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Visible-Light Photoredox-Catalyzed Formal [5 + 1] Cycloaddition of *N*-Tosyl Vinylaziridines with Difluoroalkyl Halides

Yantao Liu, Wen Luo,* Zhenjie Wang, Yuxin Zhao, Jingjing Zhao,* Xuejun Xu, Chaojie Wang, and Pan Li*

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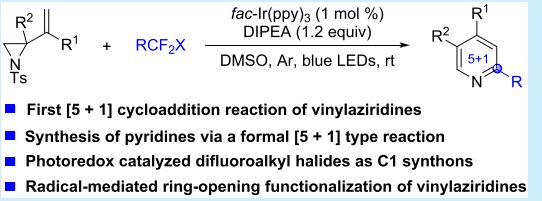
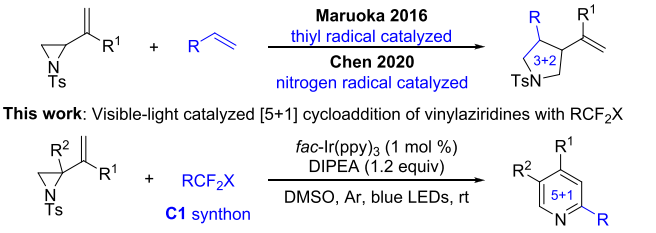
ABSTRACT: A visible-light photoredox-catalyzed formal [5 + 1] cycloaddition of *N*-tosyl vinylaziridines with difluoroalkyl halides as unique C1 synthons was developed. The procedure provides an efficient and practical method to synthesize diverse pyridines in moderate to good yields. The reaction underwent a radical-initiated kinetically controlled ring-opening of vinylaziridines and involved a key α,β-unsaturated imine intermediate, followed by an E2 elimination, a 6π electrocyclization, and defluorinated aromatization.



Cycloaddition reactions have received extensive attention in organic synthesis, because they provide an efficient and practical method for the construction of versatile carbocycles and nitrogen-containing heterocycles. Over the last few decades, extensive research has focused on the development of cycloaddition methodologies to synthesize various pyridines that are beneficial scaffolds for natural products, agrochemicals, and pharmaceuticals.[1] Compared to classic condensation protocols, which are available for the construction of pyridines, many elegant cycloaddition strategies, including [4 + 2],[2] [3 + 3],[3] [2 + 2 + 2],[4] and [3 + 2 + 1],[5] have also been developed and reported. Despite these, novel complementary cycloaddition approaches for the preparation of diversely substituted pyridines are still highly desirable.

Vinylaziridines are versatile building blocks in organic synthesis;[6] they have multiple reactive sites and are prone to various ring opening functionalization, because of the presence of the vinyl moiety and the highly strained aziridine scaffold. By utilizing nucleophilic ring-opening and metal-catalyzed ring-opening strategies, the synthesis of diverse N-heterocycles from vinylaziridines through [3 + 1],[7] [3 + 2],[8] [3 + 3],[9] [3 + 4],[10] and [5 + 2][11] cycloadditions with different synthons is well-known. In sharp contrast, radical initiated selective ring-opening functionalization[12] of aziridines via nitrogen-centered radical[13−16] remains underdeveloped. Recently, Maruoka developed the thiyl-radical-catalyzed [3 + 2] cyclization ring opening of vinylaziridines and alkenes.[14] Remarkably, identical transformations were also achieved through nitrogen radical catalysis by Chen.[15] Therefore, developing new radical reactivities and novel [5 + 1][17] cycloaddition reactions of vinylaziridines is highly desired. Inspired by difluoroalkyl halides[18] as a unique C1 synthon,[19] we wished to develop a visible-light, photoredox-catalyzed, formal [5 + 1] cycloaddition of N-tosyl vinylaziridines with difluoroalkyl halides to synthesize various pyridines via a radical-mediated ring-opening functionalization strategy (Scheme 1).[20] To the best

Scheme 1. Cycloaddition Reactions of Vinylaziridines



of our knowledge, this transformation was the first [5 + 1] cycloaddition reaction of vinylaziridines, first synthesis of pyridines via a formal [5 + 1]-type reaction, and first photoredox-catalyzed difluoroalkyl halides as C1 synthons.

We began our investigation with 2-(1-phenylvinyl)-1-tosylaziridine **1a** and ethyl 2-bromo-2,2-difluoroacetate **2a** as the model reaction; selected results are summarized in Table 1. After an extensive screening of reaction parameters, we isolated the desired product **3aa** in 85% yield using *fac*-Ir(ppy)$_3$ as the photocatalyst in the presence of diisopropylethylamine (DIPEA) in DMSO under blue LEDs. Considering that difluoroalkyl radicals are more readily generated in the presence of bases and silver salts,[21] we discovered that

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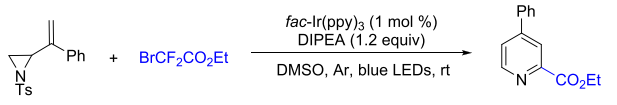
Table 1. Reaction Optimization[a]



1a 2a 3aa

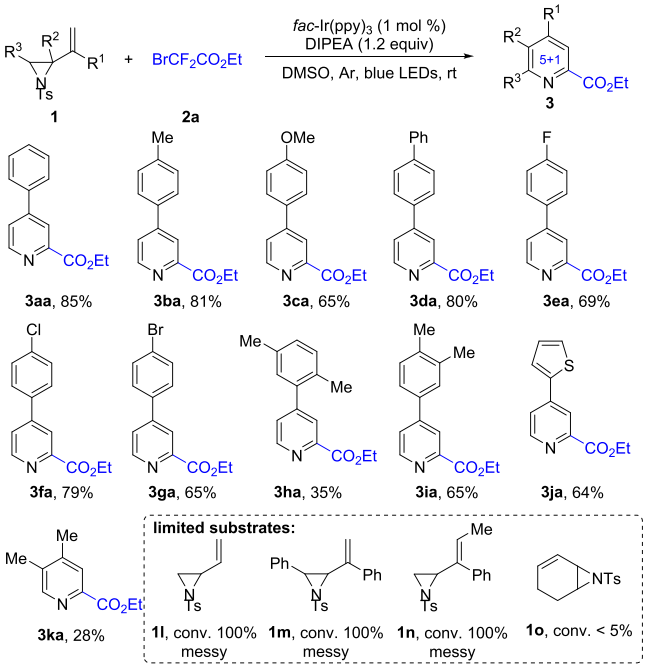
entry	variation from the standard conditions	yield (%)
1	standard conditions	88 (85[b])
2	TMEDA instead of DIPEA	42
3	K_2CO_3 instead of DIPEA	46
4	K_3PO_4 instead of DIPEA	55
5	NaOAc instead of DIPEA	60
6	AgF instead of DIPEA	53
7	Ag_2CO_3 instead of DIPEA	46
8	$Ru(bpy)_3Cl_2$ instead of *fac*-Ir(ppy)$_3$	50
9	eosin instead of *fac*-Ir(ppy)$_3$	ND[c]
10	DMF instead of DMSO	52
11	MeCN instead of DMSO	49
12	DCE instead of DMSO	52
13	$CHCl_3$ instead of DMSO	messy
14	addition of 1 equiv of Hantzsch ester	ND[c,d]
15	addition of 1 equiv of sodium ascorbate	15[d]
16	0.6 equiv DIPEA	40
17	without DIPEA	ND[c,e]
18	in air	40
19	without *fac*-Ir(ppy)$_3$	trace
20	in darkness	NR[f]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), *fac*-Ir(ppy)$_3$ (1 mol %), DIPEA (0.24 mmol), solvent (2 mL), blue LEDs, Ar, rt, 12 h. Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b]Yield of the isolated product after column chromatography. [c]ND = none detected. [d]Self-cyclization product of **1a** was observed. [e]The intermediate **3aa′** was observed in the crude ^{1}H NMR. [f]NR = no reaction.

DIPEA was the most effective adjuvant (Table 1, entries 1−7). The photocatalyst choice was critical in the transformation. For example, **3aa** was obtained in 50% yield using $Ru(bpy)_3Cl_2$ instead of *fac*-Ir(ppy)$_3$; however, no product **3aa** was observed using Eosin Y as the photocatalyst (Table 1, entries 8 and 9). Solvent screening revealed that the reaction proceeded smoothly in other solvents, such as dimethylfluoride (DMF), acetonitrile (MeCN), dichloroethane (DCE) (Table 1, entries 10−12). However, a messy reaction was found using $CHCl_3$ as the solvent (Table 1, entry 13). The byproduct 3-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole, which is generated from the self-cyclization of **1a**, was observed obviously when the Hantzsch ester or sodium ascorbate was added (Table 1, entries 14 and 15). Notably, the yield of **3aa** declined to 40% when using 0.6 equiv of DIPEA (Table 1, entry 16). To our delight, **3aa′** was observed in the crude ^{1}H NMR without DIPEA (Table 1, entry 17). In addition, conducting the reaction in air resulted in a yield of only 40% for **3aa** (Table 1, entry 18). As expected, control experiments verified the necessity of light irradiation and the photocatalyst for the current transformation (Table 1, entries 19 and 20).

Upon optimizing the reaction conditions, the scope and limitations of this reaction, with respect to N-tosyl vinylaziridines, were investigated with ethyl 2-bromo-2,2-difluoroacetate **2a** (Scheme 2). To our delight, a series of representative aryl *N*-tosyl vinylaziridines (at the R^1 site) containing either electron-donating (OMe and Me) or electron-withdrawing (F, Cl, Br, and Ph) groups all worked

Scheme 2. Scope and Limitation of *N*-Tosyl Vinylaziridines[a]



[a]Standard conditions: **1** (0.2 mmol), **2a** (0.24 mmol), *fac*-Ir(ppy)$_3$ (1 mol %), DIPEA (0.24 mmol), DMSO (2 mL), blue LEDs, Ar, rt, 12 h. Isolated yields after column chromatography.

well with **2a**, affording the desired indolin-2-ones (**3aa**−**3ga**) in yields of 65%−85%. However, the sterically hindered **1h** could also be employed as a substrate, only giving the desired product **3ha** in 35% yield. Notably, disubstituted vinylaziridines also proved to be suitable for this transformation, with **1h** giving the desired **3ia** product in 65% yield, while the thienyl-substituted vinylaziridine **1j** also worked well in the reaction, affording the desired product **3ja** in a good yield. Expanding the scope of *N*-tosyl vinylaziridines from aryl to alkyl groups (R^1 = Me) only gave the corresponding product **3ka** in 28% yield. Unfortunately, the use of 1-tosyl-2-vinylaziridine **1l** (R^1 = H) resulted in no reaction product being observed.[22] Besides, *N*-tosyl vinylaziridine **1m** (R^3 = Ph) and internal olefins (**1n** and **1o**) were not suitable for this system.

Encouraged by the above results, we investigated the scope of difluoroalkyl halides with 2-(1-phenylvinyl)-1-tosylaziridine **1a**. As shown in Scheme 3, this catalytic system showed a broad substrate scope and high functional group tolerance concerning difluoroalkyl halides. As expected, 2-iodide-2,2-difluoroacetate and methyl 2-bromo-2,2-difluoroacetate also worked well, yielding the desired **3aa** and **3ab** in 88% and 60% yields, respectively. Various types of bromodifluoroacetamide derivatives were examined, affording the corresponding pyridines (**3ac**−**3am**) in yields of 41%−95%. Unfortunately, the reactions of *N*-tosyl vinylaziridine **1a** and difluoroalkyl bromides (R = PhCO, EtCO) does not proceed under standard conditions. Significantly, bromodifluoroacetamide amino acids can serve as versatile building blocks for diversified transformations, giving the desired pyridines (**3an**−**3ar**) in yields of 44%−81%. Bromodifluorooxadiazole also worked well, yielding the desired **3as** in 82% yield, and using dibromofluoromethane instead of difluoroalkyl halides, the desired pyridine **3at** was obtained in 45% yield. When *N*-aryl

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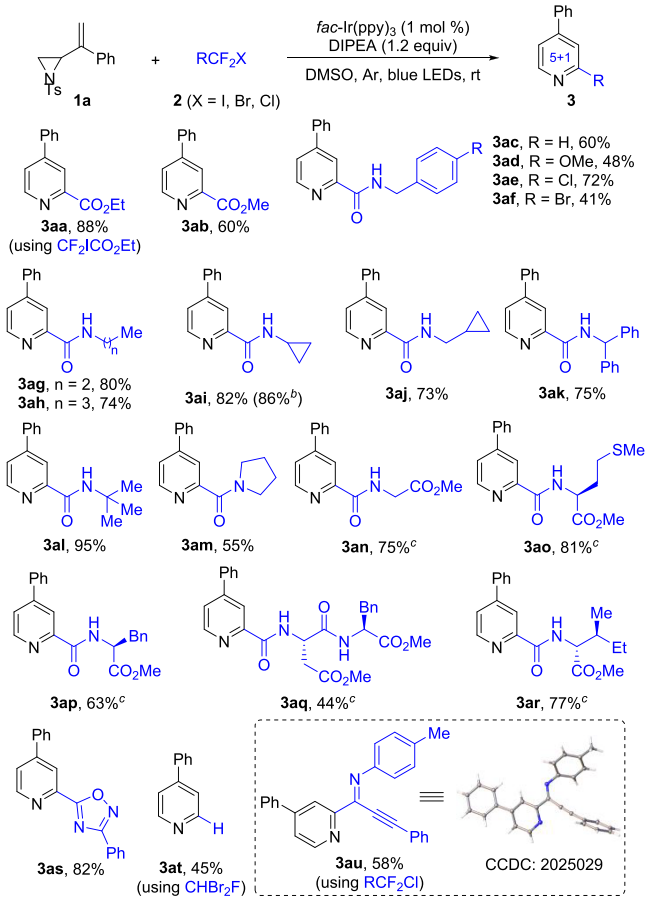
Scheme 3. Scope of Difluoroalkyl Halides[a]

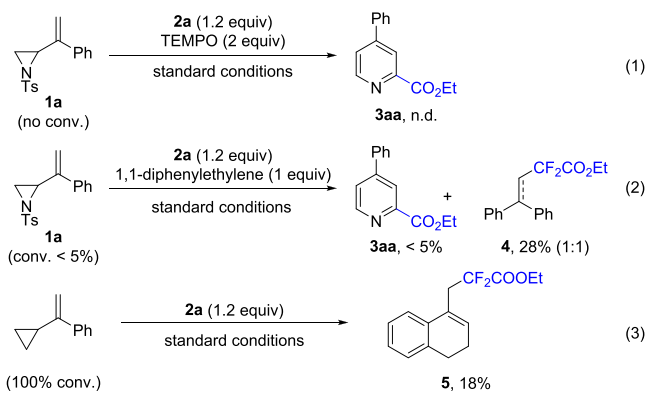


[a]Standard conditions: **1a** (0.2 mmol), **2** (0.24 mmol), *fac*-Ir(ppy)$_3$ (1 mol %), DIPEA (0.24 mmol), DMSO (2 mL), blue LEDs, Ar, rt, 12 h. Isolated yields after column chromatography. [b]**3ai** was obtained in 86% yield on a 2 mmol scale. [c]A quantity of 2 equiv of $BrCF_2R$ was used, 48 h.

chlorodifluoromethyl alkynyl ketoimines were used, the desired product **3au** was obtained in 58% yield. The structure was unambiguously confirmed by X-ray diffraction (XRD) (CCDC No. 2025029).

To elucidate the reaction mechanism, essential radical trapping experiments with substrates **1a** and **2a** were conducted as shown in Scheme 4. The reaction stopped completely when 2,2,6,6-tetramethylpiperidinooxy (TEMPO)

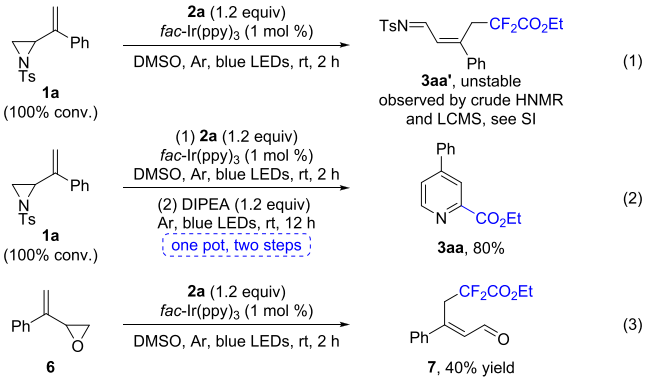
Scheme 4. Radical Trapping Experiments



was added into the model reaction (see eq 1 in Scheme 4). Only trace amounts of **3aa** were observed using ethene-1,1-diyldibenzene instead of TEMPO. Also, the adduct **4** of difluoroalkyl radical and ethene-1,1-diyldibenzene were obtained in 28% yield (see eq 2 in Scheme 4). Different from 2-(1-phenylvinyl)-1-tosylaziridine **1a**, the classic radical clock experiment revealed the corresponding **5** was obtained in 18% yield under standard conditions (see eq 3 in Scheme 4).[23] These results suggested that $\bullet CF_2CO_2Et$ may be involved during the reaction.

To gain further insight into the reaction mechanism, additional control experiments were conducted (see Scheme 5). Fortunately, a key intermediate **3aa′** (although not stable)

Scheme 5. Control Experiments



was observed in the crude ^{1}H NMR and LCMS under standard conditions without DIPEA (see eq 1 in Scheme 5),[24] and **3aa′** further transformed to **3aa** in 80% yield in the presence of DIPEA in a one pot, two-step process (see eq 2 in Scheme 5). These two results undoubtedly demonstrated that the generation of pyridine **3aa** involved the **3aa′** intermediate. In addition, using vinyl epoxide **6** instead of **1a**, the product **7** was obtained in 40% yield under standard conditions without DIPEA (see eq 3 in Scheme 5).

Based on the above results, a proposed mechanism is depicted with 2-(1-phenylvinyl)-1-tosylaziridine **1a** and ethyl 2-bromo-2,2-difluoroacetate **2a** as the standard substrates (see Scheme 6).[25] Initially, $\bullet CF_2CO_2Et$ was generated from **2a** with the assistance of a photoexcited $^*Ir^{III}$ catalyst, which was then oxidized to form an Ir^{IV} catalyst. The electrophilic $\bullet CF_2CO_2Et$ then reacted with **1a** to form the carbon radical **M1**, which rapidly undergoes selective ring-opening, because of the ring strain of aziridine. C−N bond cleavage formed a nitrogen radical **M2** (Path A); alternatively, C−C bond cleavage[26] could form a nitrogen-stabilized carbon radical **M2′** (Path B). It is well-known that the carbon radical is more stable than the nitrogen radical, the formation of carbon radical **M2′** should be thermodynamically favored. However, based on the bond dissociation energy (BDE) of the C−C bond (81 kcal/mol), relative to the C−N bond (66 kcal/mol), the formation of nitrogen radical **M2** was kinetically favored.[27] Subsequently, **M2** could donate an electron to Ir^{IV} to regenerate the Ir^{III} catalyst for the next catalytic cycle,[28] giving an α,β-unsaturated imine **3aa′** via deprotonation. Alternatively, **M2** could be easily reduced to **M3′** (Path C), then underwent an intramolecular cyclization to give **M4′**, which could also transform to the final product **3aa**. Based on the control experiments (Scheme 5) and Stern−Volmer experiments (see the Supporting Informa-

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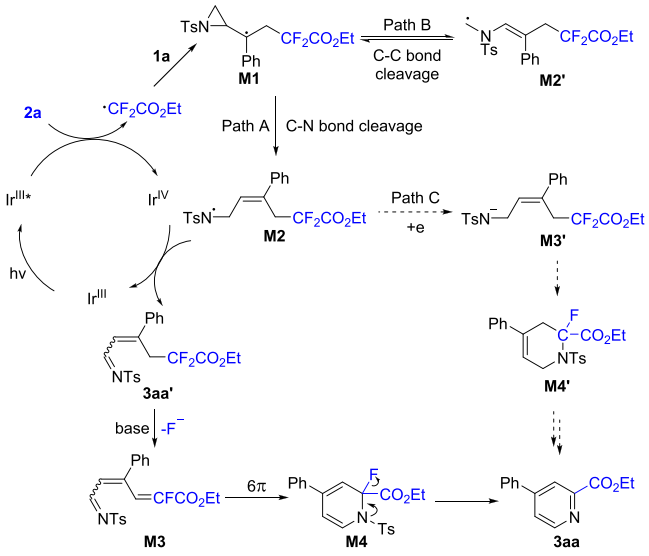
Scheme 6. Plausible Mechanism



tion for details), Path C should be excluded. With the assistance of base, **3aa′** transformed to **M3** via an E2 elimination, then underwent a 6π electrocyclization to give **M4**.[29] Eventually, the desired product **3aa** was obtained from **M4** via a defluorinated aromatization.

In summary, we have first developed a visible-light photoredox-catalyzed [5 + 1] cycloaddition of *N*-tosyl vinylaziridines. The procedure provided a novel method for the synthesis of diverse pyridines in moderate to good yields from *N*-tosyl vinylaziridines using difluoroalkyl halides as distinctive C1 synthons. These investigations showed that the reaction underwent a radical-initiated ring-opening functionalization. Significantly, control experiments undoubtedly demonstrated that an α,β-unsaturated imine is the key intermediate. Efforts in our laboratory are ongoing to explore other novel radical-initiated ring-opening functionalization of vinylaziridines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03718.

Experimental details, compound characterization data (PDF)

Accession Codes

CCDC 2025029 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Pan Li − *Institute of Functional Organic Molecular Engineering, College of Chemistry and Chemical Engineering and Key Laboratory of Natural Medicine and Immuno-Engineering, Henan University, Kaifeng 475004, People's Republic of China*; orcid.org/0000-0001-6658-9207; Email: panli@henu.edu.cn

Wen Luo − *Key Laboratory of Natural Medicine and Immuno-Engineering, Henan University, Kaifeng 475004, People's Republic of China*; Email: luowen83@163.com

Jingjing Zhao − *Institute of Functional Organic Molecular Engineering, College of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, People's Republic of China*; Email: zhaojingjing@henu.edu.cn

Authors

Yantao Liu − *Institute of Functional Organic Molecular Engineering, College of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, People's Republic of China*

Zhenjie Wang − *Institute of Functional Organic Molecular Engineering, College of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, People's Republic of China*

Yuxin Zhao − *Institute of Functional Organic Molecular Engineering, College of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, People's Republic of China*

Xuejun Xu − *Institute of Functional Organic Molecular Engineering, College of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, People's Republic of China*

Chaojie Wang − *Key Laboratory of Natural Medicine and Immuno-Engineering, Henan University, Kaifeng 475004, People's Republic of China*; orcid.org/0000-0001-6782-0650

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03718

Notes

The authors declare no competing financial interest.

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