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Intramolecular 1,5-H transfer reaction of aryl iodides through visible-light photoredox catalysis: a concise method for the synthesis of the natural product scaffolds

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The intramolecular 1,5-H transfer reaction of the aryl radicals generated from unactivited aryl iodides by photocatalysis is described. The features of this transformation are operational simplicity, excellent yields, mild reaction conditions, and good functional group tolerance. With this approach, a more concise formal synthesis of (\pm) -coerulescine and (\pm) -physovenine is accomplished.

Hydrogen-atom transfer is a reliable and widely used process in radical-mediated reactions and therefore a powerful tool to perform chemical transformations. In particular, intramolecular 1,5-H atom transfer (HAT) reactions have been extensively investigated and numerous applications have been described in organic synthesis.¹⁻³ For these reactions, highly reactive aryl and alkenvl free radicals are often involved to achieve the useful radical translocations.³ Despite the importance of this type of reactions, one of the several limitations of the traditional methods is the requirement of superstoichiometric quantities of hazardous reagents such as tributyltin hydride, azobisisobutyronitrile (AIBN), etc. to generate and/or terminate the free radicals.^{3a-3c} Another limitation is that high temperature is often required to initiate these reactions and significant amounts of waste byproducts will be produced. All these drawbacks restrict the broad applications of the traditional methods in modern synthetic chemistry. In this context, we are interested in exploring new approaches to overcome these limitations.

During the past several years, visible light photocatalysis has attracted a great deal of attention from researchers in organic synthesis.⁴ Harnessing of energy from visible light as an inexpensive and abundant means to construct complex organic molecules has emerged as a promising method in organic chemistry. Stephenson⁵ and Lee⁶ have showed that aryl radicals, generated by photoredox reaction of unactivated

aryl iodides, could be employed in the reduction and reductive cyclization reactions under mild conditions, respectively. We envisioned that intramolecular 1,5-H transfer reaction of aryl iodides might also be realized through visible-light photoredox catalysis under mild conditions without using toxic reagents. One of the difficult problems to address is to avoid the process of reductive dehalogenation, as shown in Figure **1**.

From our initial test results, we were delighted to find that visible light photoredox catalysis could truly catalyze the intramolecular 1,5-HAT reaction of o-anilide aryl radicals. The proposed mechanism of this reaction is illustrated in Scheme **1.** Irradiation of photocatalyst fac-Ir(ppy)₃ (**6**) [ppy = 2phenylpyridine] with visible light generates a long-lived ($\tau = 1.9$ $(\mu s)^{4a}$ photoexcited state, fac-*Ir(ppy)₃ (7) (E_{1/2}^{red} [fac- $Ir(ppy)_3^+/fac^{*}Ir(ppy)_3] = -1.73 \text{ V vs SCE})_5^5$ which is a strong electron donor to reduce the substrate. The unactivated aryl iodide $(E_{1/2}^{red} = -1.59 \text{ V vs SCE for iodobenzene})^7$ can accept a single electron from fac-*Ir(ppy)₃ (7) and then produce the highly activated aryl radical, which undergoes an intramolecular 1,5-HAT reaction and provides the stabilized tertiary carbon radical (4).^{3d,e} Species 4 is then converted to the cyclohexadienyl radical (5) through cyclization.⁸ In the meantime, single electron transfer (SET) from excited state of



Fig. 1. Different reactions for the aryl halides

a) reduction of alkyl iodides⁵

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⁺ Electronic Supplementary Information (ESI) available: Experimental procedures, structural proofs, and spectral data for all compounds are provided (PDF). See DOI: 10.1039/x0xx00000x

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Table 1 Initial studies and reaction optimization.

1a

Catalyst

Ru(bpy)₃Cl₂

fac-lr(ppy)3

fac-lr(ppy)3

fac-lr(ppy)3

fac-lr(ppy)3

fac-lr(ppy)3

fac-lr(ppy)3

fac-lr(ppy)3

fac-lr(ppy)

fac-lr(ppy)3

[lr(ppy)2(dtbbpy)]PF6

Entry

1

2

3

4

5

6

7

8

9

10

11



Base

iPr₂NEt

20°C, N₂, blue LED strip

Solvent (v/v)

MeCN

MeCN

MeCN

 CH_2CI_2

THF

EA

DMSO

Acetone

MeOH

DMF

THF/H₂O(7:1)



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fac-*Ir(ppy)₃ (7) to **1a** provides the oxidized fac-Ir(ppy)₃⁺ (8), which is a powerful oxidant $(E_{1/2}^{red} [fac-Ir(ppy)_3^+/fac-Ir(ppy)_3] =$ + 0.77 V vs SCE).^{4a} In the presence of the tertiary amine as the stoichiometric reductant, fac-Ir(ppy)₃⁺ (8) can be converted to the corresponding ground state photocatalyst and complete the photoredox cycle. Finally, the generated cation radical (10) undergoes hydrogen atom abstraction from the cyclohexadienyl radical (5) to give the final product.⁹

Based on the initial test reaction, we began our investigation by screening conditions for the intramolecular 1,5-HAT reaction of o-anilide aryl iodide (1a). To our delight, the only desired 1,5-HAT product (in a modest 37% yield) was observed at 20°C by irradiation with a 25W blue LED strip when fac-Ir(ppy)₃ was used as the photocatalyst and N,Ndiisopropylethylamine (DIPEA) as the organic base (entry 2).⁵ But the reaction did not occur under Ru(bpy)₃Cl₂ catalysis (entry 1). Meanwhile, when [Ir(ppy)₂(dtbbpy)]PF₆ was used instead of fac-Ir(ppy)₃, the yield of the product, accompanied with the appearance of undesired reduction product (60% yield), was decreased to 10% (Scheme 2).⁶ The examination of the solvents revealed that THF produced better yield, but the reaction took much longer time to complete (entry 5). Compared with THF, when a 1:1 THF/acetone or 7:1 THF/H₂O solvent system was used, slight improvement of yield but dramatical diminution of the reaction time could be observed (entries 11 and 12). The role of acetone or water was likely to increase the solubility of the byproduct, solid N,Ndiisopropylethylaminehydriodate (*i*Pr₂NEt'HI), which could hinder the photocatalyst from absorbing visible light. Next, the organic base as another crucial reaction parameter was also explored, and the optimal one was found to be DIPEA with 87% yield (entry 12). Interestingly, when 2,6-lutidine or K_2HPO_4 was used as the base instead of DIPEA, the reaction did not occur. This phenomenon indicated that DIPEA not only acted as the acid acceptor, but also joined the photocatalyst cycle. Lastly, control experiments demonstrated that an organic base, a photocatalyst, and a light source are all necessary in this intramolecular 1,5-HAT protocol (see ESI).¹⁰

With the optimized conditions in hand, we next focused our attention on the scope of the substrate. As shown in Table 2, a variety of substituted o-anilide aryl iodides (1) were investigated by using fac-Ir(ppy)₃ as the photocatalyt. The reaction of substrates bearing dialkyl group at α -position of the

12 fac-lr(ppv) iPr₂NEt THF/Acetone(1:1) 60h 87 13 fac-lr(ppy) Et₃N THF/Acetone(1:1) 60h 75 14 fac-lr(ppy)3 Bu₃N THF/Acetone(1:1) 60h 77 2.6-15 fac-lr(ppy)3 THF/Acetone(1:1) 60h 0 lutidine 16 K₂HPO₄ 60h 0 fac-lr(ppv)3 THF/Acetone(1:1) ^a Unless otherwise noted, the reaction of 1a (0.2 mmol) was carried out in the presence

of the photocatalyst (0.002 mmol) in the indicated solvent (4.0 mL) with a 25W blue LED strip at 20°C. ^b Isolated yield.



amide proceeded smoothly to give the corresponding 3,3dialkyloxindole (2b-2h) in good to high yields. Substrates with a double bond or a hetero atom in the alkyl group at the α position of the amide could readily convert into target compounds (2i-2j) without any undesired reduction byproducts. On the other hand, the same observation was made for 4-bromo-2-iodophenylamides (2m and 2s, with the yield of 80% and 86%, respectively) which are not tolerant in the traditional conditions. We believe that this result can be rationalized by their more negative reduction potentials $(E_{1/2}^{re})$

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2a

Time

24h

24h

24h

24h

7d

5d

12h

36h

36h

12h

60h

Yield

(%)^b

0

37

10

57

78

46

44

67

46

51

82

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= -2.07 V vs SCE for bromobenzene)⁷ than the activated photocatalyst fac-*Ir(ppy)₃ (7) $(E_{1/2}^{red} [fac$ -Ir(ppy)₃*/fac-*Ir(ppy)₃] = -1.73 V vs SCE). The results in table 2 also show that *o*-anilide aryl iodides (1) with electron-withdrawing substituents gave better yields than those with electron-donating substituents (2k-2p vs 2w-2x). However, electron-rich *o*-anilide aryl iodides required longer reaction times for full convertion into the products. In contrast, the unprotected *o*-anilide aryl iodide was entirely transformed into the product of reductive dehalogenation (2ab).

Since the oxindole moiety is widely found in the core structure of natural alkaloids and bioactive compounds, our group have focused much attention on the synthesis of the oxindole derivatives.¹¹ This convenient method mentioned above will be potentially useful for the synthesis of natural products containing the oxindole moiety. With this in mind, we decided to apply this powerful approach to the synthesis of the bioactive alkaloid coerulescine, which was isolated from the blue canary grass phalaris coerulescens in 1998 by Colegate's group.¹² In the past, one of the main challenges to address was how to construct the all-carbon quaternary



^{*a*} Reaction conditions: photocatalyst (0.002 mmol), DIPEA (1.0 mmol), reactant (0.2 mmol) in THF/Acetone (1:1) (4 mL), at 20^oC, under N₂ atmosphere, with a 25W blue LED strip, with reaction time of 60h. ^{*b*} Isolated yields. ^{*c*} Reaction time 96h. ^{*d*} Reaction time 108h. n.r. = no reaction.



stereocenter in the spirocyclic oxindole moiety. Now, this challenge can be easily overcome with this new method (Scheme 3). Spirooxindole 2ad was deprotected uneventfully to compound 3ad, which can be smoothly transformed into coerulescine, as demonstrated by Suárez-Castillo et al.¹³ In order to further widen the application of this intramolecular 1,5-H atom transformation method, we applied it to the formal synthesis of another natural alkaloid, physovenine, which has been synthesized by many groups.¹⁴⁻¹⁶ Treatment of 4-hydroxy-N-(2-iodophenyl)-N,2-dimethylbut-anamide (1ae) with the general condition afforded the desired product (2ae) in 88% yield after 96h, which was subsequently subjected to the reduction with LAH providing the cyclization product (3ae).¹⁵ Additional modification of 3ae afforded (±)physovenine.¹⁶ Based on this procedure, we created a concise synthetic route to form physovenine by using this visible light photoredox catalysis as the critical step.

Under the similar reaction conditions, reactant **1af** was also converted into the corresponding desired product **2af** (scheme 4).¹⁷ In this transformation, we realized the functionalization of the unreactive tertiary aliphatic C–H bond through visible light photocatalysis.

The proposed mechanism of the visible light catalyzed intramolecular 1,5-HAT reaction is illustrated in Scheme 1. It can also support the transformation of *m*-substituent of reactant (1ag) to a mixture of 2ag and 2ag' with a ratio of 2:1 after 96h (scheme 5).¹⁸



Scheme 4 Functionalization of the unreactive C-H bond



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In conclusion, we have developed a visible-light photoredox catalysis approach to achieve the intramolecular 1,5-H transfer reaction of *o*-anilide aryl iodides. In contrast to conventional methods, this approach does not require superstoichiometric quantities of toxic reagents. Furthermore, this reaction features operational simplicity, mild reaction conditions, exceptional functional group tolerance and good to excellent yields. Therefore, the method described herein makes a significant complementation to the research fields of HAT reactions and photoredox catalysis. The practicability of this transformation has also been demonstrated in the more concise formal synthesis of (±)-coerulescine and (±)physovenine in comparison with previous work.

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