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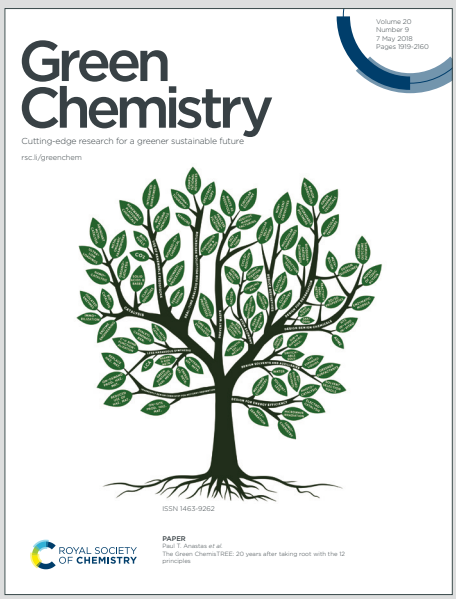

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One-pot synthesis of 2-hydroxymethylindoles via photoredox-catalyzed ketyl-ynamide coupling/1,3-allylic alcohol transposition

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An efficient visible-light-mediated ketyl-ynamide coupling by employing ynamides bearing alkyl sulfonyl substitutents to deliver eneindolin-3-ols has been developed. Subsequent 1,3-transposition of allylic alcohols in one-pot is capable of synthesizing 2-hydroxymethylindoles in generally moderate to good yields. The synthetic utility of this protocol has also been demonstrated by the facile and practical synthesis of two bioactive molecules. The use of readily available substrates, a simple procedure and benign reaction conditions render this method a viable alternative for the synthesis of 2-hydroxymethylindoles.

Introduction

2-Hydroxymethylindoles and their oxidative products, 2-acylindoles, are significant structural motifs which have been found in various bioactive molecules (Fig. 1).[1] It is surprising, however, that only a few synthetic methods have been reported.

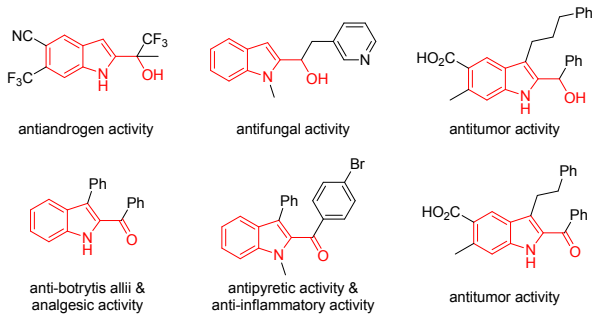

Fig. 1 Selected examples of 2-hydroxymethylindoles and 2-acylindoles in bioactive compounds.

For example, Sonogashira coupling of *o*-aminoiodobenzenes and propargyl alcohols and subsequent cyclization in situ provided a convenient route to prepare 2-hydroxymethylindoles, but this method was only applicable to 3-unsubstituted indoles.[1c] Thus, the development of novel methods for the construction of these two kinds of N-heterocycles is highly desirable, especially those with high efficiency, flexibility, and benign reaction conditions.

Ketyl radical reactions especially those generated from carbonyls by means of single electron transfer (SET) under photocatalysis have attracted much attention in recent years.[2] This protocol not only enables various carbonyl umpolung reactions induced by light to effectively construct C–C bonds, but also avoids using stoichiometric Kagan's reagent (SmI_2) which are extremely sensitive to air and difficult to obtain.[3] In addition, most reactions involving photoredox-catalyzed ketyl coupling with unsaturated bonds focused on substrates containing C=C, C=N and aromatic ring.[2] The first photocatalytic ketyl-olefin coupling taking advantage of concerted proton-coupled electron transfer (PCET) was elegantly demonstrated by Knowles and co-workers in 2013.[2f] Afterwards, the use of Lewis acids or Brønsted acids as additives was necessary in favor of ketyl radical formation in most cases. Photocatalytic ketyl-alkyne cyclization was first described by Rueping et al. in 2016, but the reaction had to rely on the alkyne bearing electron-donating groups (EDG).[2b]

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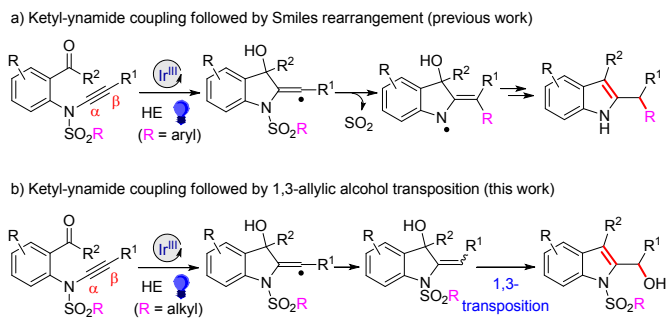
Ynamides are versatile reagents for organic synthesis and have received extensive attention over the past decades.[4,5] However, few radical reactions based on ynamides have been developed so far compared with ionic reactions.[6,7] Usually, radical addition occurs on the β position of ynamides, given that generated vinly radical can be stabilized by contiguous nitrogen atom.[6] Intramolecular radical α position addition would be achieved based on radical tethered ynamides leading to thermodynamically stable N-heterocycles.[7] In our study on developing ynamide chemistry for heterocycle synthesis,[8] we very recently disclosed the first ynamide Smiles rearrangement that was triggered by photoredox-catalyzed regioselective ketyl-ynamide coupling, allowing the facile synthesis of synthetically useful 2-benzhydrylindoles and 3-benzhydrylisoquinolines (Scheme 1a).[9] Of note, the use of arylsulfonyl group protected ynamides (R = aryl) was necessary. When R was replaced by the alkyl group, the Smiles rearrangement was inhibited, leading to the formation of eneindolin-3-ols.[9] On the basis of these findings, we envisioned that the formed eneindolin-3-ols might undergo further 1,3-transposition of allylic alcohols[10] to produce the corresponding valuable 2-hydroxymethylindoles. Herein, we describe the realization of such a visible-light-mediated ketyl-ynamide coupling by employing ynamides bearing alkyl sulfonyl substitutents, delivering functionalized eneindolin-3-ols.[11] Subsequent 1,3-allylic alcohol transposition in one-pot was capable of synthesizing various 2-hydroxymethylindoles in generally moderate to good yields under benign reaction conditions (Scheme 1b).



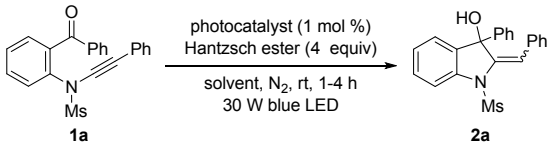
Scheme 1 Photoredox-mediated regioselective ketyl-ynamide coupling.

Results and discussion

At the outset, Ms-substituted benzoyl ynamide **1a** was employed as the model substrate to optimize this visible light-mediated ketyl-ynamide coupling, as outlined in Table 1. To our delight, solvent screening (Table 1, entries 1–9) revealed that the use of DMSO could lead to the formation of the corresponding eneindolin-3-ol **2a** in almost quantitative yield with 6/1 *E*/*Z* ratio (Table 1, entry 2). In addition, other types of photocatalysts were also investigated, but failed to further improve the reaction (Table 1, entries 10–15). Finally, it was found that reducing the loading of Hantzsch ester led to significantly decreased efficiency of the reaction (Table 1, entries 16–17).

We then wondered whether the above eneindolin-3-ol could be converted into the corresponding 2-hydroxymethylindole through 1,3-allylic alcohol transposition. As shown in Scheme 2a, eneindolin-3-ol **2a** could not be converted into the desired 2-hydroxymethylindole **3a** by just elevating the reaction temperature to 80 °C.[12] Instead, significant formation of the dehydroxylated indole **2aa** was formed presumably via the reduction of **2a** by Hantzsch ester.[13] To remove

Table 1 Optimization of reaction conditions[a]



Entry	Photocatalyst	Reaction Conditions	Yield[b] (%)	*E*/*Z*
1	$[Ir(ppy)_2(dtbbpy)]PF_6$	DMF, rt, 1 h	87	3/1
2	**$[Ir(ppy)_2(dtbbpy)]PF_6$**	**DMSO, rt, 1 h**	**99[c]**	**6/1**
3	$[Ir(ppy)_2(dtbbpy)]PF_6$	DMA, rt, 1 h	87	3/1
4	$[Ir(ppy)_2(dtbbpy)]PF_6$	MeCN, rt, 3 h	48	1/1
5	$[Ir(ppy)_2(dtbbpy)]PF_6$	MeOH, rt, 3 h	99	1/1
6	$[Ir(ppy)_2(dtbbpy)]PF_6$	1,4-dioxane, rt, 4 h	63	1/1
7	$[Ir(ppy)_2(dtbbpy)]PF_6$	^{i}PrOH, rt, 4 h	58	2/1
8	$[Ir(ppy)_2(dtbbpy)]PF_6$	DCE, rt, 1 h	72	1/1
9	$[Ir(ppy)_2(dtbbpy)]PF_6$	THF, rt, 1 h	76	2/1
10	$[Ir(dF(CF)_3ppy)_2(dtbbpy)]PF_6$	DMSO, rt, 3 h	91	4/1
11	*fac*-$Ir(ppy)_3$	DMSO, rt, 3 h	46	2/1
12	$Ru(bpy)_3(PF_6)_2$	DMSO, rt, 3 h	82	13/1
13	$Ru(bpy)_3Cl_2$	DMSO, rt, 3 h	84	7/1
14	4CzIPN	DMSO, rt, 1 h	92	17/1
15	Mes-$AcrClO_4$	DMSO, rt, 4 h	33	32/1
16[d]	$[Ir(ppy)_2(dtbbpy)]PF_6$	DMSO, rt, 3 h	89	5/1
17[e]	$[Ir(ppy)_2(dtbbpy)]PF_6$	DMSO, rt, 1 h	58	1/2

[a] Reaction conditions: **1a** (0.03 mmol), Hantzsch ester (0.12 mmol), photocatalyst (0.3 umol), solvent (0.3 mL), rt, 1-4 h, N_2; 30 W blue LED is used and the distance between light source and Schlenk tubes is about 3 cm. [b] Measured by ^{1}H NMR using Hantzsch ester and Hantzsch pyridine as internal standard. [c] Isolated yield was 84%. [d] 2 equiv of Hantzsch ester was used. [e] 3 equiv of Hantzsch ester was used.

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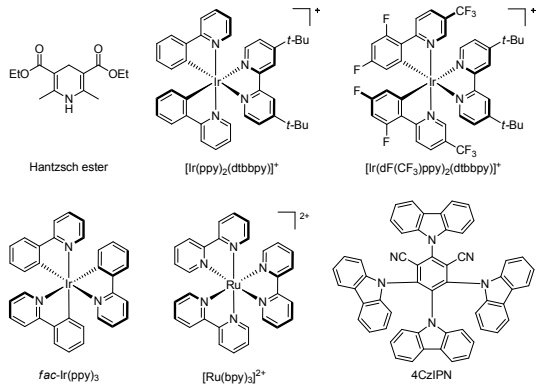
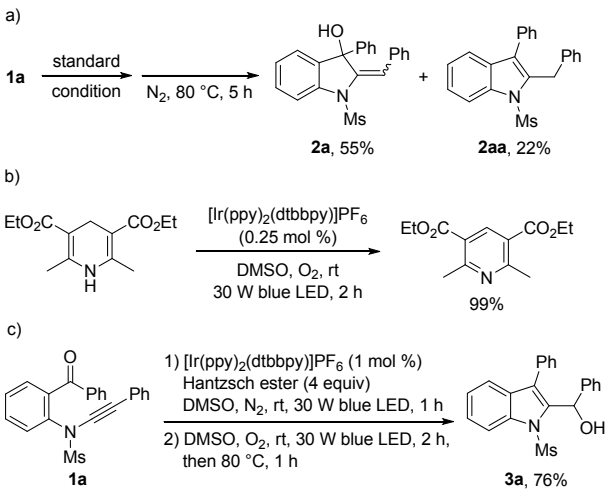


the residual Hantzsch ester, we treated it under O_2 (1 atm) atmosphere mediated by photocatalysis process and were pleased to find that the conversion of Hantzsch ester to Hantzsch pyridine was very effective (Scheme 2b).[14] Thus, we performed this one-pot reaction and found that 2-hydroxymethylindole **3a** could be formed in 76% yield, as depicted in Scheme 2c: the treatment of ynamide **1a** with Hantzsch ester in the presence of 1 mol % of $[Ir(ppy)_2(dtbbpy)]PF_6$ irradiated by blue LED at room temperature to produce **2a**; then the reaction system was charged with O_2 and the same blue LED to remove the residual Hantzsch ester; finally, the reaction was warmed up to 80 °C, delivering the desired **3a**. The molecular structure of **3a** was further confirmed by X-ray diffraction (Fig. 2).



Scheme 2 Attempts to synthesize 2-hydroxymethylindole **3a** in one-pot.

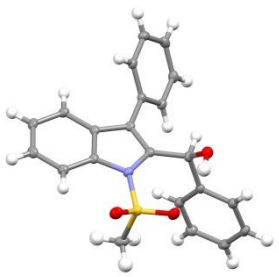
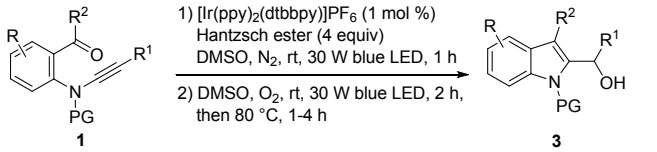
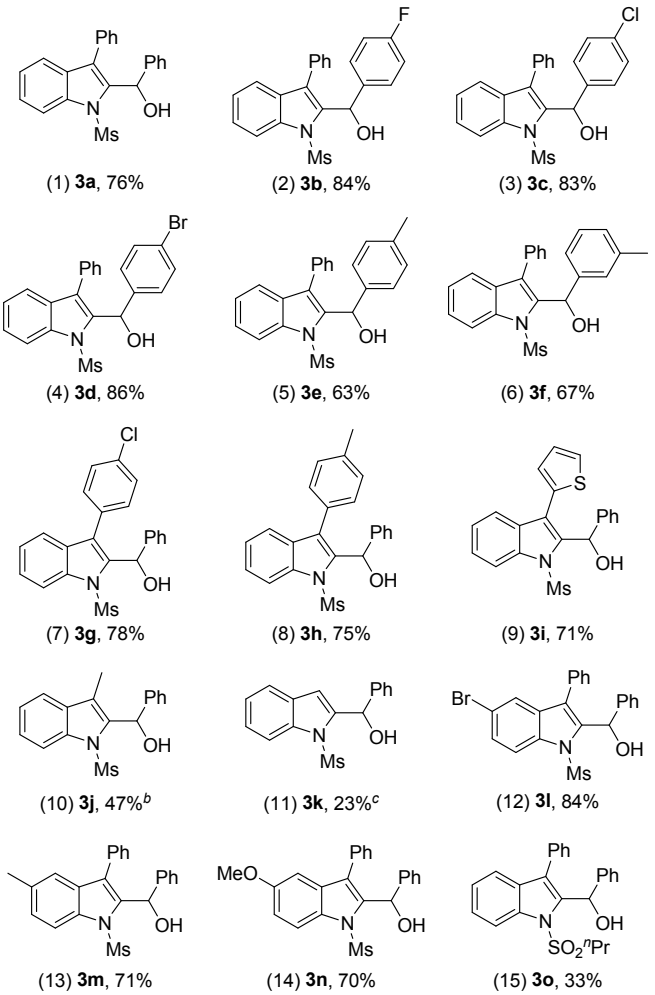


Fig. 2 Crystal structure of compound **3a**.

With the above optimized reaction conditions in hands, we next explored the substrate scope (Table 2). The one-pot reaction occurred efficiently with various Ms-substituted ynamides **1**, leading to the desired 2-hydroxymethylindoles **3** in generally moderate to good yields. A range of aryl-substituted ynamides bearing both the electron-withdrawing and electron-donating substituents were first investigated to furnish the desired products **3b**−**3f** in 63−86% yields (Table 2, entries 1–6). In addition, chlorophenyl, tolyl, even thienyl group on 2-hydroxymethylindoles **3g**−**3i** could be obtained in 71−78% yields (Table 2, entries 7–9). This reaction was also applicable to the formyl and acetyl substituted ynamides to produce the expected **3j** and **3k** in 47% and 23% yields, respectively (Table 2, entries 10 and 11). Moreover, ynamides bearing different R groups could react smoothly to deliver the desired 2-hydroxymethylindoles **3l**−**3n** in good yields (Table 2, entries 12–14). Besides Ms-substituted ynamides, *n*-propyl sulfonyl group substituted ynamide was also evaluated, delivering the corresponding product **3o** in 33% yield (Table 2, entry 15). Of note, attempts to extend the reaction to styryl-substituted ynamide **1p**, terminal ynamide **1q** and *i*-propyl sulfonyl group substituted ynamide **1r** only resulted in complex mixture of products.[15] Thus, this one-pot strategy provides a convenient and practical route for the preparation of the synthetically useful 2-hydroxymethylindoles.

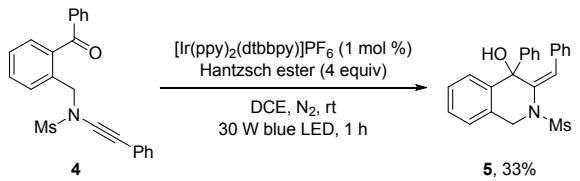
Table 2 Reaction scope study[a]





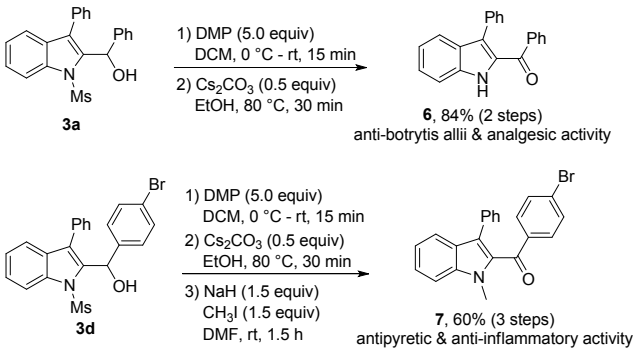
[a] Reaction conditions: step 1: **1a** (0.2 mmol), Hantzsch ester (0.8 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (0.002 mmol), DMSO (2 mL), rt, 1 h, N_2; 30 W blue LED is used and the distance between light source and Schlenk tubes is about 3 cm; step 2: rt, 2 h, O_2, 30 W blue LED; 80 °C, 1-4 h; isolated yields are reported. [b] The reaction was operated on step 1 without applying step 2, 15 h. [c] Step 1 required 2 h.

Besides, the photoredox-catalyzed ketyl-ynamide coupling reaction could be extended to one more methylene of ynamide **4** in the presence of DCE as solvent,[16] delivering the corresponding tetrahydroisoquinolin-4-ol **5** in 33% yield with only the *E* configuration of the double bond, as shown in Scheme 3. Notably in this case, the subsequent 1,3-allylic alcohol transposition of **5** failed under the above reaction conditions or even in the presence of proton acids.



Scheme 3 Photoredox-catalyzed coupling of ketyl-ynamide 4.

In addition, the synthetic applications of the synthesized 2-hydroxymethylindoles **3** were also demonstrated (Scheme 4). For example, indole compound **6** with anti-botrytis allii and analgesic activity[1e] could be obtained in 84% total yield from 2-hydroxymethylindole **3a** through DMP oxidation followed by the removal of Ms group. Moreover, the treatment of indole **3d** with the above same procedures followed by the protection with methyl group afforded 2-benzoylindole **7** in 60% yield (3 steps), which shows antipyretic and anti-inflammatory activity.[1d] We also tested the above 2-hydroxymethylindoles for their bioactivity and found that compounds **3a**–**3c** exerted significant cytotoxic effects on the melanoma cells A375 and esophageal cancer cells SK-GT-4,[16] indicating the potential utility of these compounds in medicinal chemistry.



Scheme 4 Synthetic applications.

To further probe the reaction mechanism, several control experiments were performed. To our surprise, eneindolin-3-ol **2a** could not be converted into **3a** at 80 °C in DMSO and most of **2a** (>95%) was recovered (Scheme 5a). Instead, when **2a** was exposed to photocatalyst under O_2 atmosphere, **2a** was readily transformed into **3a** in 75% yield (Scheme 5b). We believed DMSO could partly transfer into MsOH in photocatalysis process,[17] which was detected by electrospray ionization mass spectrometry (ESI-MS) in the negative-ion mode. Thus, MsOH should play the key role in promoting this 1,3-allylic alcohol transposition, as confirmed by the fact that the treatment of **2a** with 10 mol % of MsOH led to the desired **3a** in 83% yield (Scheme 5c). In other words, the second photocatalysis process under O_2 atmosphere not only removes the residual Hantzsch ester, which may lead to the formation of the dehydroxylated indole via reduction, but also promotes the 1,3-allylic alcohol transposition under benign conditions. Finally, it was found that 74% labeled oxygen was incorporated into **3a** when **1a** was exposed to standard conditions in the presence of 10 equiv of $H_2{}^{18}O$, indicating that the oxygen of the newly formed hydroxyl group originates from water but not molecular oxygen (Scheme 5d).

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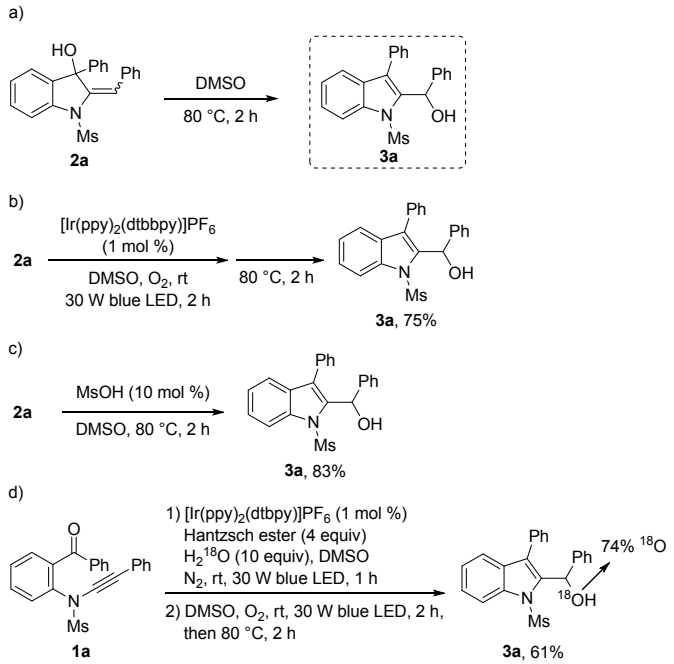
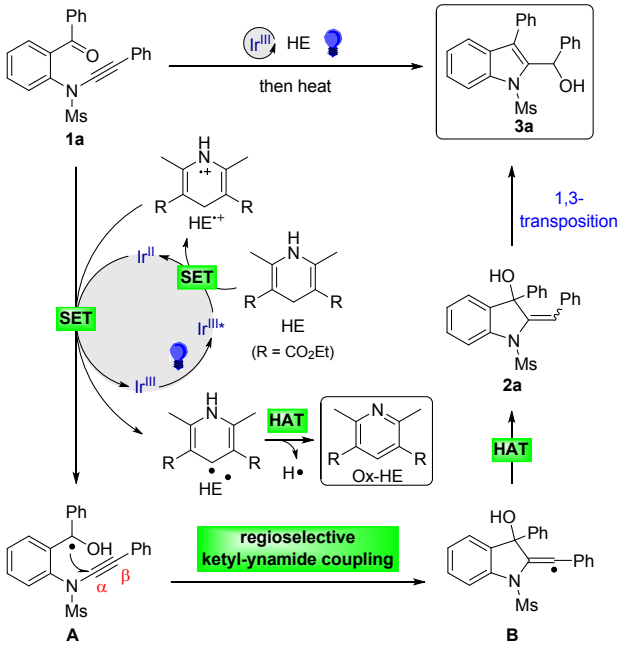


Scheme 5 Mechanistic studies.



Scheme 6 Plausible reaction mechanism.

On the basis of the above experimental observations and previous work,[8] a plausible mechanism to rationalize the formation of **3a** is proposed (Scheme 6). Initially, $\mathbf{Ir}^{III}$ is activated to $\mathbf{Ir}^{III}$* (excited-state) under blue LED irradiation. Next, Hantzsch ester (HE) reacts with $\mathbf{Ir}^{III}$* through reductive quenching to deliver $HE^{\bullet+}$ and $\mathbf{Ir}^{II}$. Subsequently, ynamide **1a** activated by $HE^{\bullet+}$ undergoes SET with $\mathbf{Ir}^{II}$ to generate ketyl radical species **A** followed by regioselective ketyl-ynamide coupling, producing the vinly radical intermediate **B**. Subsequent hydrogen atom transfer (HAT) may occur to afford enamide **2a** containing *E*/*Z* isomers. Finally, enamide **2a** is converted into the corresponding 2-hydroxymethylindole **3a** through acid-promoted 1,3-allylic alcohol transposition.

Conclusions

In summary, we have developed a photoredox-catalyzed ketyl-ynamide coupling to deliver eneindolin-3-ols by employing ynamides bearing alkyl sulfonyl substitutents. Subsequent 1,3-allylic alcohol transposition in one-pot was capable of synthesizing 2-hydroxymethylindoles in generally moderate to good yields. In addition, this chemistry enables the facile and practical synthesis of two bioactive molecules. The use of readily available substrates, a simple procedure and benign reaction conditions render this method potentially useful in organic synthesis. The development of other radical reactions based on ynamides is being investigated in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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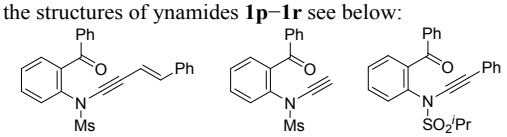

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