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Photoswitchable Regiodivergent Azidation of Olefins with Sulfonium Iodate(I) Reagent

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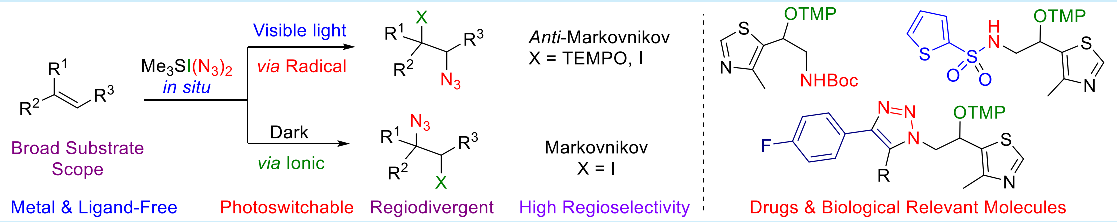
Supporting Information

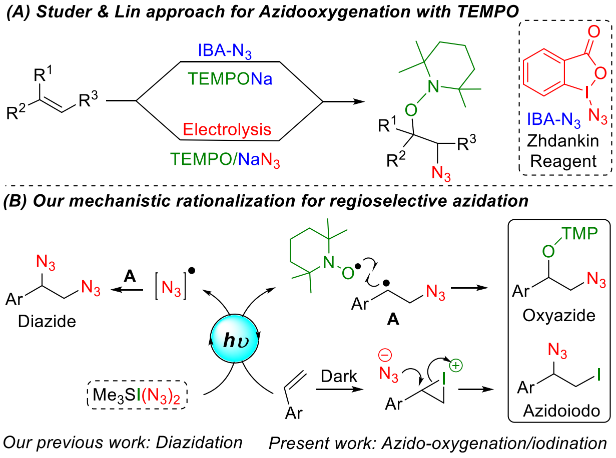


ABSTRACT: Photoswitchable strategy for selective azidation of structurally diverse olefins under transition-metal-free conditions is reported. The unprecedented reactivity of trimethylsulfonium [bis(azido)iodate(I)] species under visible light allows radical azidooxygenation of the C$=$C π bond with distinctive selectivity. In the absence of visible light, the reaction proceeds through an ionic intermediate which led to complementary regioselectivity to provide α-alkyl azides. Mechanistic studies reveal that light-controlled regiodivergent azidation involving radical or an ionic pathway can be accomplished with exclusive regioselectivity.

Azido-functionalized molecules represent a potential precursor to vital nitrogen-based scaffolds of therapeutic value and biologically active compods.[1] In addition, the azido group serves as powerful chemical tool involving several fascinating chemical transformations;[2] Aza-Wittig reaction, C−H bond amination, "Click" reaction, and Staudinger ligation to investigate biochemical actions in living organisms.[3] In recent years, the selective azidation process has gained significant advances owing to the exceptional versatility of the azido moiety in synthetic chemistry,[4] material sciences,[5] as well in pharmaceutical inventions.[6] In particular, azidooxygenation of alkene has been recognized as asynthetically useful transformation[7] attributed to the readily transferable as well late-stage utility of azido and oxy moieties.[8] Notably, the vicinal oxy azides serve as key intermediates for 1,2-amino alcohols,[9] which constitutes an important subclass of medicinally important molecules and several drugs.[10]

In this context, Studer et al. have first achieved the azidooxygenation by employing highly reducing TEMPONa as a single-electron aminoxyl radical precursor and azidobenziodoxolone (IBA-N$_3$ or Zhdankin reagent) as an azidyl radical source[7a] (Scheme 1A). More recently, other pioneering works advancing the synthetic versatility of persistent TEMPO species have been reported by Lin and co-workers and imply electrochemical oxygenation.[7b] Meanwhile, Loh et al. investigated Cu(II)-mediated oxyazidation of vinylarenes with IBA-N$_3$, illustrating the dual-role of hypervalent iodine(III) species as an electrophilic azide source as well as *O*-nucleophile.[7c] On the other hand, Greaney and co-workers outlined an elegant approach for photoswitchable azidation of styrenyl substrates employing IBA-N$_3$ in the presence of photoredox catalyst.[7d] Despite significant advances, the intrinsic shortcomings associated with transition metals and utilization of expensive photocatalysts/ligands/oxidants are some important issues and reasons for developing the improved methods. The resurgence of visible light as a milder and greener technique led to rapid development in sustainable chemistry, emanating as promising

Scheme 1. Azidooxygenation of Alkenes with TEMPO and Our Approach for Regiodivergent Azidation under Photoswitchable Conditions



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alternative strategies.[11] However, the selective radical transfer of oxygen and nitrogen functional groups on an alkene under visible-light irradiation without any precious photocatalyst/additives is still an elusive process.

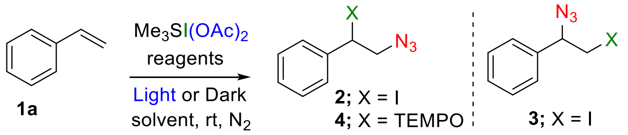
Inspired by our recent interest in developing a protocol for the selective functionalization of C−C multiple bonds by employing sulfonium iodate salts,[12] herein we present a photoswitchable approach for regiodivergent azidation of olefins under metal-free conditions. This light-controlled modular aimed for regioselective azidation will be highly advantageous in extensively studied *C*-heteroatom bond-forming reactions. We previously developed a method for the photochemical diazidation of the C═C π bond, highlighting the distinctive outcome of sulfonium iodate species under visible-light conditions[12a] (Scheme 1B). The protocol involves radical diazidation of diverse functionalized alkenes in a single step from sulfonium bis(acetoxy)iodate(I) and sodium azide as radical precursor. In this paper, we envisioned that the benzylic radical (**A**), initiated by the addition of azidyl radical, could readily combine with the aminoxyl radical to accomplish an azidooxygenation (Scheme 1B).

We further realized that the orthogonal reactivity of sulfonium iodate species toward olefinic moiety in the presence or absence of visible light and a radical scavenger aid in the diverge regioselectivity for azidation reaction. The preliminary mechanistic insights into this seminal method have ensured the scope of fundamental radical and ionic pathways by standardizing light−dark conditions.

To commence our studies on the proposed hypothesis, we first examined the radical azidation of styrene **1a** (1.0 mmol) with trimethylsulfonium [bis(azido)iodate(I)] species,[12b] generated in situ by employing Me$_3$SI(OAc)$_2$ (1.1 mmol) and NaN$_3$ (2.5 mmol) in MeCN under visible-light irradiation (CFL 27 W). The preliminary observations revealed the formation of a mixture of anti-Markovnikov and Markovnikov azidation products, **2**:**3** (1:4 ratios), in 66% yields (Table 1, entry 1).[13] Subsequently, the reaction of **1a** with the aforementioned reagent system in DCE or MeOH as the solvent resulted in no improvement in the selectivity and efficiency (entries 2 and 3). The use of acetic acid provided a mixture of **2** and **3** with considerable amount of acetoxy product (entry 4). Indeed, the reaction was working in water without any significantly changes in regioselectivity, albeit with a lower yields (entry 5).

To our delight, switching the solvent to toluene facilitated the radical azidation, furnishing exclusively the β-azide **2** in 88% yields (Table 1, entry 6). Apparently, the azidation with complementary regioselectivity could be accomplished while performing the reaction in the dark or without light irradiation, affording the α-azide **3** in 94% yield (entry 7). Consequently, we attempted to investigate a direct oxyazidation of styrene using an oxygen-radical scavenger. Gratifying, the reaction proceeded well by employing TEMPO (2.5 mmol), furnishing the desired vicinal oxyazide **4** in 65% yields (entry 8). We further observed a modest enhancement in the efficiency when the reaction was irradiated with white or green LEDs (entries 9 and 10). Finally, blue LEDs (λ_{max} ~ 460 nm) were found to be an optimal tool to probe the radical azidation, providing the **4** in higher yields (entry 11). Additional experiments performed instead with TMSN$_3$ as azide source or DCM as the solvent resulted a noticeable improvement in yields (entries 12 and 13). Further changing the solvents was found to be unsuccessful and led to diminished reactivity albeit with the formation of undesirable products (entries 14 and 15).

Table 1. Optimization of Selective Azidation Using Sulfonium Iodate Reagent[a]

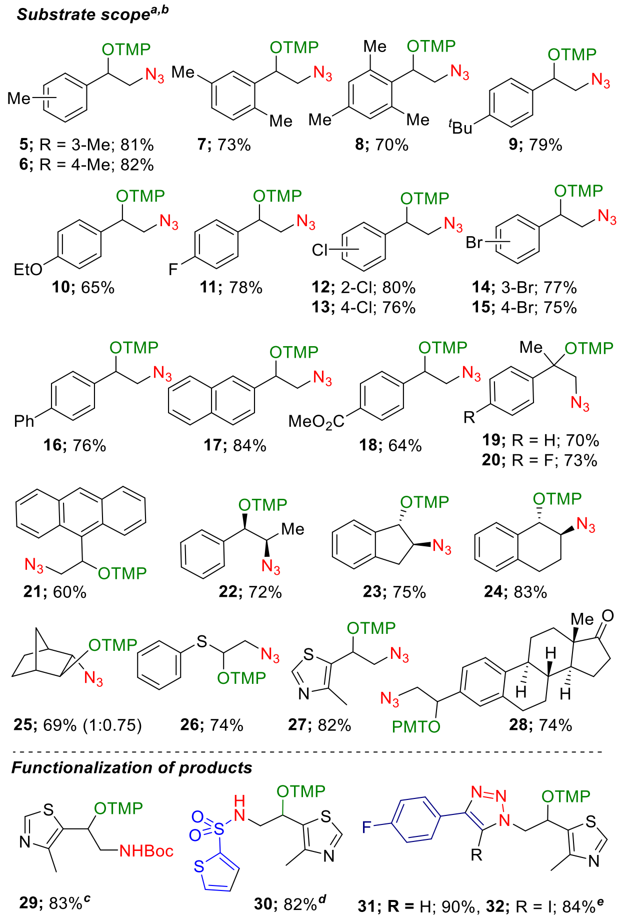


entry	solvent/azide/radical source	visible light	product(s); yields %[b] (ratio)[c]
1	MeCN/NaN$_3$	CFL (27 W)	**2**:**3**; 66 (1:4)
2	DCE/NaN$_3$	CFL (27 W)	**2**:**3**; 54 (1:2.5)
3	MeOH/NaN$_3$	CFL (27 W)	**2**:**3**; 58 (1:2)
4[d]	AcOH/NaN$_3$	CFL (27 W)	**2**:**3**; 59 (1:2)
5	H$_2$O/NaN$_3$	CFL (27 W)	**2**:**3**; 43 (1:2)
6	toluene/NaN$_3$	CFL (27 W)	**2**; 88
7	**toluene/NaN$_3$**	**dark**	**3**; **94**
8	toluene/NaN$_3$/TEMPO	CFL (27 W)	**4**; 65
9	toluene/NaN$_3$/TEMPO	white LEDs (7 W)	**4**; 72
10	toluene/NaN$_3$/TEMPO	green LEDs (7 W)	**4**; 78
11	toluene/NaN$_3$/TEMPO	blue LEDs (7 W)	**4**; 82
12	toluene/TMSN$_3$/TEMPO	blue LEDs (7 W)	**4**; 85
13	**DCM/TMSN$_3$/TEMPO**	**blue LEDs (7 W)**	**4**; **92**
14	MeCN/TMSN$_3$/TEMPO	blue LEDs (7 W)	**4**; 63
15	THF/TMSN$_3$/TEMPO	blue LEDs (7 W)	**4**; 58

[a] Reaction conditions: **1a** (1.0 mmol, 1.0 equiv), Me$_3$SI(OAc)$_2$ (1.1 equiv), TMSN$_3$ or NaN$_3$ (2.5 equiv), TEMPO (2.5 equiv), solvent (2 mL), stirred at 35 °C for 12 h, irradiated with a CFL (27 W) or LEDs (7 W), unless otherwise noted. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy. [d] Mixture of iodoacetoxy compound, observed by ^{1}H NMR.

Having identified the light-controlled azidation procedures, we first explored the scope of azidooxygenation reaction with structurally diverse olefins. All of the evaluated substrates generally performed well, giving desired products (**5**−**28**) in moderate-to-good yields (60−84%); results are illustrated in Scheme 2. A series of styrenes including electron-donating moieties (Me, ^{t}Bu, OEt) with *ortho*, *meta*, or *para* substitutions reacted smoothly to afford the desired products **5**−**10** in good yields. Notably, the sterically hindered aryl alkenes with a di- or trisubstituent at the arene ring performed well under present system (**7**−**8**). The substrates bearing halogens (F, Cl, Br) at different positions on the phenyl ring participated successfully delivering the corresponding products **11**−**15** with decent yields. Likewise, an electron-rich 4-vinylbiphenyl, 2-vinylnaphthalene, and vinylarene with an ester group were well tolerated to give the corresponding oxyazides **16**−**18**. We further observed that α-methyl styrenes with different electronic environments can be applied under standard azidooxygenation to obtain the oxyazides **19** and **20** in acceptable yields. Noteworthy, the azidooxygenation of a synthetically useful 9-vinylanthracene can be achieved to generate the desired product **21** albeit with slightly lower efficiency.

Scheme 2. Substrate Scope for the Visible-Light-Induced Azidooxygenation



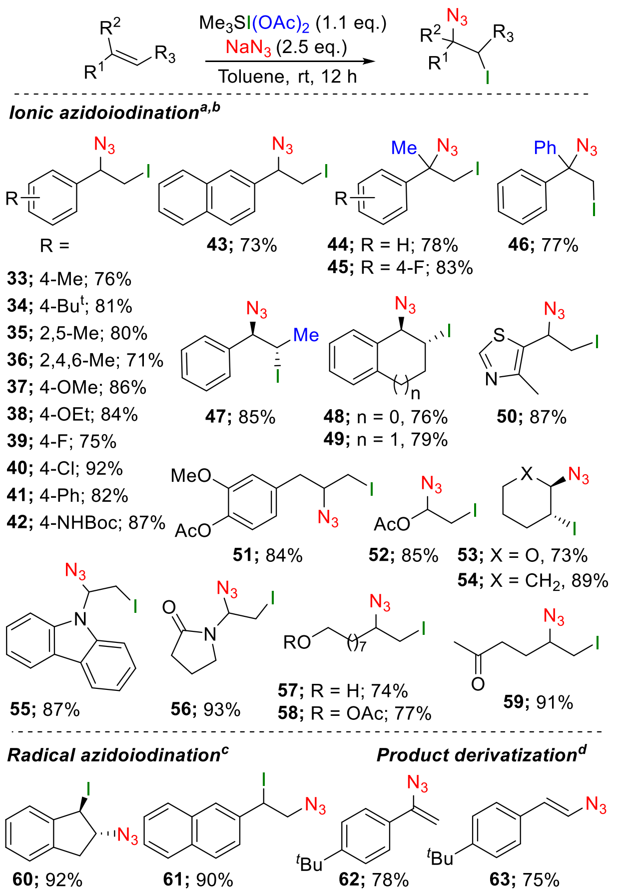
[a] Reaction conditions: olefins (1.0 equiv), $Me_3SI(OAc)_2$ (1.1 equiv), $TMSN_3$ (2.5 equiv), TEMPO (2.5 equiv), DCM (2 mL), stirred at 35 °C for 12 h, irradiated with blue LEDs (7 W). [b] The isolated and unoptimized yields after chromatography. [c] PPh_3 (2.2 equiv), H_2O/THF, reflux, then Boc_2O (3.0 equiv). [d] Reduction using PPh_3/H_2O, then 2-thiophenesulfonyl chloride (1.2 equiv), DCM (2 mL). [e] $CuSO_4$ (cat.), arylacetylenes (1.2 equiv), sodium ascorbate (cat.), ^{t}BuOH/H_2O (2 mL:1 mL).

It is pertinent to mention that *trans*-*β*-methyl styrene including an internal olefin reacted in a completely regio- and diastereoselective manner to afford the exclusive *syn*-oxyazide **22** in 72% yields. In contrast, indene and 1,2-dihydronaphthalene bearing a cyclic double bond underwent *anti*-addition of azidyl and aminoxyl radical favoring the formation of *trans*-oxyazides **23** and **24**. The *syn*- vs *trans*-addition may be attributed to the stereoelectronic and steric contribution of conjugating substituent on the relative configuration (A-strain model) of benzylic radical (**A**).[14] We next examined a bicyclic norbornene under the standardized conditions, producing the desired *endo*/*exo*-**25** in 69% yields with a dr of 1:0.75. Nevertheless, a photochemically sensitive sulfide linkage in phenylvinylsulfide was sustained to afford the desired product **26** in complete regioselectivity. Subsequently, a heterocycle such as thaizole and an estrone derivative were conveniently functionalized into their corresponding oxyazides **27** and **28**, constituting a masked 1,2-amino alcohol moiety. The synthetic versatility of prefunctionalized oxy-azido groups is amply demonstrated by late-stage transformations into relevant structures.

Accordingly, reduction of **27** employing a Staudinger condition following *N*-Boc protection and sulfonylation of intermediate free amine readily afforded the functionalized amine **29** (83%) and sulfonamide **30** (82%) respectively. A "Click" coupling of azidyl group with alkyne or an iodoalkyne under standard CuAAC provide rapid access to 5-H/iodotriazoles **31** and **32** represents potential candidates to probe the several biological activities.[15]

Having successfully established the photoinduced azidation, we next focused on investigating the feasibility of ionic azidation using sulfonium iodate species. As summarized in Scheme 3, a wide range of substrates including terminal, internal, cyclic, vinyl, and allylic olefins reacted smoothly to obtain the desired *α*-azides **33−59** in good to excellent yields (70−93%). Arylarenes substituted with both electron-donating and -withdrawing groups (Me, ^{t}Bu, OMe, OEt, F, Cl, Ph) were well tolerated to afford the corresponding azides **33−41**. Vinylarenes with a labile NH-Boc and a naphthyl substrate were transformed into their respective products **42** and **43** efficiently. Styrenes with *α*-substitutions (Me or Ph) were also found to be compatible, affording the corresponding azides **44−46** in good yields. In particular, (*E*)-*β*-methylstyrene can

Scheme 3. Substrate Scope for the Azidoiodination



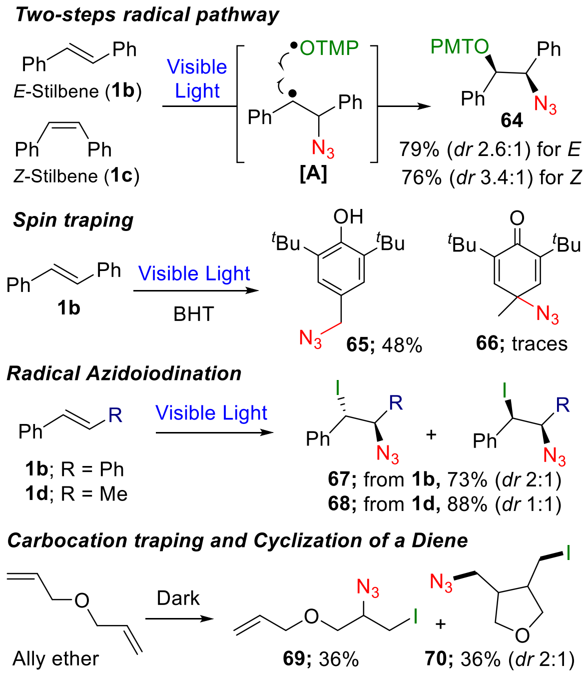
[a] Reaction conditions: olefins (1.0 equiv), $Me_3SI(OAc)_2$ (1.1 equiv), NaN_3 (2.5 equiv), toluene (2 mL), stirred at 25 °C for 12 h in the dark. [b] The isolated and unoptimized yields after purification. [c] The reaction was irradiated with a 27 W CFL for 12 h at 35 °C. [d] *tert*-BuOK (1.2 equiv), THF (2 mL).

exclusively undergo Markovnikov addition to give **47** with complete *trans*-selectivity, attributed to the *anti*-opening of putative iodonium intermediate.[12] Likewise, indene and 1,2-dihydronaphthalene followed stereoselective azidation furnishing the *trans*-**48** and -**49** with high dr. Subsequently, a disubstituted thaizole and eugenyl-derivative proved to be favorable substrate accomplishing the desired products **50** and **51** with no discrepancy in Markovnikov selectivity. Indeed, vinyl acetate, 1,2-dihydropyran, and cyclohexene reacted with exclusive *trans*-diastereoselectivity to produce the corresponding products **52**−**54** in good yields.

Notably, enamines such as *N*-vinyl carbazole and *N*-vinylpyrrolidone were competent substrates in applied protocol affording the desired azides **55**−**56** in high yields. Moreover, alkenes with a long chain or a keto group performed well to provide secondary organic azides **57**−**59**, further highlighting the synthetic advantage of our method. Specifically, the representative substrates were subjected to optimal photoazidation (Table 1, entry 6) producing the terminal azides **60** and **61** with complementary regioselectivity. Noteworthy, the vicinal azido iodides resulting from photoswitchable system are useful synthetic intermediate to enrich the heterocyclic structures of high pharmaceutical value.[16] Though, a sequential transformation of 4-*tert*-butylstyrene under light-dark azidoiodination following dehydrohalogenation afforded the corresponding α- and β-vinylazides **62** and **63** in good yields. The variant stereochemical outcomes in photoswitchable operation are plausibly attributed to the diverse radical and ionic pathways.

Several control experiments were conducted to further validate the mechanistic rationalization (Scheme 4). Photoirradiation of (*E*)- or (*Z*)-stilbene under standard conditions resulted an identical pair of isomeric-oxyazide **64** albeit with a different dr. These findings are consistent with our previous observations[12a] and unambiguously confirm the two-step radical pathway involving a nonstereospecific addition of N/O radical species on the C═C bond. The spin-trapping experiment with a competitive radical scavenger, for instance, 2,6-di-*tert*-butyl-4-methylphenol (BHT), completely inhibits the azidooxgenation. However, the azidyl radical originating from homolysis of weak I−N_3 bond from $Me_3SI(N_3)_2$ species was trapped by BHT to give an unexpected azide adduct **65** (48%), which presumably arises from radical azidation of benzylic carbon-H.[17] Another spin adduct 4-azido-cyclohexanedienone **66** was also observed occasionally in trace amounts. The experiment employing 1,2-disubstituted alkenes (**1b**, **1d**) under photoazidoiodination provided diastereomeric *syn*/*anti* **67** (dr; 2:1) and **68** (dr; 1:1), respectively.[18] The regioselective *anti*-Markovnikov addition further evidenced the intermediacy of transient β-azido benzylic carbon radical (**A**). Unlike TEMPO trapping step in the azidooxygenation, the iodine radical generated from iodoazide species may approach the radical (**A**) more readily in the absence of aminoxyl radical to provide *syn*/*anti* β-azido products.[14] Furthermore, the ionic azidation of allyl ether under the standard dark reaction conditions led to a 1:1 mixture of vicinal azidoiodo **69** and rearranged cyclized adduct **70** (dr; 2:1) in 72% overall yields.

Scheme 4. Control Experiments To Probe the Mechanistic Hypothesis for Photoswitchable Azidation Promoted by Sulfonium Iodate Species



In conclusion, we have successfully developed metal-free regioselective azidooxygenation and azidoiodination of alkene under photoswitchable conditions. Generality and functional group compatibility is amply demonstrated, employing operationally safer and economical visible-light source. The notable advantage of this protocol includes the orthogonal reactivity of sulfonium iodate(I) reagent under light-controlled conditions resulting regiodivergent azidation. This method enables rapid access to highly versatile synthetic intermediates en route to nitrogen-functionalized biologically active natural products. Light-induced selective radical processes render it a powerful tool to investigate the specific and hitherto unknown chemical transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03910.

Experimental details and copies of ^{1}H, ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(13) See the Supporting Information. All of the products were isolated as a racemic mixture.

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