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Manganese-Catalyzed Oxidative Azidation of C(sp^3)-H Bonds under Electrophotocatalytic Conditions

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Supporting Information Placeholder

ABSTRACT: The selective installation of azide groups into C(sp^3)-H bonds is a priority research topic in organic synthesis, particularly in pharmaceutical discovery and late-stage diversification. Herein, we demonstrate a generalized manganese-catalyzed oxidative azidation methodology of C(sp^3)-H bonds using nucleophilic NaN_3 as an azide source under electrophotocatalytic conditions. This approach allows us to perform the reaction without the necessity of adding an excess of the substrate and successfully avoiding the use of stoichiometric chemical oxidants such as iodine(III) reagent or NFSI. A series of tertiary and secondary benzylic C(sp^3)-H, aliphatic C(sp^3)-H, and drug-molecules-based C(sp^3)-H bonds containing in substrates are well tolerated under our protocol. The simultaneous gram-scale synthesis and the ease of transformation of azide to amine collectively advocate for the potential application in the preparative synthesis. Good reactivity of tertiary benzylic C(sp^3)-H bond and selectivity of tertiary aliphatic C(sp^3)-H bond containing in substrates to incorporate nitrogen-based functionality at tertiary alkyl group also provide opportunities to manipulate numerous potential medicinal candidates. We anticipate our synthetic protocol, consisting of metal catalysis, electrochemistry and photochemistry, would provide a new sustainable option to execute challenging organic synthetic transformations.

INTRODUCTION

The development of new and selective catalytic functionalization of readily available and abundant hydrocarbons remains a crucial goal in the organic synthesis due to their relatively lower intrinsic reactivity. The functionalization of C(sp^3)-H bonds, widespread in the most abundant and inexpensive chemical feedstock, to produce the value-added chemicals is not only significant in organic chemistry but also yet to be fully explored. Among all, the development of efficient strategies to install N-functional group on C(sp^3)-H bonds,[1] is crucial in pharma-industry, whose late-stage functionalization to gain rapid access to complex molecules from the simplest feedstock highlights the significance. For instance, typical C(sp^3)-H amination reactions are vastly dominated by 'nitrene insertion' strategy, which usually relies upon the use of stoichiometric (thus, waste generating) iodine(III) reagent.[2] To overcome this limitation, electroorganic synthesis is an ideal approach to deal with 'intractable' synthetic challenges with lesser waste generation via the utilization of electron as an oxidant or reductant.[3] However, C(sp^3)-H amination under electrochemical conditions usually follows the CDC (cross-dehydrogenative coupling) reaction mode: the carbon cation is attacked by a nucleophile,[4] while the reported substrates for electrochemical intermolecular C(sp^3)-H amination are mainly concentrated on the C(sp^3)-H bonds adjacent to N and O atom or special benzyl C(sp^3)-H bonds, and thus, arguably limiting its application in biomedicine.

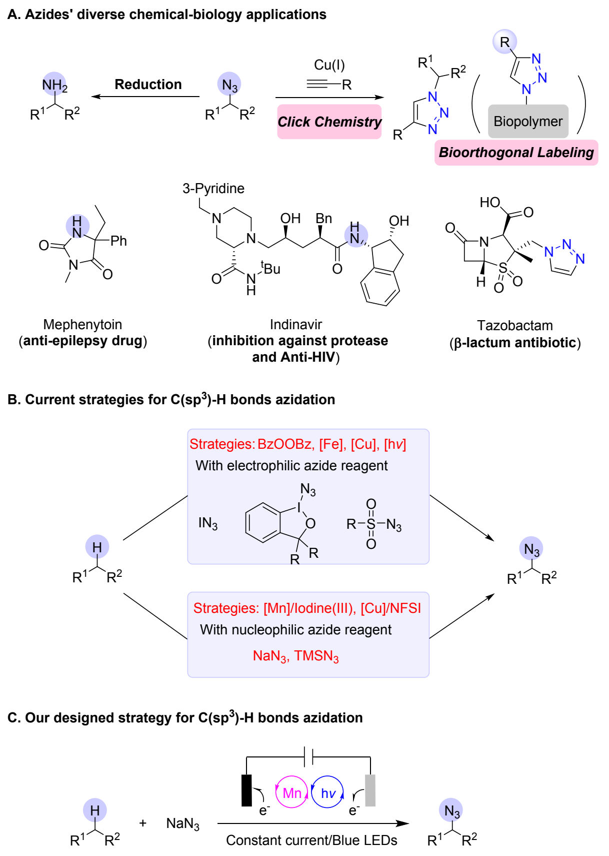


Figure 1. Azidation of C(sp^3)-H bonds for valuable N-scaffolds: (a) representative applications; (b) reported strategies and (c) our designed azidation of C(sp^3)-H bonds without involving chemical oxidants.

The photocatalytic strategy has also been recognized as a powerful tool for the functionalizing of C(sp^3)-H bonds,[5] due to natural abundance, lower cost, and fascinating application prospects. Recently, the electrophotocatalytic method is more intriguing owing to the combining advantages of electrochemistry and photochemistry, which further enriches catalytic strategies to explore more challenging chemical transformations.[6] In this work, we intended to develop a manganese-catalyzed electrochemical oxidative azidation of C(sp^3)-H bonds protocol under electrophotocatalytic conditions to deliver various alkyl azides.

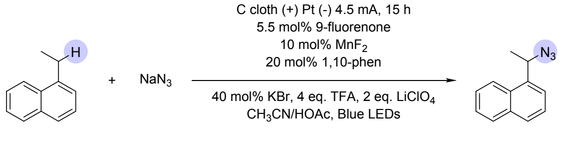
Given the ubiquitous nature of the azide motifs, a well-known and versatile reactive intermediate that can be readily transformed to amines, imines, amides, aziridines, and triazoles,[7] there is a constant need for the development of sustainable and selective methods to form C(sp^3)–N_3 bonds in synthetic organic chemistry, chemical biology, and drug discovery (e.g., azide-alkyne Huisgen cycloaddition and Staudinger ligation in the "click" chemistry, see Figure 1A).[8] Notably, their swift reduction to alkyl amine, especially for generating tertiary amine, further highlights the significance, as such nitrogen-containing molecules are often crucial in pharma-industry.[9] Azidation from the C(sp^3)-H bonds *via* radical C-H activation is an economical way to avoid the pre-functionalization steps. However, the real fact is that current catalytic methods for the azidation of C(sp^3)-H bonds via radical C-H activation, usually require electrophilic azidation reagents (IN_3, Zhdankin's aziodoiodinanes, TsN_3, etc.)[9,10] to capture the nucleophilic C(sp^3) radical.[11] For the current catalytic strategies that utilize nucleophilic azide reagents ($TMSN_3$, NaN_3, etc.), the utilization of (undesired) stoichiometric chemical oxidants such as iodine(III) and NFSI reagent is unavoidable (Figure 1B).[12] Therefore, under *the external chemical oxidants-free conditions* and to achieve oxidative azidation of C(sp^3)-H bonds, using NaN_3 as an azide source is the most atom-economical strategy.

In order to achieve a universal and sustainable C(sp^3)-H azidation protocol and, to avoid the utilization of stoichiometric chemical oxidants, we designed to merge the sustainability of electrochemical synthetic method, the assisting effect of manganese catalyst towards azide radical,[13] and the ability of visible-light catalysts to abstract H atom of C(sp^3)-H bond altogether to generate C(sp^3) radical[14] under electrophotocatalytic conditions (Figure 1C). Herein, we demonstrated that the combination of the metal catalyst, visible-light and electrosynthesis, has successfully accomplished azidation of C(sp^3)-H bonds, which would have immense implications for a diverse array of C(sp^3)-H bonds functionalization.

RESULTS AND DISCUSSION

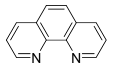
With all these research developments in mind, we first decided to investigate the azidation of benzyl C(sp^3)-H bond under our manganese-based electro-catalytic conditions in combination with the visible-light-catalysis. The model reaction between 1-ethylnaphthalene and NaN_3 has been performed in the presence of manganese catalyst, ligand, photocatalyst, additive, acids and electrolyte under blue LEDs irradiation and constant current electrolysis (Table 1, entry 1). For the electric current, we observed that the higher value of constant current (>4.5 mA) could result in the decline of yields (entries 2 and 3). All other manganese (II) salts all displayed satisfying azidation reactivity (entries 4- 6). Ligands could significantly affect the efficiency of azidation. Notably, when L_2 (1,10-phenanthroline-5,6-dione) that equipped with electron-withdrawing group (carbonyl) and L_3 (bathocuproine) with steric hindrance effect was employed to replace L_1 (1,10-phenanthroline), only 9 % and 3 % yield of desired benzyl azides were isolated (entries 7 and 8), indicating that the coordination of bidentate nitrogen ligand L_1 for manganese catalyst indeed played a crucial role for this electrophotocatalytic azidation protocol. In contrast, electron-rich L_4 (triphenylphosphine) could not be utilized as an effective ligand for the C(sp^3)-H azidation (entry 9).

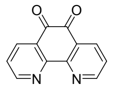
Table 1. Optimization of the reaction conditions[a]



17, 61%

Entry	Variation from the standard conditions	Yield (%)[b]
1	None	61
2	6.5 mA instead of 4.5 mA, 10.4 h	44
3	8.5 mA instead of 4.5 mA, 10.4 h	40
4	$MnBr_2·4H_2O$ instead of MnF_2	54
5	$MnCl_2$ instead of MnF_2	60
6	$MnSO_4$ instead of MnF_2	55
7	L2 instead of L1	9
8	L3 instead of L1	3
9	L4 instead of L1	n.d.
10	1.5 mmol NaN_3 were used	27
11	$TMSN_3$ instead of NaN_3	33
12	Bis(4-methoxyphenyl)methanone instead of 9-fluorenone	61
13	Xanthone instead of 9-fluorenone	61 (27)[c]
14	DDQ instead of 9-fluorenone	55 (24)[c]
15	No blue LEDs	28
16	No Mn catalyst	12
17	No 1,10-phen	25
18	No 9-fluorenone	43
19	No 9-fluorenone, and 50 °C heating instead of blue LEDs	44
20	No 9-fluorenone and blue LEDs	45


L1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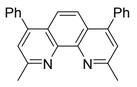

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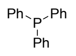

L4

[a]Reaction conditions: 1-ethylnaphthalene (0.5 mmol), NaN_3 (2.5 mmol), 9-fluorenone (5.5 mol%), MnF_2 (10 mol%), 1,10-Phen (20 mol%), KBr (40 mol%),TFA (2.0 mmol) and $LiClO_4$ (1.0 mmol) in CH_3CN (9.5 mL)/HOAc (0.5 mL) stirring under nitrogen atmosphere was electrolyzed at a constant current of 4.5 mA and irradiated by blue LEDs at 35 °C for 15 h. [b]Isolated yields. [c]Yields under darkness in parenthesis.

Then, we found that reducing the amount of sodium azide could lead to decrease of yield (entry 10), and a similar result was observed while $TMSN_3$ was utilized as azide source (entry 11). For the investigation of HAT photocatalyst, we mainly focus on the cheap and readily available aryl ketones and DDQ to improve the practicability of our method, while almost the same results were detected (entries 12- 14). Finally, several important control experiments were conducted to demonstrate the necessity of blue LEDs irradiation (entries 13-15), manganese catalyst, l,10-Phen, and HAT photocatalyst for this external chemical oxidant-free azidation protocol (entries 16- 20), which was consistent with our hypothesis that constructively merging the manganese-catalysis, electrosynthesis and visible light catalysis could achieve the azidation of $C(sp^3)$-H bonds under the metal-catalyzed electrophotocatalytic conditions.

Next, we examined the scope of benzyl $C(sp^3)$-H bonds under our optimized reaction condition (Figure 2). It is noteworthy that an excellent yield of 99% (**4**) was isolated when the triphenylmethane was examined, probably owning to the stabilization of phenyl groups for the benzyl radical. Then, a range of tertiary benzyl $C(sp^3)$-H bonds were further investigated and delivered the desired azidation products (**5-8**) in good yields. Interestingly, in the presence of multiple tertiary benzyl $C(sp^3)$-H groups, the usual mono-azidation products have been isolated in moderated yields, accompanying with the formation of minor diazidation products (**9** and **10**). Another tertiary benzyl $C(sp^3)$-H bond containing in an important framework, oxothioxanthene, that has broad application in pharmaceuticals[15] and photochemistry,[14d] also successfully provided the organic azide (**11**). Halogen atom (e.g. Br) was tolerated as well, allowing an additional opportunity for further synthetic manipulations/transformations (**12**). For the azidation of sec-butylbenzene, we could isolate the desired azidation product in a moderate yield (**13**). Next, we turned our attention to the azidation of secondary benzyl $C(sp^3)$-H bonds. Ethylbenzene derivatives in this synthetic protocol proved to be competent substrates (**14-19**), while the primary benzyl $C(sp^3)$-H bond is unaffected (**15**). For heteroaromatic-based secondary benzyl $C(sp^3)$-H bond, like alkyl-substituted thiophenes, were compatible substrate, but with the lower yield (**20**). A valuable medical intermediate,[16] 2,3- dihydrobenzofuran, selectively provided the expected benzylic azidation product (**21**). The decent reactivity was observed from indan as well (**22**). Long-chain alkyl-substituted benzenes were also well-treated in our protocol, yielding the azidation products of benzyl $C(sp^3)$-H bond with moderated yields (**23-25**). We could summarize that the azidation reactivities of tertiary benzyl $C(sp^3)$ -H bonds are generally better than secondary benzyl $C(sp^3)$-H bonds, which could be explained by the fact that the tertiary benzyl radical is more stable than the secondary benzyl radical.

Compared to the benzyl $C(sp^3)$-H bonds, the selective azidation of conventional alkyl and remote $C(sp^3)$-H bonds are indeed more challenging (Figure 3). Under the oxidant-free azidation strategy, both cyclooctane and cyclododecane provided the corresponding cycloalkyl azides in moderate yields (**26** and **27**). Considering the weaker bond dissociation energy (BDE) of the tertiary aliphatic $C(sp^3)$-H bond,[10h] selective azidation of tertiary $C(sp^3)$-H bonds could be achieved in the presence of multiple $C(sp^3)$-H bonds. Isopropylcyclohexane, decahydronaphthalene, and bicyclohexyl were also competent substrates (**28-30**), delivering the tertiary $C(sp^3)$-H azidation products. Similarly, the mono-selectivity and satisfactory yields were obtained too from adamantanes (**31** and **32**). Notably, benzoate esters and analogous protected primary amine could also selectively produce remote tertiary $C(sp^3)$-H bonds azidation products under this protocol (**33-35**).

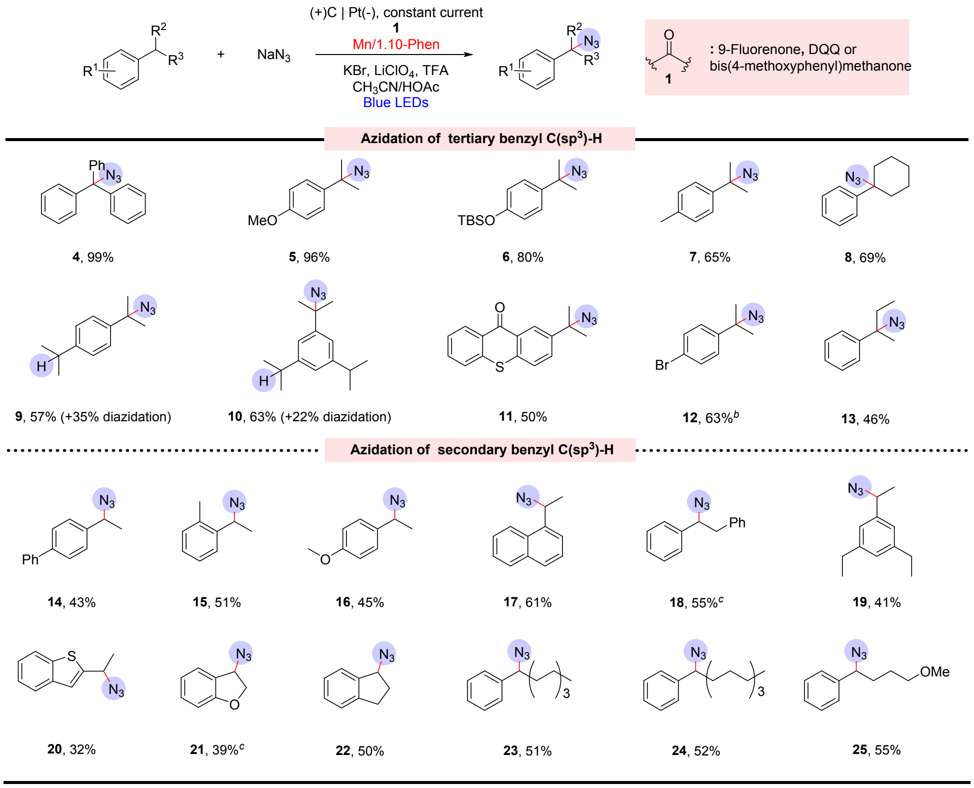

Figure 2. Substrate scope for benzyl $C(sp^3)$-H bonds. [a]Reaction conditions: carbon cloth as anode, platinum as cathode, substrate (0.5 mmol), NaN_3 (2.5 mmol), HAT photocatalyst **1** (5.5 mol% or 11 mol%), MnF_2 or $MnBr_2 \cdot 4H_2O$ (10 mol%), 1,10-Phen (20 mol%), KBr (40 mol%), TFA (2.0 mmol) and $LiClO_4$ (1.0 mmol) in CH_3CN (9.5 mL)/HOAc (0.5 mL) stirring under nitrogen atmosphere was electrolyzed at a constant current of 4.5 mA and irradiated by blue LEDs at 35 ˚C for 15 h, isolated yields. [b]Carbon felt as anode, substrate (1.0 mmol),

NaN_3 (4.0 mmol), DDQ (5.5 mol%), MnF_2 (5 mol%), 1,10-Phen (10 mol%), without KBr, CH_3CN (3.0 mL), DCE (2.5 mL), *i*= 8.0 mA, 21 h. [c]Carbon felt as anode, substrate (1.0 mmol), NaN_3 (4.0 mmol), DDQ (5.5 mol%), MnF_2 (2.5 mol%), 1,10-Phen (10 mol%), without KBr, CH_3CN (3.0 mL), DCE (2.5 mL), *i*= 4.5 mA, 24 h. See Supporting Information for further details.

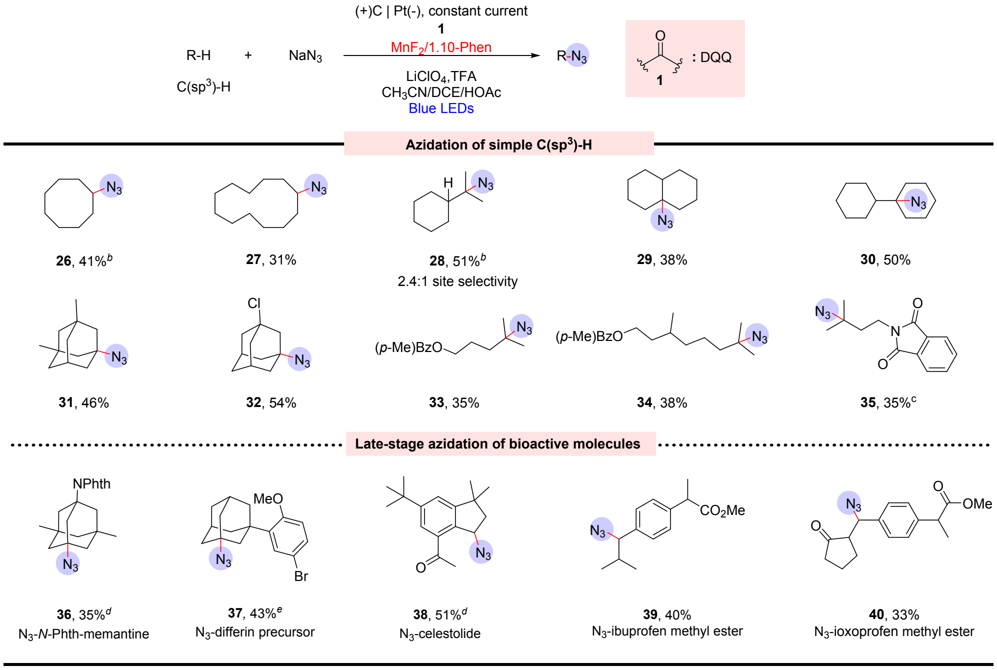

Figure 3. **Substrate scope for simple C(sp^3)-H bonds and late-stage functionalization**. [a]Reaction conditions: carbon felt as anode, platinum as cathode, substrate (1.0 mmol), NaN_3 (4.0 equiv.), DDQ (5.5 mol%), MnF_2 (5 mol%), 1,10-Phen (10 mol%), TFA (2.0 equiv.) and $LiClO_4$ (1.0 equiv.) in CH_3CN (3.0 mL), DCE (2.5 mL)/HOAc (0.5 mL) stirring under nitrogen atmosphere was electrolyzed at a constant current of 8.0 mA and irradiated by blue LEDs at 35 ˚C for 21 h, isolated yields. [b]0.5 mmol scale, NaN_3 (5.0 equiv.), MnF_2 (10 mol%), 1,10-Phen (20 mol%), TFA (4.0 equiv.) and $LiClO_4$ (2.0 equiv.), 6.0 mA, 15 h. [c]0.5 mmol substrate, NaN_3 (8.0 equiv.), DDQ (11.0 mol%), MnF_2 (7.5 mol%), 1,10-Phen (20 mol%), TFA (4.0 equiv.) and $LiClO_4$ (2.0 equiv.). [d]MnF_2 (2.5 mol%). [e]0.5 mmol scale, NaN_3 (5.0 equiv.), MnF_2 (10 mol%), 1,10-Phen (20 mol%), TFA (4.0 equiv.) and $LiClO_4$ (2.0 equiv.), 4.5 mA, 15 h. See Supporting Information for further details.

In short, the selectivity of tertiary aliphatic C(sp^3)-H bond containing in substrates to incorporate nitrogen-based functionality at the tertiary alkyl group provides opportunities to manipulate numerous potential medicinal candidates.

Based on these obtained results, the application to several bioactive molecules with multiple C(sp^3)−H bonds sites were demonstrated (Figure 3). N-phthalimide-protected memantine, a N-Methyl-D-aspartate (NMDA) receptor antagonist, utilized to treat Alzheimer's disease,[10h] afforded the tertiary C(sp^3)-H bond azidation product (**36**). In spite of the electron-rich arene on an adapalene precursor, the azidation of the tertiary C(sp^3)-H bond could still be achieved in a reasonable yield (**37**). Subjecting the celestolide spice under our methodology provided the benzylic azidation product in a satisfying yield (**38**). For the complex pharmaceutical molecule derivatives, which contain the multiple tertiary C(sp^3)-H bonds, like ibuprofen methyl ester (**39**) and ioxoprofen methyl ester (**40**), selectively favored the formation of secondary benzyl C(sp^3)-H bond azidation products with modest yields.

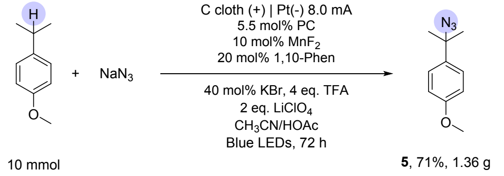

Figure 4. Gram-scale experiment. PC: bis(4-methoxyphenyl)methanone.

To demonstrate the feasibility of our protocol towards the preparative synthesis, the upscaling of our methodology has also been conducted in a 10 mmol scale (Figure 4). In this case, a good isolated yield of 71% (**5**) was isolated. It provided the opportunity for further synthetic manipulations and redeemed the few gram-scale demonstrations of previous methods on the azidation of benzylic and simple alkyl C(sp^3)-H bonds.[10e] Considering alkyl azides as versatile synthetic intermediates, and the significance of alkyl amines, especially tertiary amines in organic chemistry,[9] we further reduced the azide **5**, successfully to produce the corresponding tertiary amine (**41**) with an excellent 93% yield (Figure S1).

After completing the investigation of substrates scopes and synthetic applications, a series of designed experiments were conducted to validate the mechanistic hypothesis. The radical inhibition experiment was firstly carried out by adding stoichiometric TEMPO (2,2,6,6-tetramethylpiperidinyloxy) into our electrophotocatalytic condition. We observed that neither desired benzyl azide nor the adduct of TEMPO and benzyl radical was generated (Figure 5A). According to Lin et al.'s study on electrochemical azidooxygenation of alkenes mediated by a TEMPO−N_3 charge-transfer complex,[17] the electrochemically generated oxoammonium ion (TEMPO$^+$) can facilitate the formation of azide radical from N_3^-, and TEMPO that has the ability to capture the C(sp^3) radical to deliver corresponding radical adduct, was evidenced as well. Therefore, we propose that azide radicals were smoothly produced but the generation of C(sp^3) radical was restrained in the presence of TEMPO in our system. Then, the EPR experiments were designed to detect radical intermediates. Under the standard electrophotocatalytic conditions, we successfully captured the azide radical by employing DMPO (5,5-Dimethyl-1-pyrroline N-oxide) as radical trapping reagent (Figure 5B-a), which indicated that the azide radicals are indeed existing during this manganese catalyzed electrophotocatalytic system. Notably, we also observed the existence of carbon radical, while treating the 1-ethylnaphthalene and HAT photocatalyst under the blue LEDs irradiation (Figure 5B-b), probably providing the direct mechanistic evidence that the excited HAT photocatalyst can abstract the C(sp^3)-H to benzyl C(sp^3) radical. To get a deeper understanding of the role of visible light irradiation, we have demonstrated the accelerating effect of blue LEDs irradiation for the azidation of 4-isopropylanisole during the initial stage of the reaction (Figure 5C). Without the blue LEDs irradiation, the azidation of C(sp^3)-H could still proceed, but the reaction rate was slower than in the presence of blue LEDs irradiation. Combining the results of EPR studies, we concluded that the azide radical is also capable of abstracting the H atom of C(sp^3)-H bond.[18] Thus, we considered that the generation of C(sp^3) radical under the electrophotocatalytic condition might derive from the photocatalytic HAT process and the abstraction of N_3 radical for C(sp^3)-H bonds.

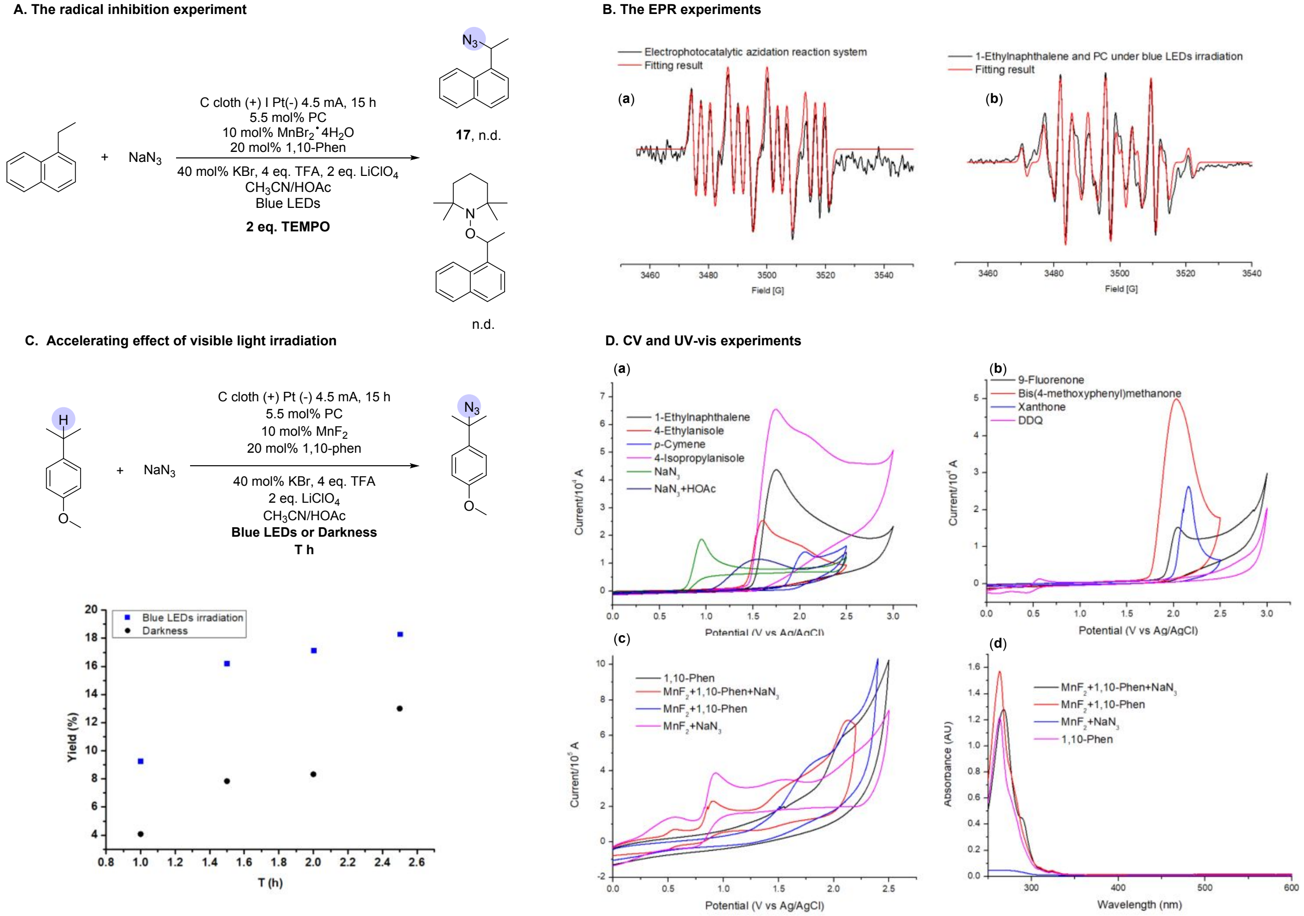

Figure 5. Gram-scale experiment and mechanistic studies. PC: 9-fluorenone (Figure 5A) or bis(4-methoxyphenyl)methanone (Figure 5B and 5C). See Supporting Information for further details.

What's more, the CV (cyclic voltammetry) experiments were designed to obtain details concerning the role of the manganese catalyst under the electrophotocatalytic conditions. As shown in Figure 5D-a and 5D-b, the oxidative potential of NaN_3 was lower than substrates and photocatalysts, even in the acidic solution system existing the protonation of NaN_3, suggesting that the oxidation of NaN_3 to azide radical on the anodic surface was fairly easy. Moreover, we also measured the anodic oxidative potential (constant current: 4.5 mA) ranges from 1.2~1.5 V (vs Ag/AgCl) in the whole azidation process, evidencing that the direct oxidation of substrates and photocatalysts was indeed difficult. For the azidation of simple alkyl C(sp^3)-H, the inert alkyl C(sp^3)-H bonds and DDQ were also not likely oxidized by anodic oxidation (8.0 mA electric current) that the oxidative potential is about 1.9~2.2 V (vs Ag/AgCl). Further, we found that the oxidation peak of Mn(II)/1,10-Phen was at ~1.75 V (Figure 5D-c). By contrast, we observed a new oxidation peak at ~0.55 V when Mn(II), 1,10-Phen and NaN_3 were mixed under electrochemical CV conditions, which was assigned as the oxidation of Mn(II)/L-N_3 to Mn(III)/L-N_3. The similar result was also noted after removing 1,10-Phen.[13b] Besides, the coordination of N_3^- and 1,10-Phen to Mn(II) was evidenced by UV-vis experiments (Figure 5D-d). Given that the excess amount of sodium azide and the lower oxidative potential of Mn(II)/L-N_3, we proposed the direct oxidation of Mn(II)/L to Mn(III)/L is not realistic even under the 8.0 mA electric current condition.

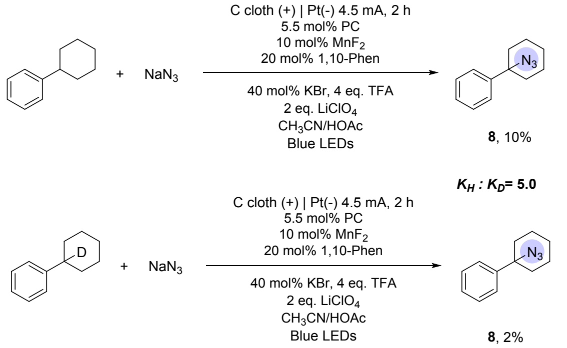

Figure 6. Kinetic of isotopic effect experiments. PC: bis(4-methoxyphenyl)methanone.

The cleavage of C(sp^3)-H bonds, possibly involving the rate-determining step was evidenced by the parallel KIE (kinetic isotope effect) experiments (Figure 6). Next, the kinetic studies of manganese catalyst, 1,10-phenanthroline, sodium azide, and 4-isopropylanisole were also conducted for further understanding of the reaction mechanism. According to the kinetic curves of the manganese catalyst, 1,10-Phen and NaN$_3$ (Figure S2, S3 and S4), increasing the loading of Mn(II) catalyst could lead to the decrease of the azidation rate, while the 1,10-Phen and NaN$_3$ appeared to have the facilitating effects for azidation in the reasonable concentration ranges. Considering the concentration of 1-isopropyl-4-methoxybenzene has little effect on the initial reaction rate (Figure S5) and the cleavage of C(sp^3)-H bonds involving the rate-determining step, we proposed that the concentrations of azide radical and Mn(III)/L-N$_3$ have important effects for our azidation reaction. It is due to the fact that azide radicals were involved in the abstraction of C(sp^3)-H step, which also possibly react with Mn(II)/L-N$_3$ to Mn(III)/L-N$_3$, and Mn(III)/L-N$_3$ determines the capture of C(sp^3) radical to deliver the final product. Since the oxidative potential of Mn(II)/L-N$_3$ is lower than N$_3^-$, and in the presence of excess sodium azide, both the oxidation of NaN$_3$ to azide radical and Mn(II)/L-N$_3$ to Mn(III)/L-N$_3$ might proceed at the same time and have a competitive relationship. We have observed that the rate-determining abstraction of C(sp^3)-H step is probably driven by the azide radical and the excited HAT photocatalyst. If the concentration of Mn(II)/L-N$_3$ was too high, then the concentration of Mn(III)/L-N$_3$ by the anodic oxidation of Mn(II)/L-N$_3$ would also increase, while the excited HAT photocatalyst might also participate in the oxidation of Mn(II)/L-N$_3$, and simultaneously, the concentration of azide radical generated by the direct anodic oxidation would decrease. These two possible facts might induce the rate of abstraction of C(sp^3)-H slowing down, causing a decrease of azidation rate. On the other hand, if the concentration of Mn(II)/L-N$_3$ was too low, the generation of C(sp^3) radical would not be affected. However, a very small amount of Mn(III)/L-N$_3$ would influence the azide transfer to C(sp^3) radical, which could still decrease the efficiency of azidation. Therefore, we proposed that the constructive combination of manganese catalysis, electrosynthesis and visible light catalysis would successfully achieve the transformation of C(sp^3)-H bonds.

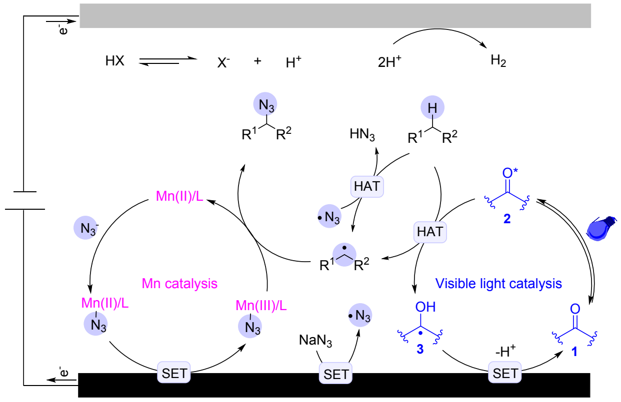

Figure 7. Proposed mechanism for electrophotocatalytic azidation of C(sp^3)-H bonds. (X$^-$: OAc$^-$, CF$_3$COO$^-$ or N$_3^-$).

With all these mechanistic studies taken together, the proposed mechanism has been illustrated in Figure 7. On the anodic surface, NaN$_3$ could directly be oxidized to azide radical, while the Mn(II) coordinated by N$_3^-$ and ligand (1,10-Phen or OAc$^-$, etc.) have undergone the anodic oxidation to deliver Mn(III)/L-N$_3$ intermediate.[13b] We considered that the addition of azide radical to Mn(II)/L to Mn(III)/L-N$_3$ was also possible. In the photocatalytic cycle, the excitation of HAT photocatalyst by blue LEDs irradiation[14] induced the hydrogen atom transfer (HAT) event on C(sp^3)-H bond to generate the C(sp^3) radical. The regeneration of this visible-light catalyst could be accomplished by anodic oxidations. At the same time, we could not exclude the possibility that Mn(III)/L-N$_3$ involving the turnover of the HAT photocatalyst: oxidation of **3** back to **1**. Notably, the azide radical could also abstract H atom of C(sp^3)-H bonds to offer alkyl radical.[18] The final formation of alkyl azide was accomplished by the azide-transfer of Mn(III)/L-N$_3$ to an alkyl radical, simultaneously completing the turnover of the Mn(II) catalyst. On the other hand, the acidic reaction system provided enough protons for hydrogen evolution on the cathode, avoiding the reduction of manganese catalyst.

In conclusion, we have successfully achieved manganese-catalyzed electrochemical oxidative azidation of benzylic C(sp^3)-H, alkyl C(sp^3)-H, and selective remote C(sp^3)-H bonds accelerated by visible light catalysis with nucleophilic sodium azide as an azidation reagent (i.e., successfully avoiding the use of stoichiometric chemical oxidants). The ability to install N$_3$ group successfully at the tertiary alkyl group indeed highlights the significance of our protocol. The late-stage azidation of valuable drug-like molecules and gram-scale synthesis demonstrate the potential application in the preparative pharmaceutical synthesis. The detailed mechanistic studies were also conducted for an in-depth understanding of the reaction mechanism. The development of more challenging N-scaffolds construction from C(sp^3)-bonds is underway in our laboratory. Inspiring from our work, we anticipate that the scientific community will develop more emerging technologies in organic synthesis in the near future.

ASSOCIATED CONTENT

Supporting Information

The experimental procedure, characterization data, and copies of ^{1}H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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DEDICATION

This paper is dedicated to P.H. Dixneuf for his meaningful contribution to organometallic chemistry and catalysis.

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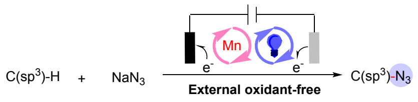
TOC



✓ Avoiding iodine(III) reagent or NFSI

✓ Azidation of benzylic C(sp^3)-H and aliphatic C(sp^3)-H

✓ Gram-scale synthesis and late-stage azidation

✓ Detailed mechanistic studies