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Letter

Radical-Mediated Functionalization of Internal Alkenes: Synthesis of Multisubstituted Allylic and Homoallylic Azides

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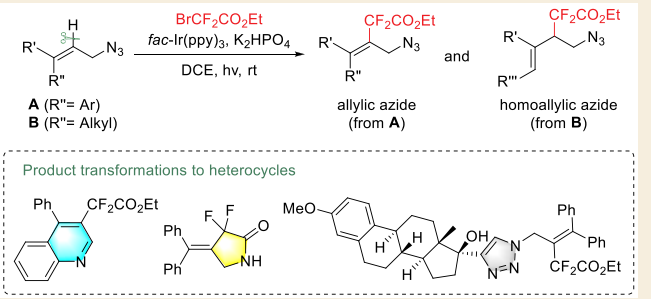
ABSTRACT: Radical-mediated functionalization of alkenes provides a powerful tool for transformation of simple alkenes into numerous value-added products. The precedent radical functionalization of alkenes is mainly restricted to terminal alkenes, while the conversion of internal alkenes generally remains challenging, as the increased steric congestion on alkenes significantly conflicts with the intermolecular addition of radicals. Herein, we describe an efficient photoredox catalytic functionalization of internal trisubstituted alkenes, leading to a plethora of valuable multifunctionalized allylic and homoallylic azides, which are otherwise difficult to obtain. The azide products serve as versatile feedstock for construction of useful heterocycles. Allylic or homoallylic azides are selectively generated in the transformation, regulated by the regioselective deprotonation process. This method also features mild reaction conditions and high product diversity.



KEYWORDS: *radical reaction, azide, internal alkene, photoredox catalysis, fluoroalkyl, N-heterocycle*

Organic azides are versatile synthetic intermediates that provide access to a diversity of nitrogenous compounds.[1−3] Their synthetic utility is extensively illustrated by participating in many useful organic and bio-orthogonal transformations, such as the "click" reaction (Huisgen cycloaddition),[4−6] Staudinger ligation,[7,8] Curtius rearrangement,[9] and the Schmidt reaction.[10] Therefore, the preparation of organic azides is of considerable importance in interdisciplinary fields crossing synthetic chemistry, chemical biology, and materials sciences. Allylic azides are a unique azide subclass and heavily suffer from the Winstein rearrangement that can occur at room temperature or even lower temperatures.[11,12] Consequently, they often exist as the form of regioisomeric mixtures. Development of practical approaches to access allylic azides, in particular, multifunctionalized allylic azides, as single regioisomers, is in high demand.

Radical-mediated functionalization of alkenes supplies a powerful tool for conversion of simple alkenes to numerous value-added products.[13−18] We apply this strategy for the formation of structurally complex multisubstituted allylic and homoallylic azides that are otherwise difficult to obtain.[19−22] In our hypothesis, oxidative quenching of the excited photocatalyst (PC*) by alkyl bromide **2** generates an alkyl radical, which then adds to 1,1-disubstituted allylic azide **1** (or **4**). The resulting radical intermediate **a** can be single-electron oxidized by $PC^{\bullet+}$, leading to the cation species **b**. Deprotonation of **b** gives rise to allylic azide **3** (or homoallylic azide **5**).[23] However, the precedent radical functionalization of alkenes is mainly restricted to terminal alkenes, whereas the conversion of internal alkenes usually remains challenging,[24] as the increased steric congestion on alkenes significantly conflicts with the intermolecular addition of radicals (Scheme 1A).

Herein, we provide a proof-of-principle experimental study for the hypothesis (Scheme 1B). An efficient radical-mediated functionalization of internal alkenes is disclosed, selectively generating allylic and homoallylic azides dependent on the substitution of substrates. The product diversity and complexity can be improved by simply altering external radicals. The transformation features mild photoredox catalytic conditions and unique regioselectivity. The azide products serve as versatile feedstock for construction of useful heterocycles.

At the outset, the easily accessed 1,1-diphenyl allylic azide **1a** was harnessed as the starting material and reacted with bromodifluoroacetate **2a** to survey the reaction parameters (Table 1). Under photochemical conditions,[25−29] evaluation of photosensitizers indicated that *fac*-Ir(ppy)$_3$ delivered the best catalytic efficiency (entries 1−6). A series of inorganic and organic bases was then investigated (entries 7−12). The use of K_2HPO_4 significantly improved the reaction outcome, which might neutralize the HBr generated in situ during the reaction. Among the common solvents examined, 1,2-dichloroethane (DCE) further improved the yield to 74% (entries 13−18).

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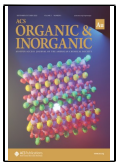


Scheme 1. Synthesis of Multisubstituted Allylic and Homoallylic Azides

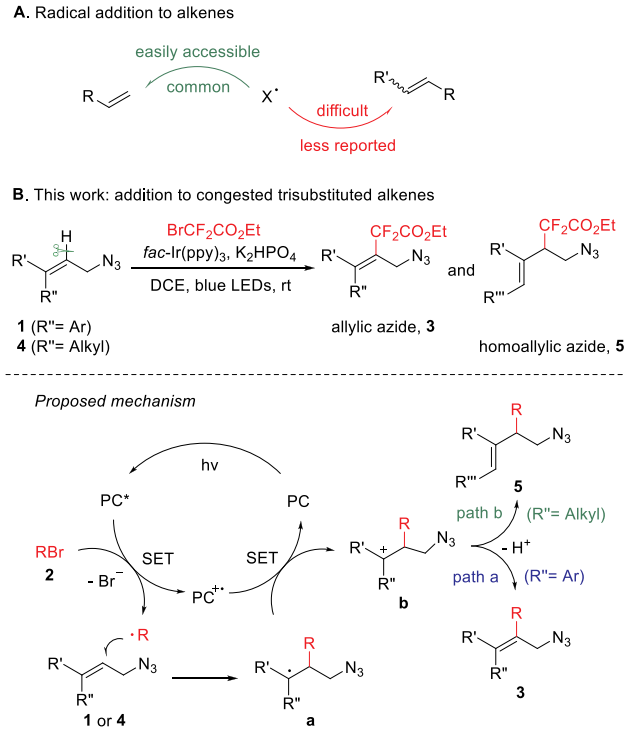
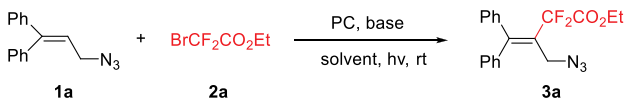


Table 1. Reaction Parameter Survey[a]



entry	PC	base	solvent	yield (%)[b]
1	4CzIPN	K_2CO_3	DMF	12
2	$Ru(bpy)_3(PF_6)_2$	K_2CO_3	DMF	15
3	PTH	K_2CO_3	DMF	0
4	cat. **1**[c]	K_2CO_3	DMF	16
5	cat. **2**[d]	K_2CO_3	DMF	8
6	*fac*-Ir(ppy)$_3$	K_2CO_3	DMF	41
7	*fac*-Ir(ppy)$_3$	K_3PO_4	DMF	42
8	*fac*-Ir(ppy)$_3$	K_2HPO_4	DMF	62
9	*fac*-Ir(ppy)$_3$	KH_2PO_4	DMF	52
10	*fac*-Ir(ppy)$_3$	Na_2HPO_4	DMF	52
11	*fac*-Ir(ppy)$_3$	NaOH	DMF	51
12	*fac*-Ir(ppy)$_3$	Et_3N	DMF	38
13	*fac*-Ir(ppy)$_3$	K_2HPO_4	THF	31
14	*fac*-Ir(ppy)$_3$	K_2HPO_4	CH_3CN	60
15	*fac*-Ir(ppy)$_3$	K_2HPO_4	DMSO	19
16	*fac*-Ir(ppy)$_3$	K_2HPO_4	DCM	68
17	*fac*-Ir(ppy)$_3$	K_2HPO_4	DCE	74
18	*fac*-Ir(ppy)$_3$	K_2HPO_4	EtOAc	46

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), photocatalyst (2 mol %), and base (0.2 mmol, 1.0 equiv) in solvent (2.0 mL) under N_2, irradiated with 15 W blue LEDs at rt. [b]Isolated yield. [c]Cat. **1** = Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)(PF$_6$). [d]Cat. **2** = Ir(ppy)$_2$(dtbbpy)(PF$_6$). 4CzIPN = 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene. PTH = 10-phenylphenothiazine.

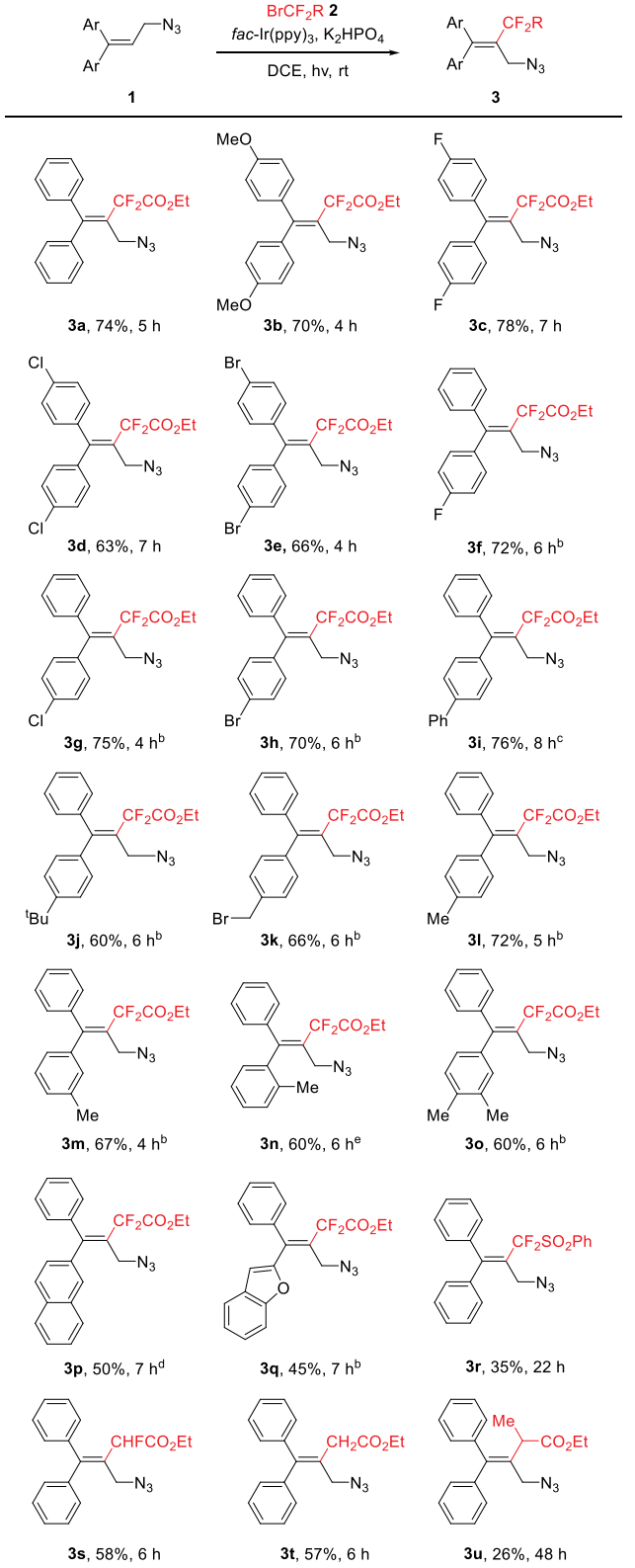


Figure 1. Reaction scope. [a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), *fac*-Ir(ppy)$_3$ (2 mol %), and K_2HPO_4 (0.2 mmol, 1.0 equiv) in DCE (2.0 mL) under N_2, irradiated with 15 W blue LEDs at rt. The yields of isolated products are given. [b]Z/E = 1/1. [c]Z/E = 2/1. [d]Z/E = 1.4/1. [e]Z/E = 1.5:1.

With the optimized reaction conditions in hand, we assessed the generality of the protocol (Figure 1). A set of symmetric 1,1-diaryl allylic azides **1b**−**1e** was first examined in the reaction with **2a**. The substrates bearing either electron-

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donating (e.g., methoxy) or electron-withdrawing (e.g., halides) groups were compatible with the reaction, leading to the desired products **3b**−**3e** in comparable yields. Unsymmetric 1,1-diaryl substrates also readily afforded the corresponding products **3f**−**3q** in useful yields, but the products were obtained, in general, as a mixture of *Z*/*E* isomers. Positional change (from *para* to *meta* or *ortho*) on the aryl substitution to phenyl, naphthyl, and heteroaryl, such as benzofuryl, was also tolerated in the transformation (**3p** and **3q**). The reaction using the congeners bromodifluoromethyl sulfone **2b**, bromomonofluoroacetate **2c**, bromoacetate **2d**, and bromopropanoate **2e** instead of **2a** consistently gave rise to the desired products in synthetically useful yields (**3r**−**3u**). This approach demonstrated a high product diversity in which the tetrasubstituted allylic azides can be easily modified by variation of external radicals and substrates. It should be noted that monoaryl substrates, such as (3-azidoprop-1-en-1-yl)benzene, were not amenable to the reaction, as the reaction proceeded via an alternative atom transfer radical addition (ATRA) process and gave the corresponding bromide product.

The protocol could be extended to the synthesis of homoallylic azides starting from alkyl-substituted materials. Some representative examples are illustrated in Figure 2.

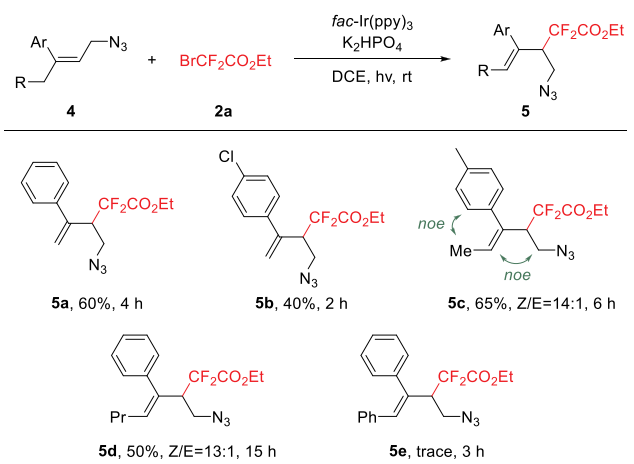

Figure 2. Representative examples for synthesis of allylic azides. [a]Reaction conditions: **4** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), *fac*-Ir(ppy)$_3$ (2 mol %), and K_2HPO_4 (0.2 mmol, 1.0 equiv) in DCE (2.0 mL) under N_2, irradiated with 15 W blue LEDs at rt. The yields of isolated products are given.

Under the same conditions, the use of 1-methyl-1-phenyl allylic azide **4a** furnished homoallylic azide **5a** via the regioselective deprotonation to generate terminal alkene instead of internal alkene. It might be attributed to base-promoted deprotonation which generally prefers a less hindered site. Changing the electronic property of phenyl by installation of functionalities might impact the outcome of the reaction (**5b**). The consumption of **4a** and **4b** should be carefully monitored in the reaction, as the over-reaction involving the generated **5a** and **5b** significantly decreased the yields. Altering methyl to other alkyl (e.g., ethyl and butyl) groups resulted in the corresponding products (**5c** and **5d**), of which (*Z*)-alkenes are the major isomers. The configuration of **5c** was determined by the NOE NMR analysis, where the allylic CH_3 group has a correlation with the phenyl C−H bonds, and the alkenyl C−H bond shows the correlation with the CH_2 moiety adjacent to azide. It could be anticipated that more homoallylic azide products could be afforded by varying either the aryl or the alkyl substituents. Surprisingly, the reaction with the substrate bearing a benzyl group was messy, and only a trace amount of corresponding product **5e** was detected by the mass spectrum.

The practicality of the method could be illustrated by the gram-scale preparation, leading to a synthetically useful yield of **3a** (Figure 3A). Allylic azide **3a** serves as a versatile

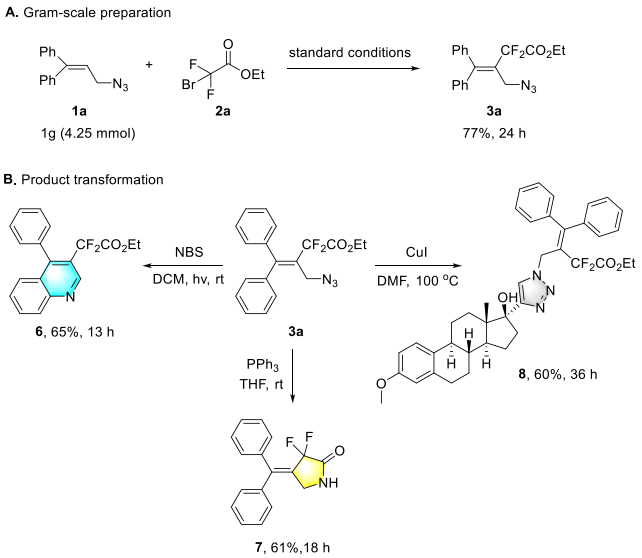

Figure 3. Gram-scale synthesis and product transformations.

intermediate to construct various nitrogenous heteroarenes (Figure 3B). For instance, irradiation of the reaction of **3a** with NBS under compact fluorescent light resulted in the difluoroalkyl-substituted quinoline **6**.[30] Treatment of **3a** with PPh_3 delivered the α,α-difluorobutyrolactam **7** via the Staudinger reduction of azide to amine followed by intramolecular cyclization. Furthermore, the existence of azide provides a platform of "click" reaction to attach the tetrasubstituted alkene to bioactive molecules (**8**), such as ethynyl estradiol 3-methyl ether.

In summary, we have disclosed an efficient photoredox catalytic approach for elusive radical-mediated functionalization of internal trisubstituted alkenes. A portfolio of valuable multifunctionalized allylic and homoallylic azides are obtained in synthetically useful yields. The regioselective deprotonation leading to different products is predominated by the substitution of substrates. The products serve as versatile feedstock for the construction of useful nitrogenous heterocycles. The protocol features mild reaction conditions and high product diversity and paves a new avenue for the synthesis of complex azides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.2c00017.

All experimental details including further optimization studies; detailed procedures; proper characterization of all products; and copies of ^1H, ^{19}F, ^{13}C NMR, and NOE spectra (PDF)

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Author Contributions

Y.C. and J.W. contributed equally. Y.C. and J.W. performed all experiments. Y.C., J.W., X.W., and C.Z. conceived the project and analyzed the results. C.Z. wrote the manuscript with the input of all the authors.

Notes

The authors declare no competing financial interest.

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