; El-Sagheer A; Porter R; Peña J; Brown T; Anderson E; Lovett J 2′-Alkynylnucleotides: A Sequence- and Spin Label-Flexible Strategy for EPR Spectroscopy in

DNA. J. Am. Chem. Soc 2016, 138, 9069 See also ref 26a. CHAMPO's $E_{1/2}$ = +0.29 V. [PubMed: 27409454]

(31). When the electrolysis was left continued for 12 h instead, the color remained persisted in the end of the reaction.

(32). Schafer H Oxidative Addition of the Azide Ion to Olefins. A Simple Route to Diamines. Angew. Chem., Int. Ed. Engl 1970, 9, 158.

(33). For instance, CAN gave < 10% diazide in addition to 42% azidoalcohol among other byproducts; K2S2O7 or PhIO led to minimal conversion of the alkene.

(34). Azidooxygenation byproducts were observed with TEMPO or ACT as the catalyst.

(35). Workentin MS; Wagner BD; Lusztyk J; Wayner DDM A Molecular Lock. J. Am. Chem. Soc 1995, 117, 119.

(36). For bistriazole synthesis via dipolar cycloaddition, see SI; for dinitroalkane synthesis, see: Carmeli M; Rozen S Oxidation of Azides by the HOF·CH3CN: A Novel Synthesis of Nitro Compounds. J. Org. Chem 2006, 71, 4585. [PubMed: 16749792]

(37). (a)Yan M; Kawamata Y; Baran PS Synthetic Organic Electrochemistry: Calling All Engineers. Angew. Chem., Int. Ed 2018, 57, 4149.(b)Fu N; Sauer GS; Lin S A general, electrocatalytic approach to the synthesis of vicinal diamines. Nat. Protoc 2018, 13, 1725. [PubMed: 30072721]

(38). (a)Zhu Q; Gentry EC; Knowles RR Catalytic Carbocation Generation Enabled by the Mesolytic Cleavage of Alkoxyamine Radical Cations. Angew. Chem., Int. Ed 2016, 55, 9969.(b)Gentry EC; Rono LJ; Hale ME; Matsuura R; Knowles RR Enantioselective Synthesis of Pyrroloindolines via Noncovalent Stabilization of Indole Radical Cations and Applications to the Synthesis of Alkaloid Natural Products. J. Am. Chem. Soc 2018, 140, 3394. [PubMed: 29432006] (c)O'Brya G; Braslau R Terminal Functionalization of Polymers via Single Electron Oxidation of N-Alkoxyamines. Macromolecules 2006, 39, 9010.

(39). Xiong P; Long H; Song J; Wang Y; Li J-F; Xu H-CJ *Am. Chem. Soc.* Electrochemically Enabled Carbohydroxylation of Alkenes with H2O and Organotrifluoroborates. J. Am. Chem. Soc 2018, 140, 16387.

(40). Legnani L; Prina-Cerai G; Delcaillau T; Willems S; Morandi B Efficient access to unprotected primary amines by iron-catalyzed aminochlorination of alkenes. Science 2018, 362, 434. [PubMed: 30361368]

(41). Legnani L; Morandi B Direct Catalytic Synthesis of Unprotected 2-Amino-1-Phenylethanols from Alkenes by Using Iron(**II**) Phthalocyanine. Angew. Chem., Int. Ed 2016, 55, 2248.
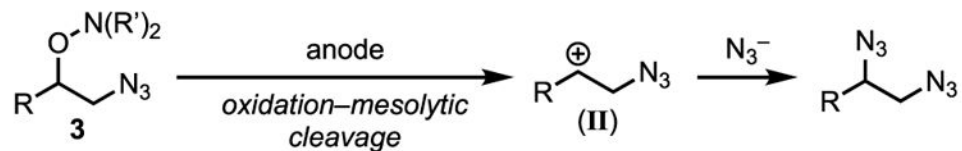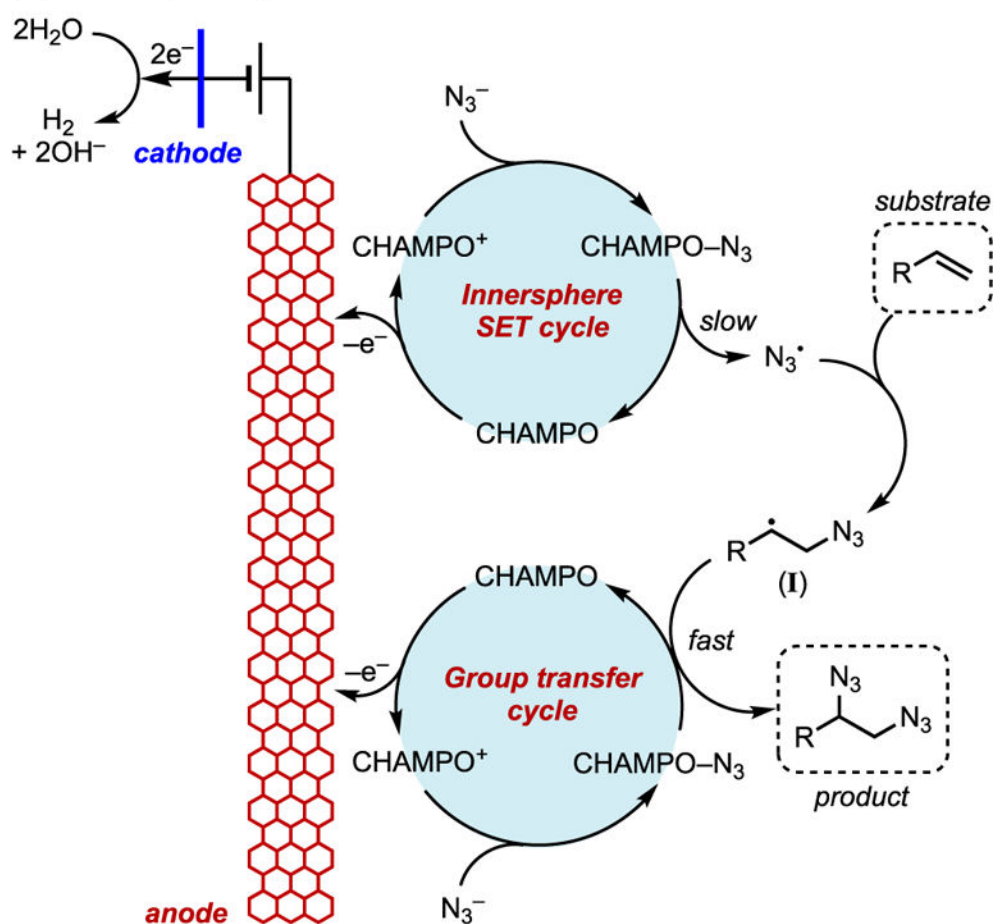
(A) Background: Electrochemical diazidation and azidooxygenation

(B) Working mechanistic hypothesis for aminoxyl (NO•)-catalyzed alkene diazidation
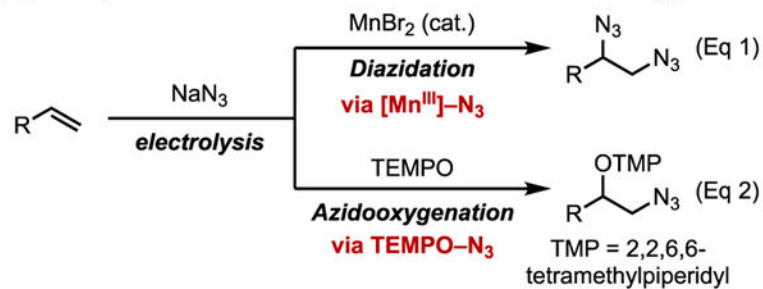
For seminal developments in chemical diazidation, see refs. 14–18.
For seminal developments in chemical azidooxygenation, see ref. 20b.

TMP = 2,2,6,6-tetramethylpiperidyl
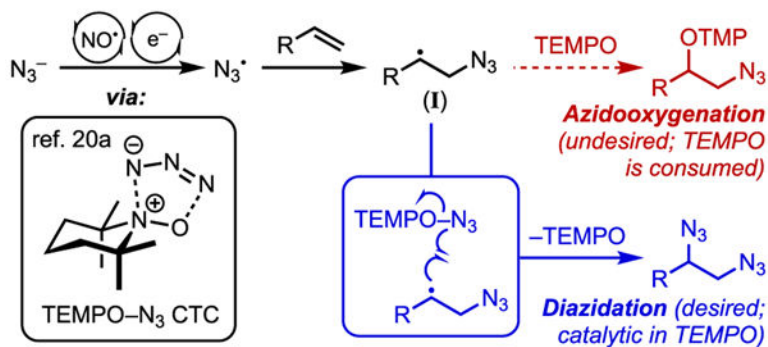
Scheme 1.
Mechanistic Hypothesis for *N*-Oxyl-Catalyzed Alkene Diazidation

(A) *Cationic pathway I: Direct oxidation of carbon-centered radical **I***
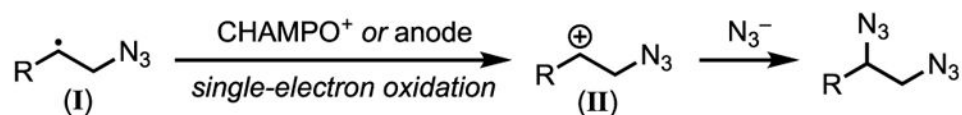
(B) *Cationic pathway II: Oxidation of the azidooxygenation product **3***

(C) *Radical pathway*

Scheme 2.
Plausible Mechanistic Pathways

(A) *Radical clocks:*

8, 61% (*E:Z* >20:1)

9 (R = H)
10 (R = Me)

11 (R = H), 17%, dr = 3:1
(76% **9** recovered)
12 (R = Me), 85%, dr = 1:2

(B) *Carbocation trap:*

14, 71%   **15, not observed**

(C) *Stabilized carbocations:*

16   **17**, 11% (dr = 2:1)   **18**, 42%   **19, not observed**

1g   **2g**, 79%   **20**, 16%

(D) *Mesolytic cleavage control:*

3g or **3k**

2g or **2k, not observed**
(>85% **3g** or **3k** recovered)
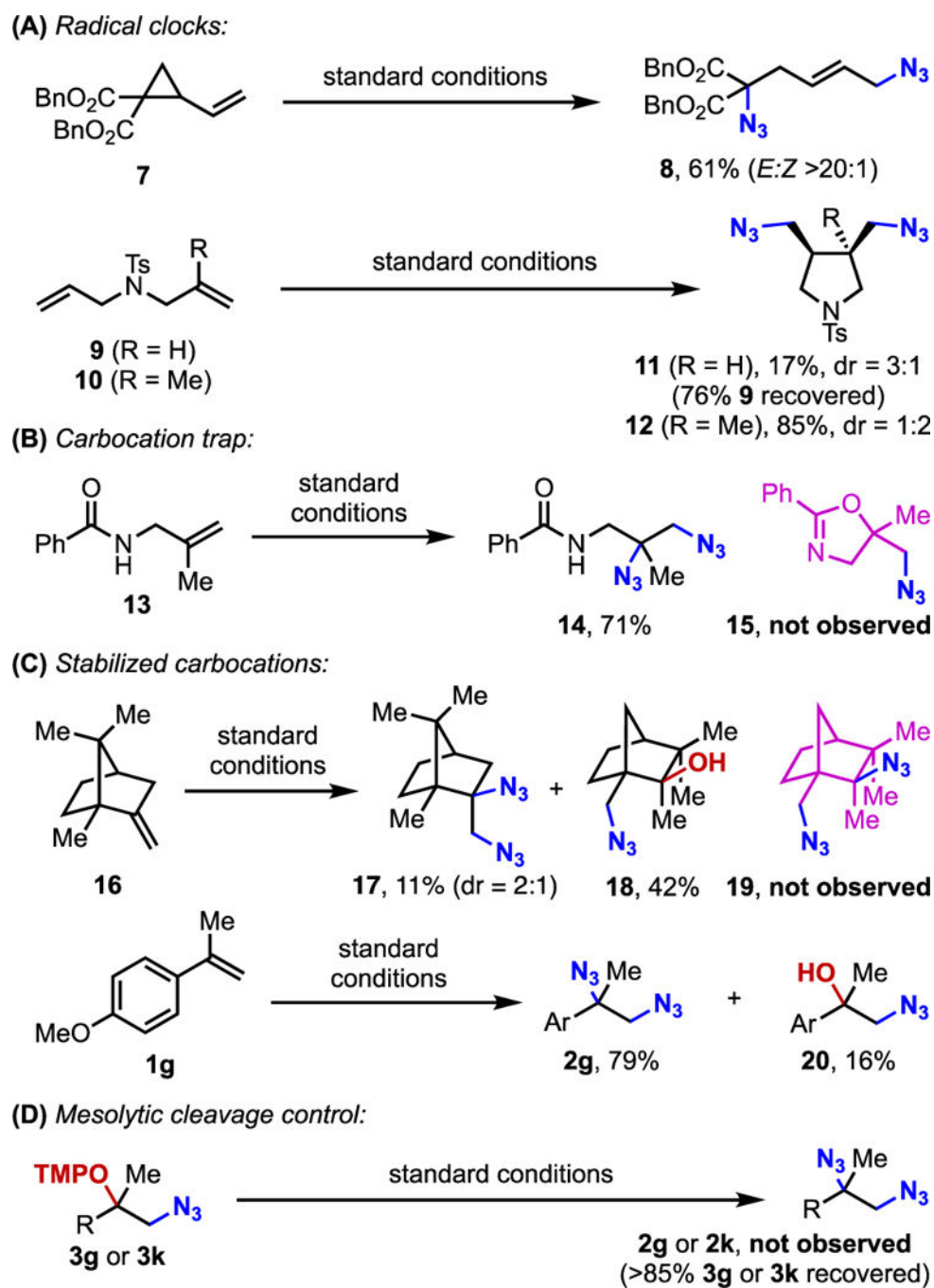
Scheme 3.
Mechanistic Probes[a]
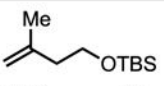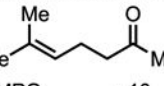
Table 1.

Reaction Optimization[a]
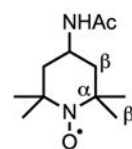
^{a}Conditions: **1** (0.2 mmol, 1 equiv), NaN$_3$ (3 equiv; 1.5 equiv per C−N bond), LiClO$_4$ (1.8 equiv), MeCN/H$_2$O (3.8 mL, 12:1); cell voltage (E_{cell}) = 2.7 V; yields determined by ^{1}H NMR. ^{b}With 1 equiv TEMPO. ^{c}Isolated yield.

Table 2.

Substrate Scope[a]

Table 3.

Optimization of the Electrolysis Setup[a]

entry	variation from "standard conditions"	yield (%)
1	none	>99
2	Ni(−) instead of Pt(−)	92
3	divided cell, constant current of 8 mA	81
4	ElectraSyn 2.0 as power source, 0.3 mmol **1k**	82
5	AA batteries (×2) as power source	89
6	using TBAPF$_6$ instead of LiClO$_4$	95
7	no LiClO$_4$, E_{cell} = 3.4 V[b]	>99
8	1 mmol scale	69[c]

[a]Reaction conditions: see Table 1, entry 6.

[b]A higher cell voltage is applied to compensate for the increased solution resistance between cathode and anode.

[c]Isolated yield; reaction was carried out at a higher substrate concentration (see SI).