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Photoredox-Induced Intramolecular 1,5-H Transfer Reaction of Aryl Iodides for the Synthesis of Spirocyclic γ-Lactams

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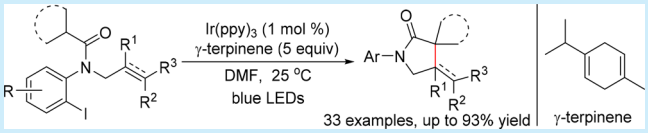
Supporting Information

ABSTRACT: This work develops a photocatalysis method for the synthesis of γ-spirolactams through a tandem intramolecular 1,5-HAT reaction−cyclization process. A variety of novel γ-spirolactams are prepared in good to excellent yields with this method. This transformation features mild reaction conditions and exceptional functional group tolerance. Additionally, γ-terpinene is applied to this transformation as a hydrogen atom donor for the first time.



As a conformationally rigid scaffold, *N*-containing spirocyclic compounds play an important role in medicinal and pharmaceutical sciences.[1] In particular, γ-spirolactam and spiropyrrolidine structures have been frequently found in pharmaceutical products and biologically active molecules.[2−6] A few selected examples are shown in Figure 1. Atiprimod

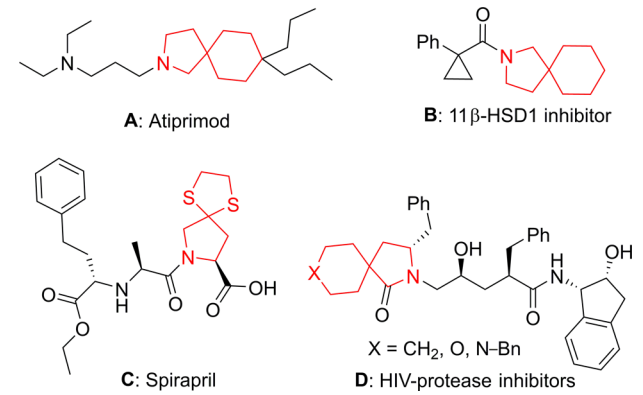
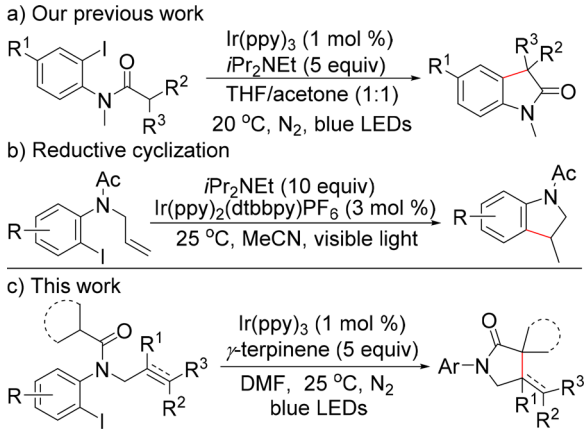


Figure 1. Pharmaceuticals and bioactive molecules containing spiropyrrolidine and spiropyrrolidone scaffolds.

(SK&F-106615), an orally bioavailable cationic amphiphilic molecule, is an effective anti-inflammatory and anticancer agent;[3] Spirapril is a potent antihypertensive agent that can significantly reduce blood pressure;[4] Spiro-carboxamide compound **B** has been identified as a powerful and selective inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1);[5] Compound **D** containing the γ-spirolactam scaffold exhibits HIV-protease inhibitory activity.[6] As an essential structural element, a γ-spirolactam can be easily reduced into a spiro-pyrrolidine. Therefore, the efficient synthesis of γ-spirolactams is still highly desirable in contemporary organic chemistry.

During the past three years, intramolecular 1,5-H atom transfer (HAT) processes mediated by *O*-, and *N*-centered radicals have been applied to the functionalization of C−H bonds via visible-light photoredox catalysis.[7] The heteroatom radical-based 1,5-H atom transfer reaction has been shown as a reliable and highly selective process in these reactions, and is therefore a powerful technique to perform the functionalization of unactivated C(sp^3)−H bonds under mild conditions. However, compared with heteroatom radicals, carbon radicals have still remained largely unexplored under the visible-light photocatalysis. On the basis of our previous work,[8] and as shown in Scheme 1a, we have achieved the intramolecular 1,5-H transfer reaction of *o*-anilide aryl iodides for the synthesis of oxindole derivatives. To widen the application of this radical transformation process further, we applied this strategy to the synthesis of γ-spirolactams. To achieve this goal, the major challenge to address is how to avoid the reductive cyclization process,[9] as shown in Scheme 1b.

Scheme 1. Different Reactions for the Aryl Halides



Inspired by the traditional methods,[10] we started to apply this 1,5-HAT process to synthesize complex molecules via

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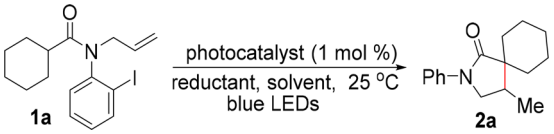
visible light photoredox catalysis. To construct the γ-spirolactam skeleton, we initially examined the reaction of the *N*-allyl-*N*-(2-iodophenyl)cyclohexanecarboxamide (**1a**) at 25 °C in the presence of 1 mol % of commercially available photocatalyst $Ir(ppy)_3$; the reductant iPr_2NEt,[9,11c,20] under irradiation with blue LEDs, and the desired γ-spirolactam product **2a** was obtained in a yield of 62% (Table 1, entry 1).

Table 1. Screening of the Reaction Conditions for the Synthesis of γ-Spirolactams 2a[a,b]



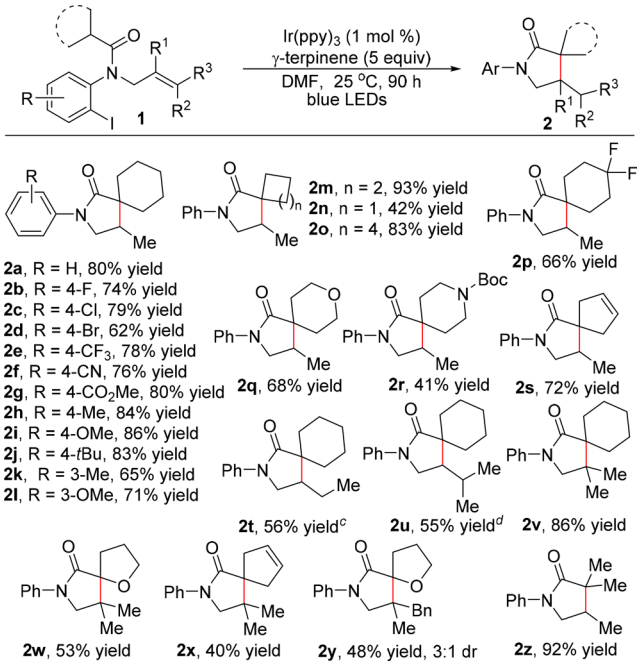
entry	photocatalyst	solvent	reductant	time	yield (%)
1	$Ir(ppy)_3$	acetone	iPr_2NEt	18 h	62
2	$Ir(ppy)_2(dtbbpy)PF_6$	acetone	iPr_2NEt	36 h	58
3	$Ru(bpy)_3(PF_6)_2$	acetone	iPr_2NEt	36 h	0
4	$Ir(ppy)_3$	MeCN	iPr_2NEt	12 h	46
5	$Ir(ppy)_3$	DMF	iPr_2NEt	12 h	66
6	$Ir(ppy)_3$	CH_2Cl_2	iPr_2NEt	36 h	59
7	$Ir(ppy)_3$	THF	iPr_2NEt	7 d	62
8	$Ir(ppy)_3$	DMSO	iPr_2NEt	12 h	41
9	$Ir(ppy)_3$	MeOH	iPr_2NEt	60 h	37
10	$Ir(ppy)_3$	DMF	Et_3N	18 h	65
11	$Ir(ppy)_3$	DMF	DBU	90 h	57
12	$Ir(ppy)_3$	DMF	ascorbic acid	90 h	53
13	$Ir(ppy)_3$	DMF	1,4-CHD	84 h	70
14	$Ir(ppy)_3$	DMF	γ-terpinene	90 h	80
15	$Ir(ppy)_3$	DMF	γ-terpinene/ iPr_2NEt (1/1)	90 h	55
16	–	DMF	γ-terpinene	90 h	0
17[c]	$Ir(ppy)_3$	DMF	γ-terpinene	90 h	0

[a]Unless otherwise noted, reaction conditions are as follows: **1a** (0.2 mmol), photocatalyst (0.002 mmol), reductant (1.0 mmol), solvent (4 mL), blue LEDs, 25 °C, and under a N_2 atmosphere. [b]Isolated yield. [c]In the dark. 1,4-CHD: 1,4-cyclohexadiene.

When $Ir(ppy)_2(dtbbpy)PF_6$ was used as the photocatalyst, the yield of the product was decreased to 58% (entry 2). However, substrate **1a** did not react to afford the product when $Ru(bpy)_3(PF_6)_2$ was used as the catalyst, which was consistent with literature reports that the reduced species $Ru(bpy)_3^+$ ($E_{1/2}[Ru(ppy)_3^{2+}/Ru(ppy)_3^+] = -1.33$ V vs SCE)[11] could not reduce the unactivated aryl iodide ($E_{1/2}^{red} = -1.59$ V vs SCE for iodobenzene).[12] A survey of solvents revealed that DMF was the optimal reaction medium (entries 4–9). The choice of reductant was also found to have a significant influence on the reaction yield. When triethylamine,[13] ascorbic acid[14a] or DBU[14b] was selected as the reductant, the yield of the product **2a** was decreased (entries 10–12). Fortunately, inspiring improvement of the reaction yield was observed when 1,4-cyclohexadiene (1,4-CHD)[15] was used, instead of iPr_2NEt (entry 13). Finally, the commercially available reagent γ-terpinene, which has the similar structure to 1,4-CHD, was found to provide the best yield (entry 14). When *i*-Pr_2NEt and γ-terpinene were both used as the reductants, the yield of **2a** was decreased to 55% (entry 15). The desired product **2a** was always accompanied by a trace of the byproduct (entries 1–15). Lastly, both the light source and the photocatalyst were required, as demonstrated by the control experiments (entries 16 and 17).

Having identified the optimal reaction conditions for synthesis of spirocyclic γ-lactams, we next sought to examine the scope of the aryl iodide precursor. As shown in Scheme 2, a

Scheme 2. Scope of the Substrate: 5-*exo*-trig Cyclization[a,b]



[a]Unless otherwise noted, reaction conditions are as follows: **1** (0.2 mmol), $Ir(ppy)_3$ (0.002 mmol), γ-terpinene (1.0 mmol), DMF (4 mL), blue LEDs, 25 °C, and under a N_2 atmosphere with a reaction time of 90 h. [b]Isolated yield. [c]Reaction time of 96 h. [d]Reaction time of 108 h.

range of substituted *o*-anilide aryl iodides reacted very well in this radical transformation protocol. Generally, the *o*-anilide aryl iodides with electron-donating groups at the C4 position gave better results under the conditions than those with the electron-withdrawing ones (**2b–2j**). Notably, the substrate with a methoxyl group in the aromatic ring gave the best yield, while the substrate with a methyl or methoxy group at the C5 position only gave a 65% or 71% yield (**2k–2l**). The starting materials possessing various cycloalkyl groups at the α-position of the amide also delivered the corresponding γ-spirolactams in modest to excellent yield (**2m–2p**). Particularly, *N*-(*o*-iodophenyl)-alkylamides with an oxygen atom, a *tert*-butyloxycarbonyl-protected amine or a double bond in the alkyl group could also be smoothly converted into the corresponding target products (**2q–2s**). The product **2r** might be unstable in the presence of HI. The γ-spirolactam compound **2** resulted from 1,5-HAT followed by the 5-*exo*-*trig* radical cyclization onto the allyl double bond. We next sought to investigate the influence of the olefin component on the cyclization process of this reaction. A range of di- and trisubstituted alkenes with different substitution patterns was found to be tolerated (**2t–2v**). However, substrates **1t** and **1u** required longer reaction times to be converted into the corresponding products (**2t** and **2u**). In addition, we also realized the construction of contiguous quaternary carbon centers through visible light photocatalysis (**2v–2y**). Furthermore, an acyclic amide substrate was also

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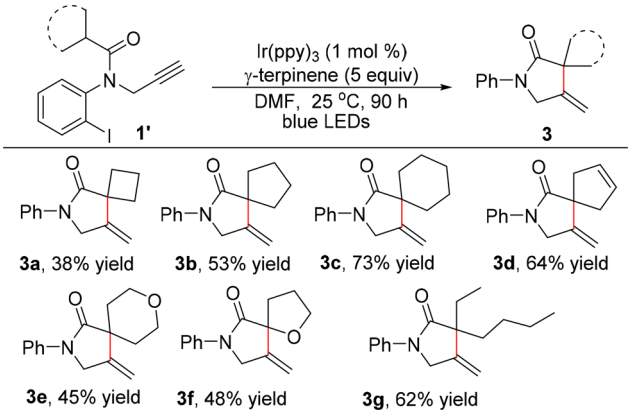
transformed into the γ-lactam compound (**2z**) in an excellent 92% yield.

Similarly, the 5-*exo-dig* ring-closing reaction was also investigated under the same reaction conditions. A series of 4-methylenepyrrolidones (Scheme 3, products **3a**−**3g**, 38−73%

Scheme 3. Scope of the Substrate: 5-*exo*-dig Cyclization[a,b]



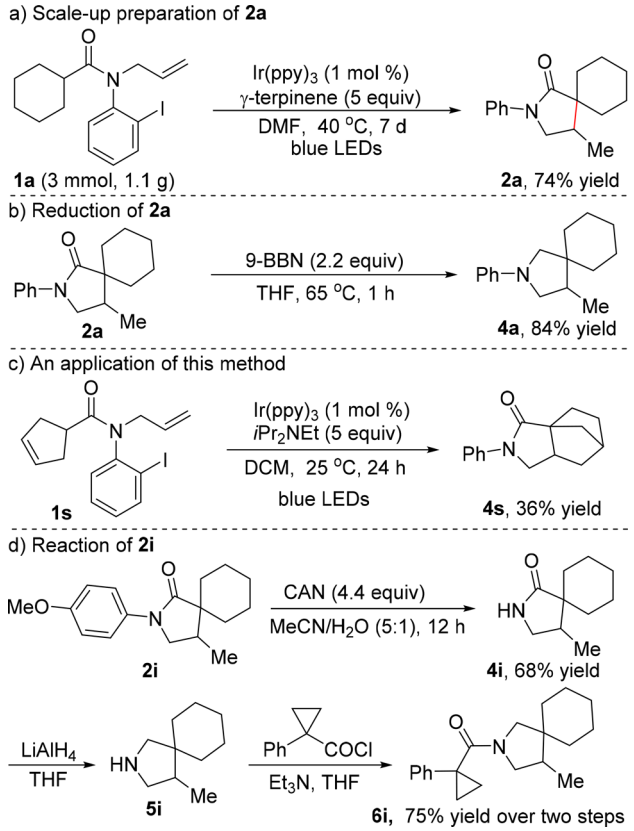
[a]Unless otherwise noted, reaction conditions are as follows: **1′** (0.2 mmol), $Ir(ppy)_3$ (0.002 mmol), γ-terpinene (1.0 mmol), DMF (4 mL), blue LEDs, 25 °C, and under a N_2 atmosphere with a reaction time of 90 h. [b]Isolated yield.

yield) have been synthesized by using this 5-*exo-dig* radical cyclization reaction as the critical step. These products bearing a double bond could be readily functionalized and applied to complex molecular synthesis.[16]

To confirm the practicability of this tandem process, a scale-up experiment was carried out, which afforded the corresponding γ-spirolactam **2a** in good yield (Scheme 4a). As mentioned before, the spiro-pyrrolidine moiety is also commonly found in the structures of pharmaceutical products and biologically active molecules. Treatment of **2a** under reducing conditions[17] afforded the spiro-pyrrolidine product **4a** in 84% yield after 1 h (Scheme 4b). Under similar reaction conditions, a bridged compound **4s** was synthesized from the reactant **1s** with a modest yield. A similar bridged compound could also be found in the transformation of **1x**. The removal of the *p*-methoxyphenyl group was investigated by using ceric ammonium nitrate (CAN) as the stoichiometric oxidant. Additional modification of **4i** afforded **6i**, an analogue of the 11β-HSD1 inhibitor (Scheme 4d).[10c,18] Further analysis demonstrated that the product **6i** had an anti/syn rotamer population of 1:1.

Control experiments demonstrated that both the visible light and the photocatalyst were essential components for this tandem 1,5-H atom abstraction/cyclization process. On the basis of these results, as well as our previous work,[8,19] a plausible reaction mechanism is depicted in Figure 2. Irradiation of the photoredox catalyst $Ir(ppy)_3$ (**10**) with visible light generates a photoexcited state, $*Ir(ppy)_3$ (**11**), which is quenched by the unactivated aryl iodide **1a** with generation of the oxidized $Ir(ppy)_3^+$ (**12**) and the highly activated σ-radical **7**.[20] The rate constant for 1,5-HAT from a secondary C−H bond is $>5 \times 10^8$ s^{-1} which is faster than most of the radical ring-closure reactions, and the 1,5-HAT becomes even faster for tertiary C−H bonds.[21] Radical **7** undergoes an intramolecular 1,5-HAT process to produce the stabilized tertiary carbon radical **8**. Then, a 5-*exo-trig* radical-alkene

Scheme 4. Further Applications



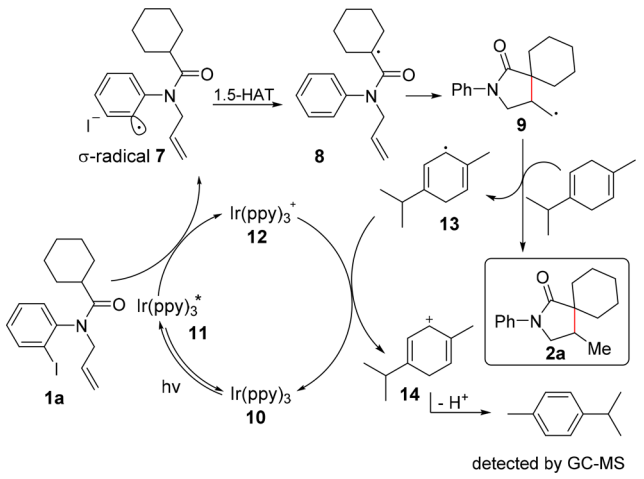


Figure 2. Proposed mechanism.

cyclization occurs to provide the spiro structure **9**, which undergoes H atom abstraction from γ-terpinene to generate the desired product **2a** and the cyclohexadienyl radical **13**.[15] Finally, the oxidized $Ir(ppy)_3^+$ (**12**) can be reduced to the ground state by species **13**, which completes the photoredox catalytic cycle. By the way, cyclohexadienyl cation **14** formed in the process could be easily converted into *p*-cymeme, which could be detected by GC-MS. The "I" atom would convert into HI.

In summary, we have developed a photocatalytic method for the synthesis of γ-spirolactams through a tandem intramolecular 1,5-HAT reaction-cyclization process. A variety of novel γ-spirolactams were prepared from *o*-anilide aryl iodides

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in good to excellent yields. Furthermore, the method reported here features mild reaction conditions and exceptional functional group tolerance, and γ-terpinene, which is a commercially available reagent, has been applied to this transformation as a new hydrogen atom donor. We anticipate that this method will find broad application in the field of pharmaceutical sciences.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00731.

Experimental details on experimental procedures for the catalytic reactions and spectroscopic data for the products (PDF)

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Notes

The authors declare no competing financial interest.

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