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Visible-Light-Induced Aza-Pinacol Rearrangement: Ring Expansion of Alkylidenecyclopropanes

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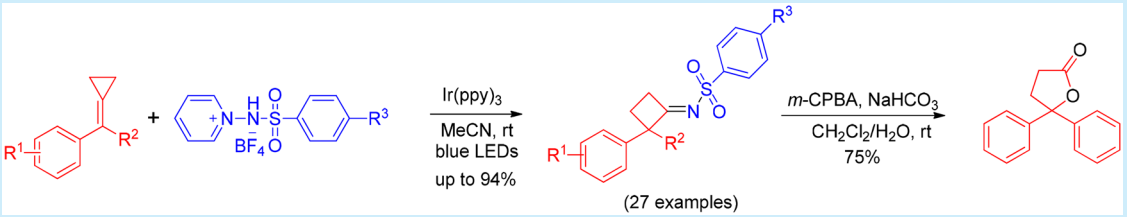
Supporting Information



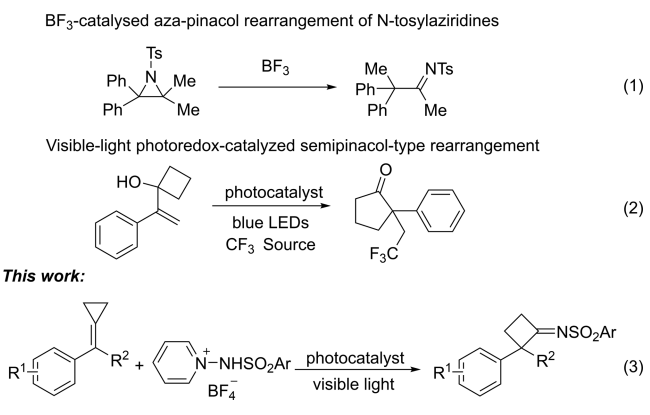
ABSTRACT: A novel visible-light-induced aza-pinacol rearrangement was developed for the first time. In this approach, the addition of the N-centered radical to the C=C bond of alkylidenecyclopropanes delivers a variety of cyclobutanimines and γ-butyrolactones, with all-carbon quaternary centers via the ring expansion of the cyclopropyl group, in moderate to good yields under mild reaction conditions.

Very often, modern medicinal molecules contain some new and unconventional structural motifs such as small strained ring systems.[1] However, developing methods to rapidly and directly construct these valuable scaffolds is still a big challenge for medicinal chemists. Considering the ubiquity of nitrogen-containing molecules in pharmaceuticals and bioactive natural products,[2] we herein describe a simple method to build strained cyclobutanimine skeleton via visible-light photocatalytic aza-pinacol rearrangement.

Pinacol[3] and semipinacol[4] rearrangements are among the most well-known classical reactions in organic synthesis, which play an important role in the construction of α-quaternary carbon centers, especially all-carbon quaternary centers. These rearrangement reactions via transition metal catalysis and organic catalysis have been extensively investigated and widely used in the total synthesis of natural products.[5] However, the aza-pinacol rearrangement is rarely reported[6] (Scheme 1, eq 1) due to its weak driving force compared with the pinacol rearrangement and the relatively high activity of the aza-pinacol rearrangement product—imine. Thus, the development of a novel, environmentally benign aza-pinacol rearrangement under mild conditions remains a significant challenge.

Over the past decades, photoredox catalysis has emerged as a powerful and sustainable synthetic technology for the generation of various radical intermediates via a single-electron-transfer pathway, which could participate in many valuable chemical reactions.[7] For example, Frank Glorius and co-workers have reported a photoredox-catalyzed semipinacol-type rearrangement with the CF_3 radical (Scheme 1, eq 2).[8] The N-centered radical, a powerful intermediate in organic synthesis, could also be readily generated via visible-light photoredox catalysis, which has been widely employed in addition reactions and cross-coupling reactions.[9] Given that

Scheme 1. Designed Aza-Pinacol Rearrangement by Visible-Light Photoredox Catalysis



alkylidenecyclopropanes (ACPs) as versatile synthons have been broadly used in the synthesis of cyclobutane derivatives and larger rings,[10] we devised a novel aza-pinacol rearrangement, which was initiated by a highly reactive nitrogen radical generated via visible-light photocatalysis, to construct the synthetically useful cyclobutanimine scaffold under the mild conditions. (Scheme 1, eq 3)

To test our hypothesis, the investigation began with the reaction of diphenylmethylenecyclopropane **1a** with *N*-Ts-protected 1-aminopyridinium **2a** using $Ir(ppy)_3$ as a photocatalyst at room temperature under irradiation with a 25 W blue LED for 36 h (Table 1). To our delight, the rearrangement

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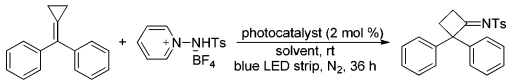
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

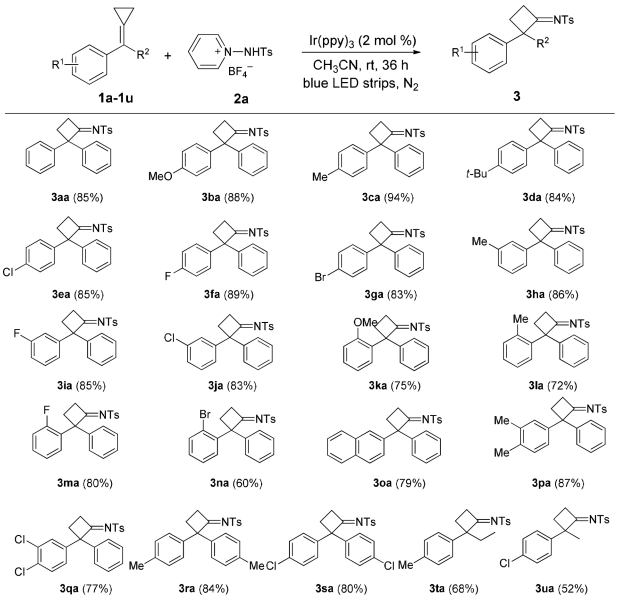
entry	catalyst	1a/2a	solvent	yield[b] (%)
1	$Ir(ppy)_3$	1:1.5	MeCN	61
2	$Ir(ppy)_2(dtbbpy)PF_6$	1:1.5	MeCN	54
3	$Ru(bpy)_3Cl_2$	1:1.5	MeCN	57
4	$Ir(ppy)_3$	1:1.5	DCM	42
5	$Ir(ppy)_3$	1:1.5	DCE	50
6	$Ir(ppy)_3$	1:1.5	CH_3OH	48
7	$Ir(ppy)_3$	1:1.5	acetone	55
8	$Ir(ppy)_3$	1:1.5	DMSO	30
9	$Ir(ppy)_3$	1:1.5	THF	NR
10	$Ir(ppy)_3$	1:2	MeCN	65
11	$Ir(ppy)_3$	1:3	MeCN	76
12	$Ir(ppy)_3$	1:4	MeCN	85
13		1:4	MeCN	NR
14[c]	$Ir(ppy)_3$	1:4	MeCN	NR

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.5–4 equiv), photocatalyst (0.002 mmol), MeCN (4 mL), 25 W blue LED strip, room temperature, under a N_2 atmosphere. [b]Isolated yield. [c]In the dark.

product of *N*-tosyl-2,2-diphenylcyclobutanimine **3aa** was obtained in a yield of 61% (Table 1, entry 1). When $Ir(ppy)_2(dtbbpy)PF_6$ and $Ru(bpy)_3Cl_2$ were used as the photocatalysts, the yield of **3aa** was 54% and 57%, respectively (Table 1, entries 2 and 3). Solvent screening showed that MeCN was an optimal solvent for this transformation (Table 1, entries 4–9). Moreover, increasing the quantity of *N*-Ts-protected 1-aminopyridinium **2a** could lead to higher yields (Table 1, entries 10–12). Further control experiments revealed that both $Ir(ppy)_3$ and visible-light were necessary for this rearrangement protocol (Table 1, entries 13 and 14).

With the reaction conditions optimized, the substrate scope of this aza-pinacol rearrangement was then evaluated. Generally, good to excellent yields were achieved with a variety of electron-donating and electron-withdrawing substituents on one of aromatic rings of ACPs (**3aa**–**3na**), which are listed in Scheme 2. When an electron-donating substituent, such as a methoxyl group, methyl group, and tertiary butyl group, or an electron-withdrawing substituent, such as a halogen atom, was at the *para*-position of the aromatic ring, the reaction proceeded smoothly to give the corresponding rearrangement product in good to excellent yields (**3ba**–**3ga**, 83%–94% yield). Similar results were obtained for substituents at the *meta*-position of the aromatic ring (**3ha**–**3ja**, 83%–86% yield). Lower yields of the desired products were seen for the substrates with the substituents at the *ortho*-position of the aromatic ring (**3ka**–**3na**, 60%–80% yield). Notably, the substrate with a naphthyl group also gave the desired product **3oa** in a yield of 79%. Furthermore, substrates with two substituents on the aromatic ring were also studied, and the corresponding products were formed in good yields (**3pa** and **3qa**, 87% and 77% yield). Two symmetrical ACPs underwent ring expansion under the optimal conditions to afford **3ra** and **3sa** in 84% and 80% yields, respectively. In addition, substrates containing an alkyl group instead of a phenyl group also gave moderate yields (**3ta** and **3ua**, 68% and 52% yield, respectively). However, neither pyridyl-substituted ACP nor dialkyl-substituted ACP afforded the desired product. The

Scheme 2. Scope of Alkylidenecyclopropanes in the Aza-Pinacol Rearrangement Reaction[a,b]

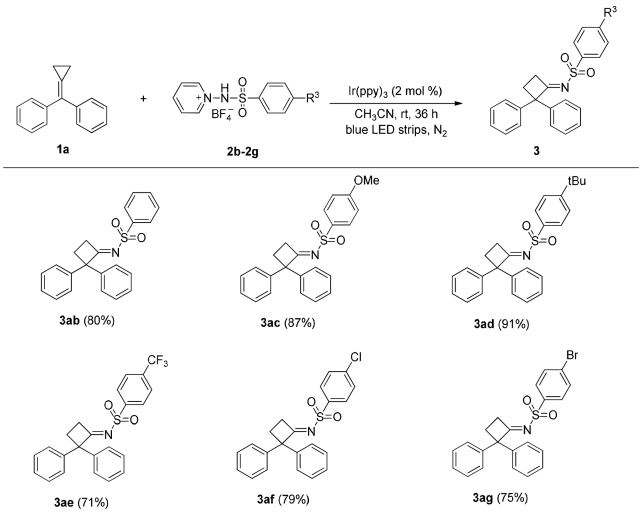


[a]Reaction conditions: substrate **1a**–**1u** (0.1 mmol), substrate **2a** (0.4 mmol), $Ir(ppy)_3$ (0.002 mmol) in MeCN (anhydrous, 4 mL) under irradiation of a 25 W blue LED strip at rt under a N_2 atmosphere for 36 h. [b]Isolated yields.

configuration of compound **3aa** was determined by X-ray crystal structure analysis. The data of the X-ray crystal structure can be found in the Supporting Information.[11]

We next explored the scope of the nitrogen-centered radical precursors with **1a** as the substrate in Scheme 3. It was found that the *N*-protected 1-aminopyridium salts with electron-rich substituents, such as methoxyl and *tert*-butyl group, afforded the desired products in excellent yields (**3ac** and **3ad**, 87% and 91% yield, respectively). The *N*-protected 1-aminopyridium salts

Scheme 3. Scope of The Nitrogen Radical Precursors in the Aza-Pinacol Rearrangement Reaction[a,b]



[a]Reaction conditions: substrate **1a** (0.1 mmol), substrate **2b**–**2g** (0.4 mmol), $Ir(ppy)_3$ (0.002 mmol) in MeCN (anhydrous, 4 mL) under irradiation of a 25 W blue LED strip at rt under a N_2 atmosphere for 36 h. [b]Isolated yields.

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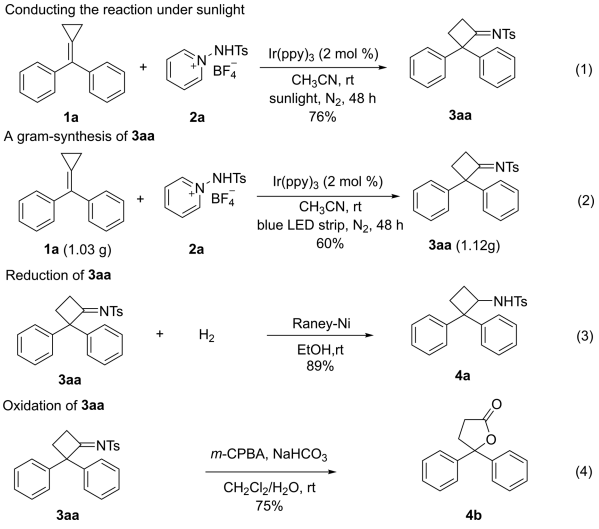
with halogen atom substituents reacted smoothly to give the rearrangement products in good yields (**3af** and **3ag**, 79% and 75% yield, respectively). Trifluoromethylbenzenesulfonyl 1-aminopyridium salt, which has a powerful electron-withdrawing group on the aromatic ring, afforded the corresponding product **3ae** in 71% yield. Interestingly, when electron-neural benzenesulfonyl group was used, the yield of the product **3ab** was still 80%.

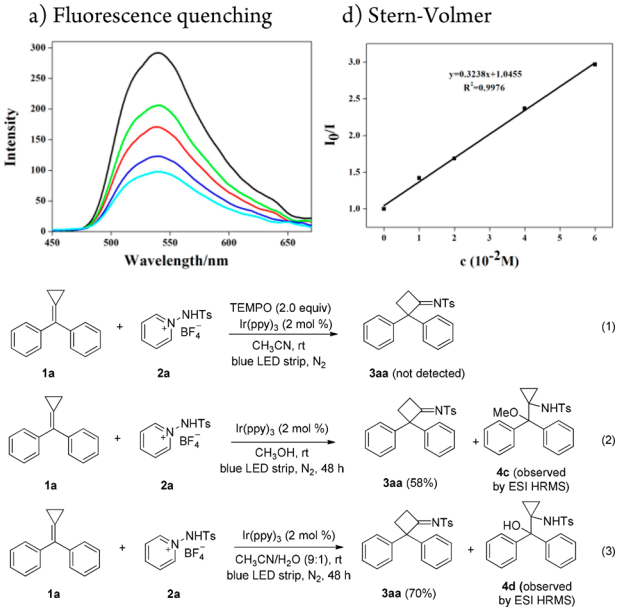
Notably, the rearrangement product could also be obtained with good yield when the reaction was carried out under natural sunlight irradiation (Scheme 4, eq 1). Moreover, when a gram-scale reaction was performed, 1.03 g of diphenylmethylenecyclopropane **1a** yielded 1.12 g (60% yield) of the *N*-tosyl-2,2-diphenylcyclobutanimine product **3aa** with a slightly decreased yield (Scheme 4, eq 2). Furthermore, to demonstrate the synthetic utility of this rearrangement reaction, *N*-Ts-protected cyclobutylamine **4a** which is prevalent in bioactive molecules and natural products was obtained from **3aa** (Scheme 4, eq 3), and product **3aa** could also be directly transformed to the γ-butyrolactone **4b** in the presence of *m*-CPBA[12] (Scheme 4, eq 4).

Scheme 4. Further Applications



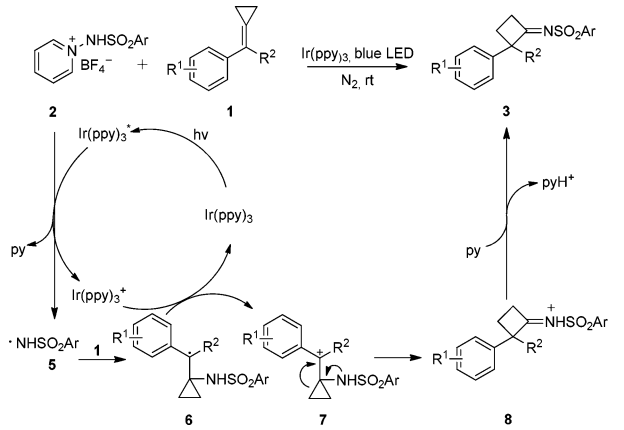
Next, to gain mechanistic insight into this reaction, several control experiments were conducted as shown in Scheme 5. Fluorescence quenching techniques (Scheme 5a) and the Stern−Volmer analysis (Scheme 5d) revealed that the photoluminescence of $Ir(ppy)_3$ was quenched by *N*-Ts-protected 1-aminopyridinium **2a** in acetonitrile. When the reaction mixture was stirred under the standard conditions in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) (2.0 equiv), **3aa** could not be detected (Scheme 5, eq 1). All these results suggested that this radical reaction was initiated by the N-centered radical generated from *N*-Ts-protected 1-aminopyridinium. When anhydrous methanol was used as the solvent, product *N*-tosyl-2,2-diphenylcyclobutanimine **3aa** was obtained in 58% yield as the major product, and a new species (found 408.1624) was observed when this reaction was monitored by ESI-HRMS, which was assigned to species **4c** (cal. 408.1628) (Scheme 5, eq 2). In the same way, a new species (found 394.1468) was observed, which is assigned to species **4d** (cal. 394.1471) (Scheme 5, eq 3).[12]

Scheme 5. Mechanistic Investigations



A plausible mechanism is illustrated in Scheme 6 based on the aforementioned control experiments and our previous work as well as other reported literatures.[13] At the beginning, irradiation of the photoredox catalyst $Ir(ppy)_3$ by blue light at room temperature generates a photoexcited state $*Ir(ppy)_3$, which is a strong reductant. This excited state can undergo single-electron transfer (SET) with oxidative species such as substrate **2**.[14] Then, The *N*-protected 1-aminopyridinium **2** obtains an electron from $*Ir(ppy)_3$ to afford the *N*-centered radical **5** and the oxidized photocatalyst $Ir(ppy)_3^+$. The addition of the N-centered radical to the C=C bond of ACP gives stabilized radical intermediate **6**.[15] Radical **6** is then oxidized by the powerful oxidant $Ir(ppy)_3^+$ to afford tertiary cation **7** while oxidant $Ir(ppy)_3^+$ returns to its ground state, thereby accomplishing the photocatalytic cycle. Species **7** undergoes 1,2-alkyl migration to form intermediate **8**. Finally, intermediate **8** can form product **3** upon loss of a proton.

Scheme 6. A Plausible Mechanism



In conclusion, we have successfully developed a novel azapinacol rearrangement reaction through the photoredox catalysis for the first time. In this transformation, a variety of strained cyclobutanimine derivatives were readily constructed

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via a nitrogen radical initiated ring expansion process under the mild conditions. Additionally, this method provided an alternative route for the construction of γ-butyrolactones with all-carbon quaternary centers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02989.

General information; preparation of substrates, syntheses procedures, X-ray crystallographic data of compound **3aa**; NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(11) CCDC 1424067 (**3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) See the Supporting Information.

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