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

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Supporting Information Placeholder

**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<sub>3</sub><sup>•</sup>, 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.<sup>1</sup> 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.<sup>2</sup> 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<sup>3</sup> and electrochemical techniques,<sup>4</sup> which has given rise to synthetically useful processes for small-molecule and polymer syntheses.

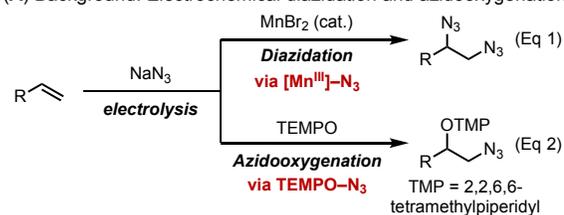
Despite significant advances, we contend that the scope of TEMPO chemistry remains to be fully explored. TEMPO and related *N*-oxyl radicals can undergo one-electron redox processes, granting access to three discrete oxidation states.<sup>4</sup> This feature distinguishes these radicals from common 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.<sup>5,6</sup> Nevertheless, the systematic use of the “metallic” character of *N*-oxyls in catalyst development remains meager.<sup>7</sup> To date, reactions catalyzed by *N*-oxyls are largely confined to oxidations of alcohols,<sup>8</sup> aldehydes,<sup>9</sup> amines,<sup>10</sup> (thio)amides,<sup>11</sup> and peroxy radicals.<sup>12</sup> 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).<sup>13</sup> This work was built on foundational contributions by Minisci,<sup>14</sup> Magnus,<sup>15</sup> Snider,<sup>16</sup> Xu,<sup>17</sup> and others<sup>18</sup> 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.<sup>19</sup> 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<sub>3</sub><sup>•</sup>. Although our electrochemical protocol<sup>13</sup> 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.

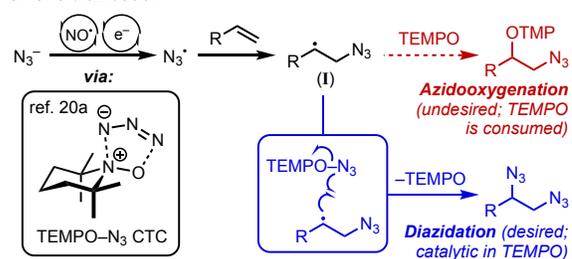
**Scheme 1.** Mechanistic hypothesis for *N*-oxyl-catalyzed alkene diazidation

(A) Background: Electrochemical diazidation and azidoxyoxygenation



For seminal developments in chemical diazidation, see refs. 14–18.  
For seminal developments in chemical azidoxyoxygenation, see ref. 20b.

(B) Working mechanistic hypothesis for aminoxyl (NO<sup>•</sup>)-catalyzed alkene diazidation



While studying the electrochemical alkene diazidation, we discovered a new electrochemical method for the

azidoxygenation of alkenes mediated by TEMPO (Scheme 1A, Eq 2).<sup>20</sup> 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  $N_3^\bullet$ .<sup>21</sup> This process is mediated by a metastable charge-transfer complex (CTC) formed between anodically generated TEMPO<sup>+</sup> and  $N_3^-$ . Upon azidyl addition, the nascent carbon-centered radical **I** rapidly combines with TEMPO to deliver the masked vicinal aminoalcohol (Scheme 1B, black-red pathway).

We envisioned that the TEMPO-consuming azidoxygenation 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, black-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 azidoxygenation, 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 azidoxygenation. For example, the electrolysis of alkene **1a**,  $NaN_3$ , and 1 equiv TEMPO in MeCN/H<sub>2</sub>O at a cell voltage of 2.7 V<sup>22</sup> 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 azidoxygenation 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 minutes as a result of TEMPO depletion. This visual indicator thus provided a convenient readout for reaction optimization.

**Table 1.** Reaction optimization<sup>a</sup>

Entry	Catalyst	T (°C)	Yield (%)
1 <sup>b</sup>	TEMPO	22	36
2	TEMPO	22	11
3	TEMPO	0	46
4	TEMPO	-10	61
5	ACT	-10	71
6	CHAMPO	-10	97 <sup>c</sup>
7	none	-10	0
8	TEMPO	-10	47
9	ACT	-10	68
10	CHAMPO	-10	87 <sup>c</sup>

<sup>a</sup>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<sub>2</sub>O (3.8 mL, 12:1); cell voltage ( $E_{cell}$ ) = 2.7 V; yields determined by <sup>1</sup>H NMR. <sup>b</sup>With 1 equiv TEMPO. <sup>c</sup>Isolated yield.

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.<sup>23</sup> 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, 4). However, the color of the CTC decayed after 2 h with concomitant formation of **3a** (ca. 5%).

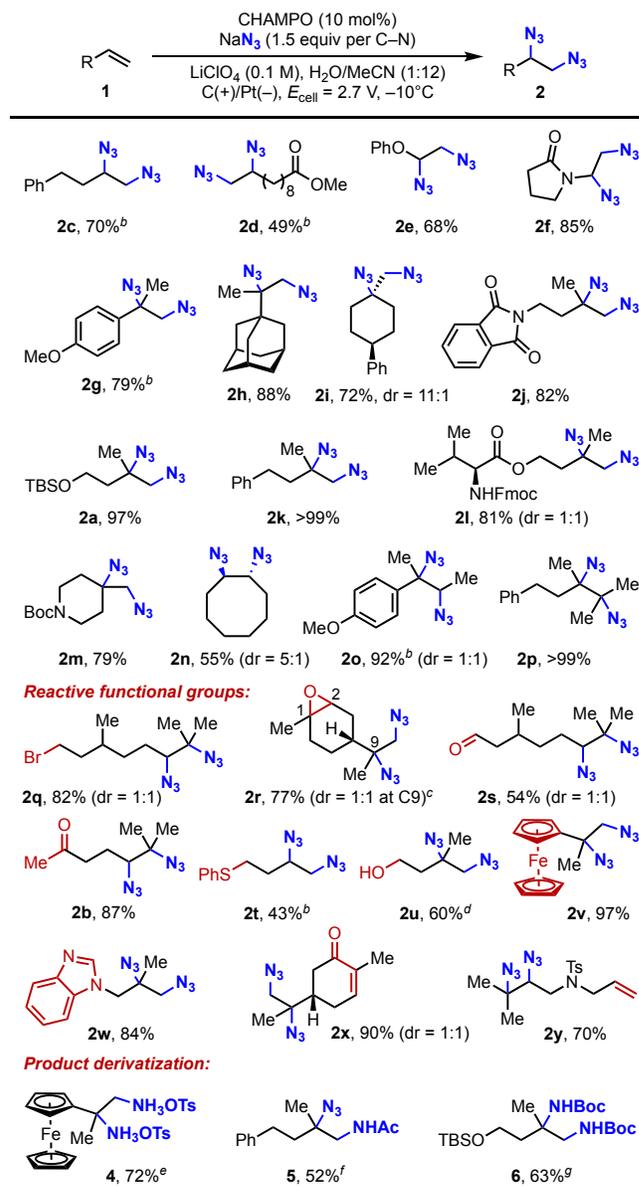
Studies by Bobbitt,<sup>8k</sup> Minter/Sigman<sup>24</sup>, and Stahl<sup>25</sup> showed that the distal C4 substituent of the aminoxyl has a profound influence on its reactivity in alcohol oxidation. Accordingly, we surveyed various catalysts<sup>26</sup> and found that 4-acetamido-TEMPO (ACT) proved the most promising, furnishing 71% **2a** and <5% **3a** (entry 4). However, the CTC decayed after ca. 3 h. We hypothesized that catalyst degradation could also occur via  $\beta$ -H<sup>+</sup> elimination of the corresponding oxoammonium ion<sup>27</sup> 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 azidoxygenation<sup>28</sup> and  $\beta$ -elimination.<sup>29</sup> Accordingly, we synthesized cyclohexane-substituted (4-acetamidopiperidin-1-yl)oxyl (CHAMPO).<sup>27,30</sup> 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).<sup>31</sup> Diazide **2a** was obtained in 97% isolated yield with complete elimination of the *N*-oxyl trapping product (entry 5). Importantly, exclusion of catalyst led to olefin consumption but negligible diazide formation (entry 6).<sup>32</sup> In addition, common single-electron oxidants in lieu of electricity did not provide appreciable diazide.<sup>33</sup> 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 7–9).

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 (**2c–p**). Unactivated monosubstituted alkenes were less reactive toward  $N_3^\bullet$  addition and more prone to azidoxygenation due to reduced steric hindrance.<sup>20a,34</sup> 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 (**2q–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.<sup>35</sup>

**Table 2.** Substrate scope<sup>a</sup>



<sup>a</sup>Conditions: **1** (0.2 mmol, 1 equiv), CHAMPO (10 mol%),  $NaN_3$  (3 equiv),  $LiClO_4$  (1.8 equiv),  $MeCN/H_2O$  (3.8 mL, 12:1). <sup>b</sup>15 mol% CHAMPO. <sup>c</sup>Limonene-1,2-oxide (**1r**) was purchased as a pair of diastereomers at C1,2. <sup>d</sup>Determined by <sup>1</sup>H NMR owing to the volatility of the product. <sup>e</sup>Conditions: **2v**,  $PPh_3$ ,  $H_2O/THF$ , reflux; then *p*TSA. <sup>f</sup>Conditions: **2k**,  $PPh_3$ ,  $H_2O/THF$ , reflux; then  $Ac_2O$ ,  $NEt_3$ , DCM, 0 °C. <sup>g</sup>Conditions: **2a**,  $H_2$ , Pd/C, ETOAc,  $Boc_2O$ .

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  $\beta$ -azidoamide **5**. The diazides could also be readily converted to bistriazoles or 1,2-dinitro compounds,<sup>36</sup> 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<sup>37</sup> or AA batteries as the power source (entries 4, 5). Electrolyte choice proved unimportant (entry 6). In fact, given the ionic nature of NaN<sub>3</sub>, 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).

**Table 3.** Optimization of the electrolysis setup<sup>a</sup>

"Standard conditions":  
CHAMPO (10 mol%)  
NaN<sub>3</sub> (1.5 equiv per C–N)

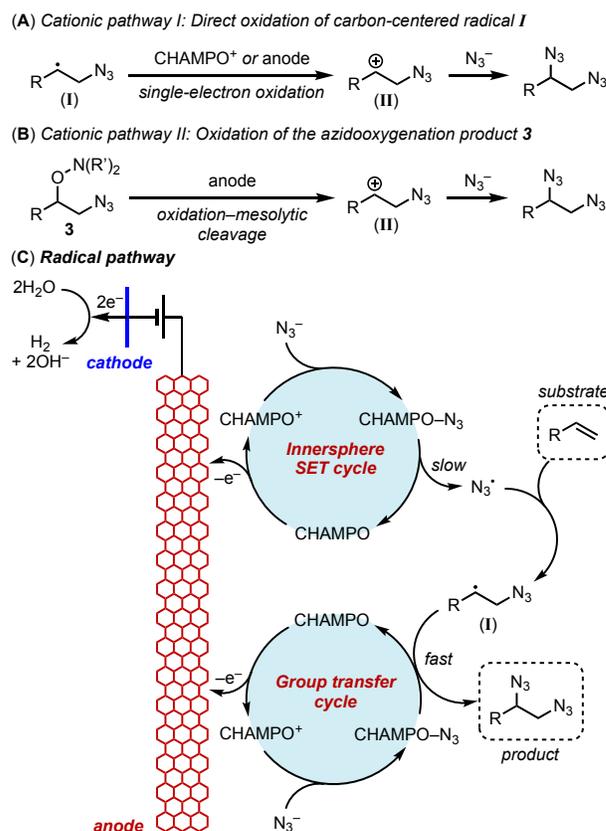
LiClO<sub>4</sub> (0.1 M), MeCN/H<sub>2</sub>O (12:1)  
C(+)/Pt(–), E<sub>cell</sub> = 2.7 V, –10 °C

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 <b>1k</b>	82
5	AA batteries (x2) as power source	89
6	Using TBAPF <sub>6</sub> instead of LiClO <sub>4</sub>	95
7	No LiClO <sub>4</sub> , E <sub>cell</sub> = 3.4 V <sup>b</sup>	>99
8	1 mmol scale	69 <sup>c</sup>

<sup>a</sup>Reaction conditions: see Table 1, entry 5. <sup>b</sup>A higher cell voltage is applied to compensate for the increased solution resistance between cathode and anode. <sup>c</sup>Isolated yield; reaction was carried out at a higher substrate concentration (see SI);

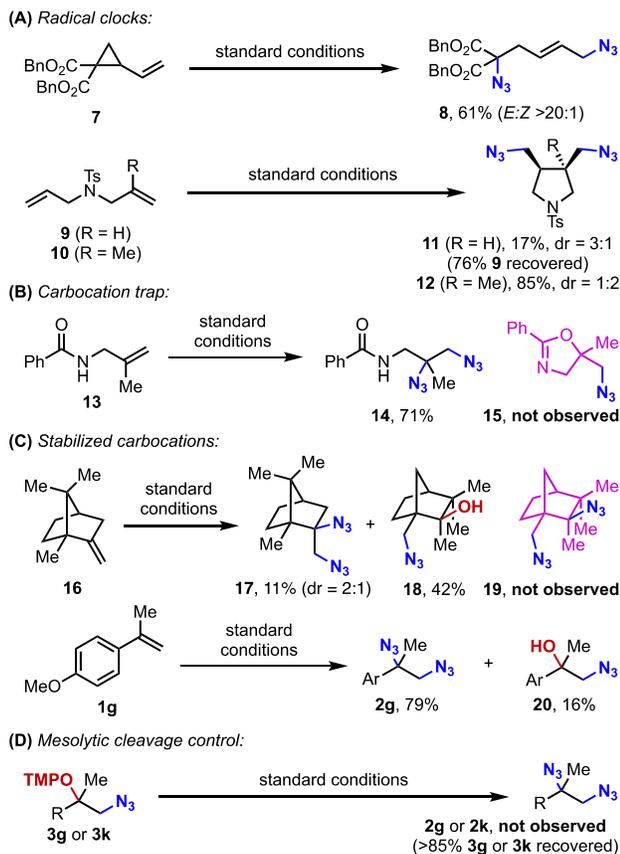
Aside from the radical pathway in our initial working mechanistic hypothesis (see Scheme 1B), two additional reaction pathways may be plausible to account for diazidation reactivity. Carbon-centered radical **I** may undergo single-electron oxidation, either directly on the anode or by CHAMPO<sup>+</sup>,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

**Scheme 2.** Plausible mechanistic pathways



Experimental evidence (Scheme 3) is consistent with our original mechanistic proposal in which the aminoxyl–N<sub>3</sub> 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*-trig 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**.<sup>39</sup> However, electrolysis produced diazide **14** cleanly as the only observable product. Together, these data strongly support the radical mechanism.

**Scheme 3.** Mechanistic probes. Structures in purple are expected products if the second C–N<sub>3</sub> formation were via a cationic pathway.



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-azidoalcohol products were observed. This result strongly supports the hypothesis that the alkene diazidation undergoes predominantly a radical pathway,<sup>17b,40</sup> whereas the azidoalcohol adopts a cationic pathway that triggers the rearrangement.<sup>41</sup> Furthermore, 4-methoxy- $\alpha$ -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<sub>2</sub>O 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 azidoxygenated product **21** 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*<sub>3</sub>-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*<sub>3</sub><sup>•</sup> from *N*<sub>3</sub><sup>-</sup>.<sup>21</sup> In light of our new mechanistic information, we conclude that the CHAMPO-*N*<sub>3</sub> CTC plays two key roles—promoting the generation of free *N*<sub>3</sub><sup>•</sup> 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*<sub>3</sub> bond formation is slower than the second owing to the relatively slow, endergonic fragmentation of the CTC to CHAMPO and *N*<sub>3</sub><sup>•</sup>. 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.

#### ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website, including experimental procedures and characterization data (PDF) and crystallographic data for CHAMPO (CCDC1881714) (CIF).

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##### Notes

The authors declare no competing financial interests.

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