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Synthesis of cyclohexylidenehydrazines-fused polycyclics via photocatalytic radical cascade reaction of 2-ethynylaldehyde hydrazones

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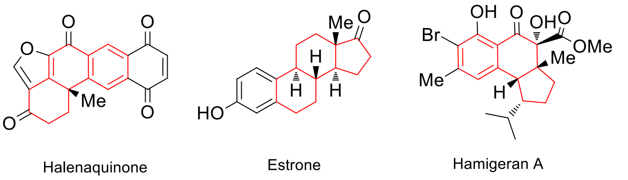
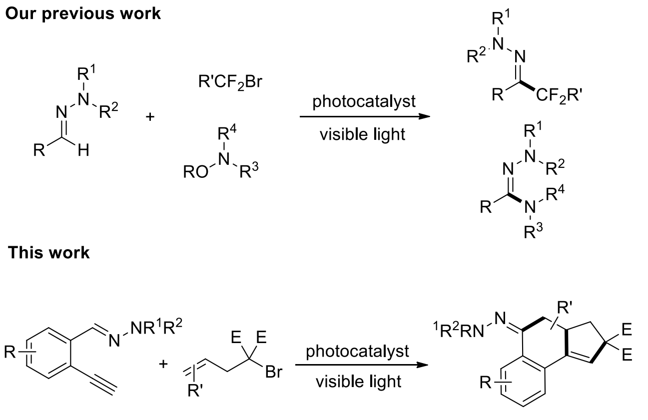
A general and efficient visible-light photoredox-catalyzed cascade annulation of 2-ethynylaldehyde hydrazones with α-bromo-carbonyls for the synthesis of various cyclohexylidene-hydrazines-fused polycyclic compounds is described. This protocol is characterized by a broad substrate scope, mild conditions and amenability to gram-scale synthesis.

Cyclopenta[α]naphthalenes are an important structure unit in agrochemicals and materials because of their unique chemical properties and biological activities (Scheme 1).[1] Therefore, a large number of methods for their construction have been extensively researched in the past decades.[2] However, many previous methods suffered from harsh conditions and required the utilization of multi-step process, which limit their applications. Very recently, some well-designed one-pot procedures for building these skeletons have been established.[3] Although significant achievements have been made, a milder and more efficient method for synthesizing complex organic compounds is still in demand.



Scheme 1 Selected examples of cyclopenta[α]naphthalene in natural products or pharmacally interesting compounds

Visible light photoredox catalysis has attracted widespread attention in the field of synthetic organic chemistry as a fascinating tool owing to its attractive features including mild reaction conditions, natural abundance and environmental friendliness.[4] In the past few years, visible light induced cascade reactions have proven to be highly valuable for the synthesis of polycyclic compounds because of their highly atom economic and simple operation.[5] For instance, our group successfully achieved important heterocyclic scaffolds via radical cyclizations and annulations under visible-light catalysis.[6] Hydrazones are important and easily accessible organic intermediates that are widely applied in the synthetic organic chemistry.[7] Recently, the others' group and our group has paid more attention on the C–H bond functionalization of aldehyde hydrazones (scheme 2).[8] As our follow-up work, herein, we intend to establish a facile and efficient protocol for the synthesis of cyclohexylidenehydrazines-fused polycyclic compounds by visible-light photoredox catalysis (scheme 2). In this reaction, three new C-C bonds can be formed, and polycyclic rings can also be constructed in a one-pot manner.



Scheme 2 Visible light promoted C–H bond functionalization of aldehyde hydrazones.

Initially, the reaction was performed using *N*-(2-ethynylbenzylidene)morpholin-4-amine (**1a**) and diethyl α-allyl-α-bromomalonate (**2a**) as model substrates in the presence of the photocatalyst *fac*-Ir(ppy)$_3$ and inorganic base K_2CO_3 at room temperature in CH_3CN (Table 1). To our delight, the desired product **3aa** was obtained at a 41% isolated yield

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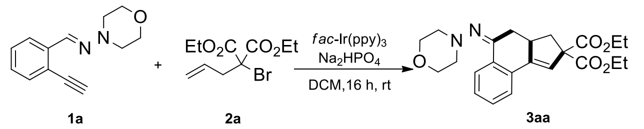
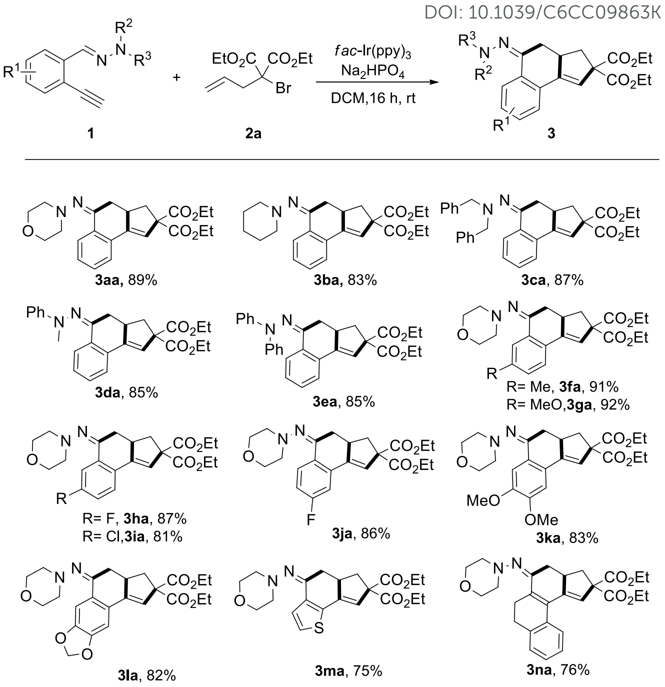
Table 1 Optimization of reaction conditions[a]



Entry	photocatalyst	Base	solvent	Yield(%)[b]
1	*fac*-Ir(ppy)$_3$	K_2CO_3	CH_3CN	41
2	Ru(bpy)$_3$(PF$_6$)$_2$	K_2CO_3	CH_3CN	trace
3	Eosin Y	K_2CO_3	CH_3CN	trace
4	*fac*-Ir(ppy)$_3$	K_2CO_3	DCM	68
5	*fac*-Ir(ppy)$_3$	K_2CO_3	CH_3OH	19
6	*fac*-Ir(ppy)$_3$	K_2CO_3	DMF	51
7	*fac*-Ir(ppy)$_3$	K_2CO_3	DMSO	39
8	*fac*-Ir(ppy)$_3$	$NaHCO_3$	DCM	85
9	*fac*-Ir(ppy)$_3$	Na_2HPO_4	DCM	89
10	*fac*-Ir(ppy)$_3$	K_2HPO_4	DCM	84
11	*fac*-Ir(ppy)$_3$	NaOAc	DCM	26
12	*fac*-Ir(ppy)$_3$	KOAc	DCM	25
13[c]	*fac*-Ir(ppy)$_3$	Na_2HPO_4	DCM	NR
14	-	Na_2HPO_4	DCM	NR
15	*fac*-Ir(ppy)$_3$	–	DCM	15

[a] reaction condition: **1a** (0.1 mmol), **2a** (0.2 mmol), base (0.2 mmol), photocatalyst (2 mol%), solvent (1 mL), 33 W fluorescent light bulb under Ar at room temperature for 16 h. [b] Isolated yield. [c] In the dark.

Table 2 Scope of aldehyde hydrazones [a]



[a] reaction condition: **1** (0.1 mmol), **2a** (0.2 mmol), base (0.2 mmol), photocatalyst (2 mol%), solvent (1 mL), 33 W fluorescent light bulb under Ar at room temperature for 16 h. [b] Isolated yield.

(Table 1, entry 1) under irradiation with 33 W fluorescent light bulb for 16 hours. To improve the reaction efficiency, the reaction conditions of this cascade were further optimized. A serious of photoredox catalysts were evaluated, and *fac*-Ir(ppy)$_3$ was the most effective catalyst (entries 1-3). Then, different solvents were examined (entries 4-7). Among the solvents, dichloromethane was determined to be the best choice (entry 4). It was observed that the use of inorganic bases such as $NaHCO_3$, Na_2HPO_4, K_2HPO_4 promoted the reaction and Na_2HPO_4 gave the best result. Other bases were tested including NaOAc, KOAc, which gave poor yields of **3aa** (Table 1, entries 8–12). The control experiment disclosed that no reaction occurred in the absence of a photoredox catalyst or visible light (Table 1, entries 13 and 14), and only 15% yield of **3aa** was obtained without a base (Table 1, entry 15). Consequently, the reaction proceeded efficiently in the presence of Ir(ppy)$_3$ (2 mol%) and Na_2HPO_4 (2 equiv.) in DCM at room temperature.

With the optimized conditions in hand, we investigated the scope of this photocatalytic domino annulations by varying hydrazones and diethyl α-allyl-α-bromomalonate (**2a**). The results are summarized in Table 2. When the nitrogen atom was connected two alkyl groups, the corresponding products were obtained in excellent yields (**3ba, 3ca**). Moreover, replacement of one alkyl group with a phenyl group did not affect the reaction efficiency, and the desired product was also obtained in 85% yield (**3da**). The hydrazone connected with two phenyl groups was also suitable for this protocol in 85% yield (**3ea**). The *N*-morpholine hydrazones bearing either electron-rich groups (Me or MeO) or electron-poor groups (F, Br) on the benzene ring could react smoothly to furnish the desired products in good yields (**3fa-3ia**). In addition, the position of the substituent on the aryl ring has no effect on this reaction and the corresponding product was obtained in 86% yield (**3ja**). Substrates with multiple substituents on the aryl ring provided the products in excellent yields (**3ka, 3la**). Even thiophene derivative was found to be tolerated in this reaction (**3ma**). Meanwhile, the alkynyl hydrazine on the aliphatic ring was also suitable for this protocol in 76% yield (**3na**).

Then, the scope of the reaction was explored by studying the reactions of various α-bromo γ,δ-unsaturated carbonyl compounds **2** with *N*-(2-ethynylbenzylidene)morpholin-4-amine **1a**. As shown in Table 3, it was found that a methyl group at the C5 position of **2** produced **3ab** in 79% yield (dr = 5:1). In contrast, substitution of the C–C double bond of **2** by phenyl group was obtained the corresponding product in 35% yield (**3ac**). Introduction of two methyl groups at the C5 position of **2** produced **3ad** in an excellent yield. Installation of a methyl group at the C3 or C4 position of **2** were also tolerated well in this process and smoothly converted into products **3ae** and **3af** in 83% and 75% yields, respectively. Under the standard reaction conditions, **2g** proved to be viable substrate to provide **3ag** in 86% yield. Unfortunately, secondary bromide **2h** failed to give the desired product. It is noteworthy that an α-bromo δ, ε-unsaturated carbonyl such as **2i** could also successfully got the desired product in 75% yield (**3ai**).

To further show the practical application of this method, a gram-scale reation was carried out under standard reaction conditions. We were delighted to find that the synthesis of **3aa** with a good yield of 81% on a 5 mmol scale (Scheme 3a). Hydrozones are important organic intermediates for a series of transformations in organic chemistry. **3aa** can be easily converted to ketone **4** in 85% when treated with simple acid

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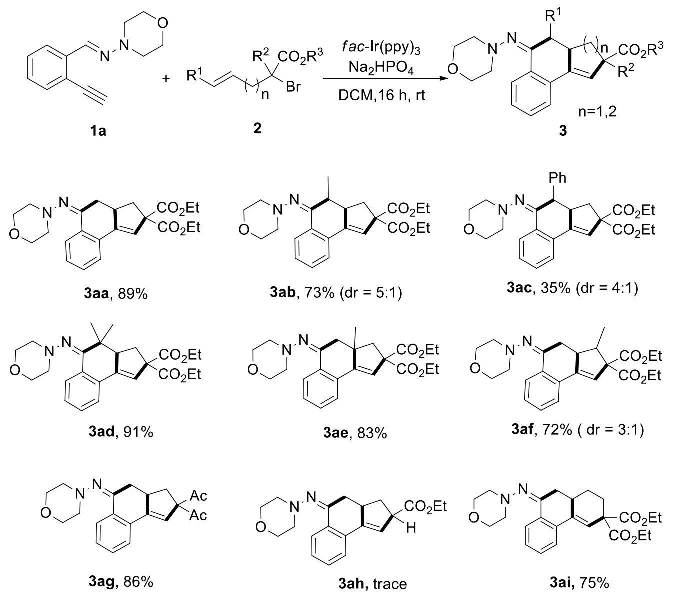
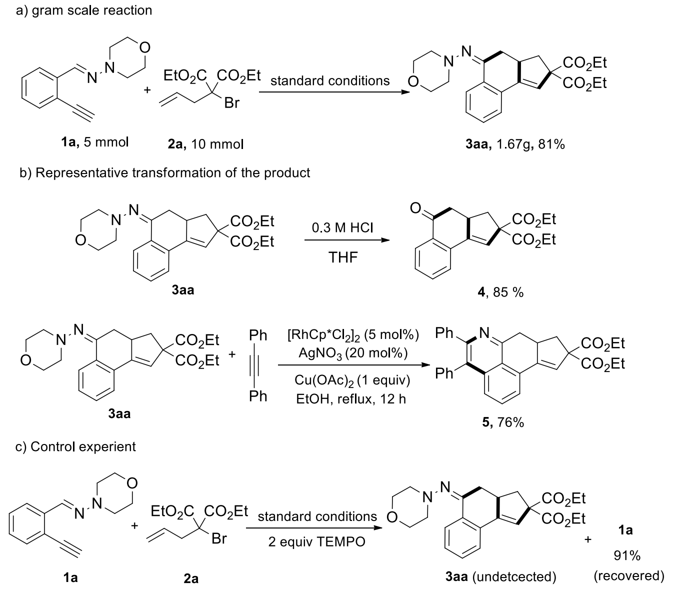
Table 3 Scope of α-bromocarbonyl compounds [a]



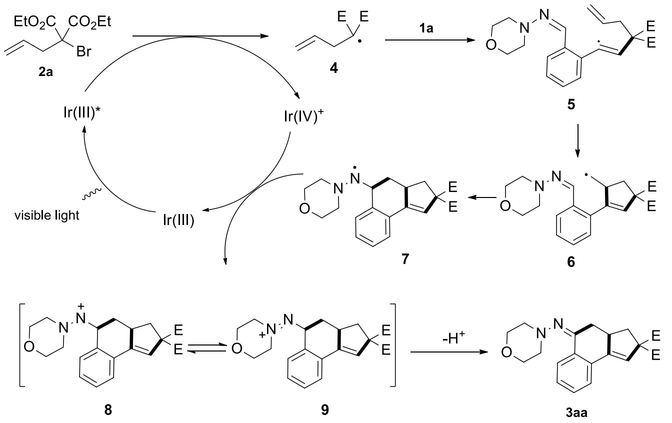
[a] reaction condition: **1a** (0.1 mmol), **2** (0.2 mmol), base (0.2 mmol), photocatalyst (2 mol%), solvent (1 mL), 33 W fluorescent light bulb under Ar at room temperature for 16 h. [b] Isolated yield.

(Scheme 3b). Moreover, **3aa** could react with diphenylacetylene toward isoquinoline **5** in 76% by using the [(RhCp*Cl$_2$)$_2$]/AgNO$_3$/Cu(OAc)$_2$ catalytic system (Scheme 3b).[9] The product isoquinoline is ubiquitous structural component of multitudinous natural products and biomolecules.[10] To gain further understanding of this mechanism, a preliminary mechanistic experiment was performed. When the reaction was conducted with a radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), the reaction was substantially inhibited and **1a** was almost completely recovered, suggesting that the reaction involves a single electron transfer (SET) process (Scheme 3c).



Scheme 3 Synthetic utility of methodology.

Based on the above-mentioned experiments and literature precedents,[3b,8a] a possible reaction mechanism was proposed (Scheme 4). Under visible-light irridation, the photocatalyst Ir(ppy)$_3$ undergoes a metal-to-ligand charge transfer (MLCT) process to produce the excited state Ir^{III}*. A SET process then occurs between Ir^{III}* and **2a** with the generation of Ir^{IV} and radical precursor **4**. Subsequently, active radical **4** will react with **1a** to generate intermediate **5**, which is converted to the alkyl radical species **6** via a 5-*exo*-trig cyclization. Then, anintramolecular addition of carbon radical to the C=N bond leads to the aminyl radical intermediate **7**, which should be stabilized by the adjacent nitrogen through possible three-electron π bonding interaction. At this stage, a key aminyl radical/polar crossover step between **7** and Ir^{IV} can take place, thus regenerating the photocatalyst and either the diazenium cation **8** or **9**. Further tautomerization and deprotonation of diazenium cation would give the product **3**. Finally, the diazenium cation can be easily tautomerized and deprotonated, generating the desired product **3**.



Scheme 4 Proposed mechanism.

Conclusions

In summary, we have successfully developed a visible-light photocatalyzed cacased annulation of hydrazones with alkenyl α-bromocarbonyls, providing a direct access to various cyclohexylidenehydrazines-fused polycyclic compounds. This reaction accommodates a broad substrate scopes and is distinguished by its mild conditions and excellent functional group compatibility (fluorides chlorides, and methyl as well as methoxy included).

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