

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

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Cite This: *ACS Org. Inorg. Au* 2022, 2, 392–395

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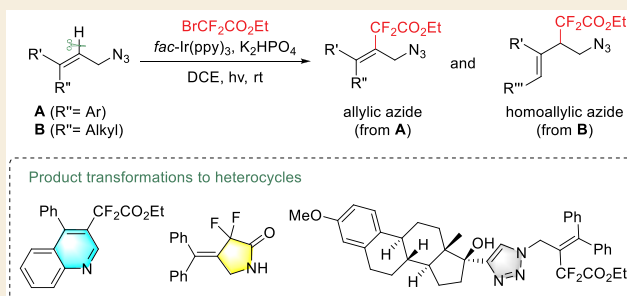
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**ABSTRACT:** Radical-mediated functionalization of alkenes provides a powerful tool for transformation of simple alkenes into numerous value-added products. The precedent radical functionalization of alkenes is mainly restricted to terminal alkenes, 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



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.

Organic azides are versatile synthetic intermediates that provide access to a diversity of nitrogenous compounds.<sup>1–3</sup> Their synthetic utility is extensively illustrated by participating in many useful organic and bio-orthogonal transformations, such as the “click” reaction (Huisgen cycloaddition),<sup>4–6</sup> Staudinger ligation,<sup>7,8</sup> Curtius rearrangement,<sup>9</sup> and the Schmidt reaction.<sup>10</sup> 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.<sup>11,12</sup> 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.<sup>13–18</sup> We apply this strategy for the formation of structurally complex multisubstituted allylic and homoallylic azides that are otherwise difficult to obtain.<sup>19–22</sup> 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\*, leading to the cation species **b**. Deprotonation of **b** gives rise to allylic azide **3** (or homoallylic azide **5**).<sup>23</sup> However, the precedent radical functionalization of alkenes is mainly restricted to terminal alkenes, whereas the conversion of internal alkenes usually remains challenging,<sup>24</sup> 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.

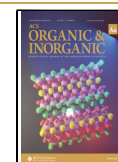
At the outset, the easily accessed 1,1-diphenyl allylic azide **1a** was harnessed as the starting material and reacted with bromodifluoroacetate **2a** to survey the reaction parameters (Table 1). Under photochemical conditions,<sup>25–29</sup> evaluation of photosensitizers indicated that *fac*-Ir(ppy)<sub>3</sub> 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<sub>2</sub>HPO<sub>4</sub> 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).

Received: April 14, 2022

Revised: May 5, 2022

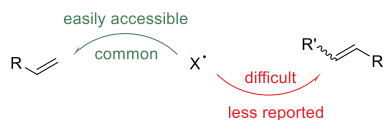
Accepted: May 5, 2022

Published: May 9, 2022

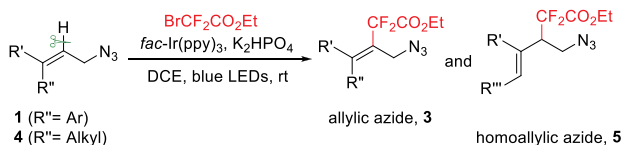


## Scheme 1. Synthesis of Multisubstituted Allylic and Homoallylic Azides

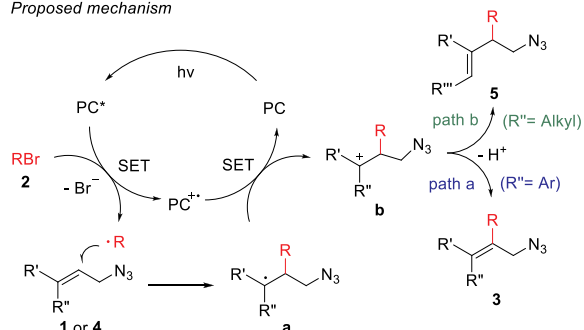
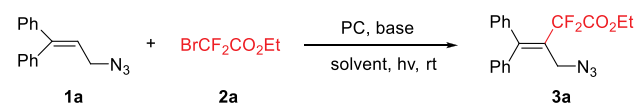
## A. Radical addition to alkenes



## B. This work: addition to congested trisubstituted alkenes



## Proposed mechanism

Table 1. Reaction Parameter Survey<sup>a</sup>

entry	PC	base	solvent	yield (%) <sup>b</sup>
1	4CzIPN	K <sub>2</sub> CO <sub>3</sub>	DMF	12
2	Ru(bpy) <sub>3</sub> (PF <sub>6</sub> ) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	DMF	15
3	PTH	K <sub>2</sub> CO <sub>3</sub>	DMF	0
4	cat. 1 <sup>c</sup>	K <sub>2</sub> CO <sub>3</sub>	DMF	16
5	cat. 2 <sup>d</sup>	K <sub>2</sub> CO <sub>3</sub>	DMF	8
6	fac-Ir(ppy) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	DMF	41
7	fac-Ir(ppy) <sub>3</sub>	K <sub>3</sub> PO <sub>4</sub>	DMF	42
8	fac-Ir(ppy) <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub>	DMF	62
9	fac-Ir(ppy) <sub>3</sub>	KH <sub>2</sub> PO <sub>4</sub>	DMF	52
10	fac-Ir(ppy) <sub>3</sub>	Na <sub>2</sub> HPO <sub>4</sub>	DMF	52
11	fac-Ir(ppy) <sub>3</sub>	NaOH	DMF	51
12	fac-Ir(ppy) <sub>3</sub>	Et <sub>3</sub> N	DMF	38
13	fac-Ir(ppy) <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub>	THF	31
14	fac-Ir(ppy) <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub>	CH <sub>3</sub> CN	60
15	fac-Ir(ppy) <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub>	DMSO	19
16	fac-Ir(ppy) <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub>	DCM	68
17	fac-Ir(ppy) <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub>	DCE	74
18	fac-Ir(ppy) <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub>	EtOAc	46

<sup>a</sup>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<sub>2</sub>, irradiated with 15 W blue LEDs at rt. <sup>b</sup>Isolated yield. <sup>c</sup>Cat. 1 = Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)(PF<sub>6</sub>). <sup>d</sup>Cat. 2 = Ir(ppy)<sub>2</sub>(dtbbpy)(PF<sub>6</sub>). 4CzIPN = 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene. PTH = 10-phenylphenothiazine.

With the optimized reaction conditions in hand, we assessed the generality of the protocol (Figure 1). A set of symmetric

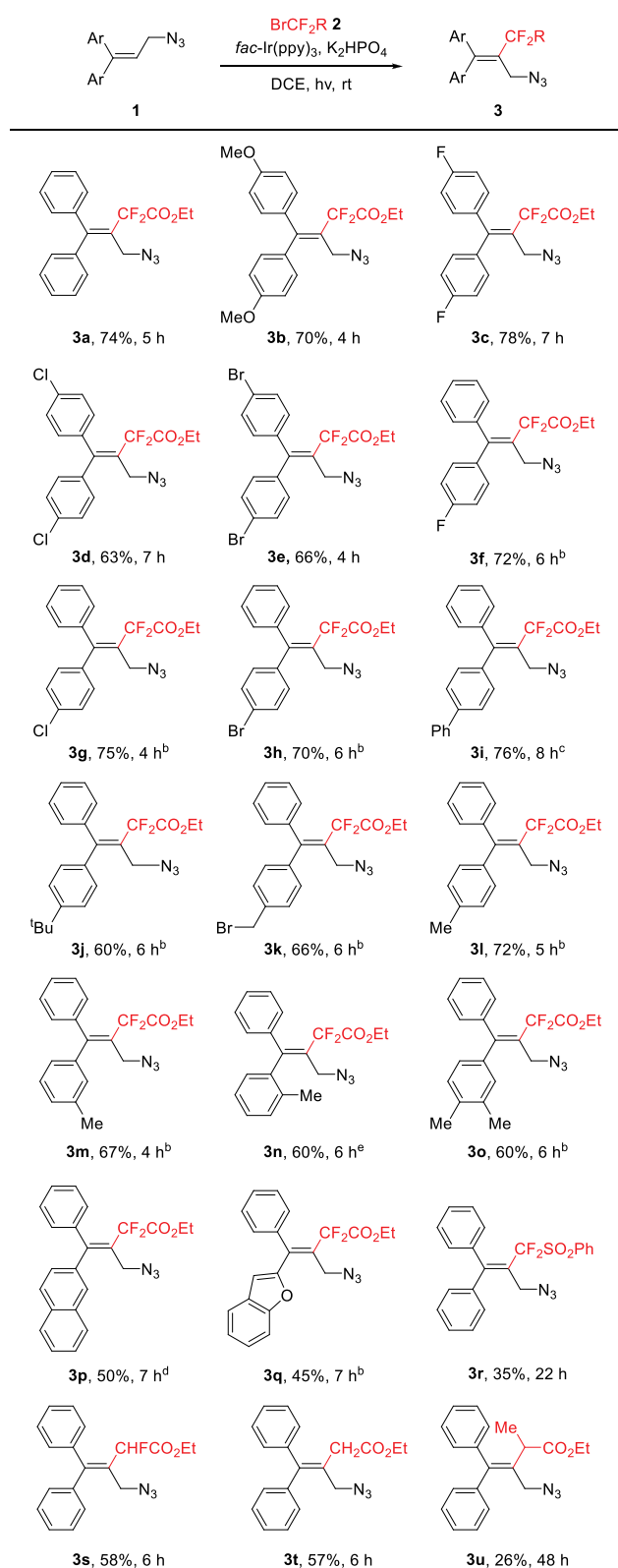
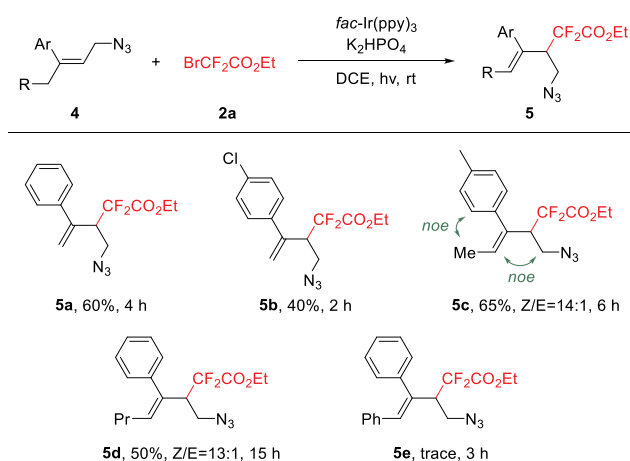


Figure 1. Reaction scope. <sup>a</sup>Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), fac-Ir(ppy)<sub>3</sub> (2 mol %), and K<sub>2</sub>HPO<sub>4</sub> (0.2 mmol, 1.0 equiv) in DCE (2.0 mL) under N<sub>2</sub>, irradiated with 15 W blue LEDs at rt. The yields of isolated products are given. <sup>b</sup>Z/E = 1/1. <sup>c</sup>Z/E = 2/1. <sup>d</sup>Z/E = 1.4/1. <sup>e</sup>Z/E = 1.5/1.

1,1-diaryl allylic azides **1b–1e** was first examined in the reaction with **2a**. The substrates bearing either electron-

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.

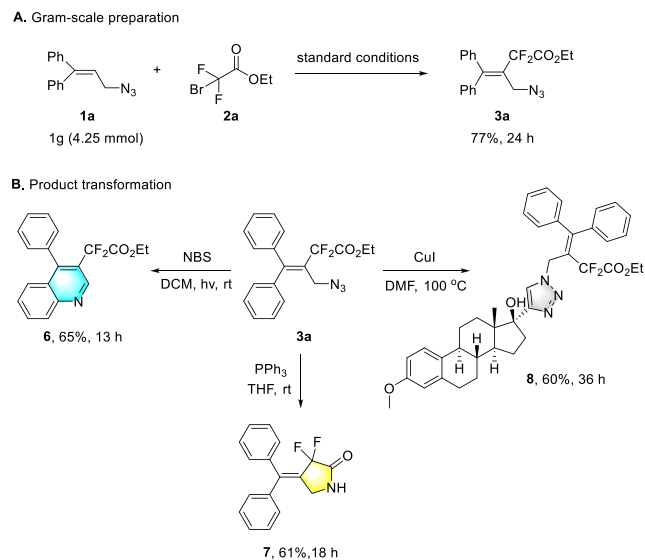


**Figure 2.** Representative examples for synthesis of allylic azides. <sup>a</sup>Reaction conditions: **4** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv),  $\text{fac-Ir(ppy)}_3$  (2 mol %), and  $\text{K}_2\text{HPO}_4$  (0.2 mmol, 1.0 equiv) in DCE (2.0 mL) under  $\text{N}_2$ , irradiated 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  $\text{CH}_3$  group has a correlation with the phenyl C–H bonds, and the alkenyl C–H bond shows the correlation with the  $\text{CH}_2$  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**.<sup>30</sup> Treatment of **3a** with  $\text{PPh}_3$  delivered the  $\alpha,\alpha$ -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  $^1\text{H}$ ,  $^{19}\text{F}$ ,  $^{13}\text{C}$  NMR, and NOE spectra (PDF)

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<https://pubs.acs.org/10.1021/acsorginorgau.2c00017>

## 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.

## ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (Grant Nos. 21971173, 22001185, and 22171201), the Project of Scientific and Technologic Infrastructure of Suzhou (SZS201905), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

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