SCIENCE CHINA
Chemistry

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doi: 10.1007/s11426-015-5530-7

Regioselective synthesis of α-bromo-α,β-unsaturated carbonyl compounds via photocatalytic α-bromination reactions

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Received August 18, 2015; accepted September 21, 2015

A visible light-mediated approach for the preparation of α-bromo-α,β-unsaturated ketones and aldehydes was developed. In comparison to traditional methods that generally take two steps to afford the above compounds, this protocol was highlighted by its operational simplicity, avoiding using hazardous bromine and mild reaction conditions.

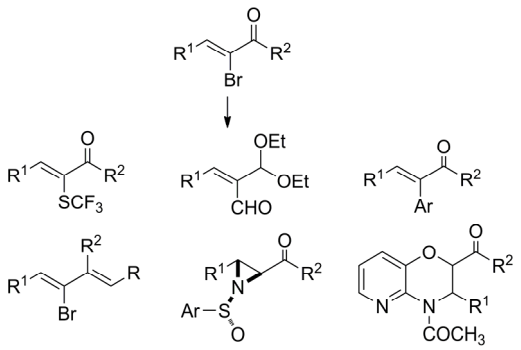
visible light, α-bromination, α,β-unsaturated ketones and aldehydes, operational simplicity

Citation: Wang D, Zhao YT, Yang C, Xia WJ. Regioselective synthesis of α-bromo-α,β-unsaturated carbonyl compounds via photocatalytic α-bromination reactions. *Sci China Chem*, doi: 10.1007/s11426-015-5530-7

1 Introduction

α-Bromo-α,β-unsaturated ketones or aldehydes are important building blocks in synthesis of natural products and pharmaceutical compounds. They also can be transformed into many synthetically useful compounds (Scheme 1) [1–7]. With respect to their synthesis, the traditional method through direct dibromination of the double bond followed by elimination of a molecule hydrogen bromide promoted by base is undoubtedly one of the most practical pathways (Scheme 2) [8,9]. In addition, they are also accessible by treatment of aldehyde with brominated reagents [10,11]. However, the above methods suffered from the tough reaction conditions and/or employment of hazardous reagents. With this regard, the development of a novel method with cleaner reagents and milder conditions seems to be appealing.

Recently, photoredox catalysis has emerged as an effective and versatile method for the use of visible light to activate molecules and promote synthetic transformations [12–17]. Studies have demonstrated that photocatalysts, such as $Ru(bpy)_3Cl_2$ and *fac*-$Ir(ppy)_3$, can initiate the single electron transfer (SET) process under visible light irradiation. In previous work, we have developed a highly efficient method to prepare α-bromo ketones and diketones by ring opening of epoxides via photoredox catalysis [18]. However,



Scheme 1 Various transformation from α-bromo-α,β-unsaturated ketones or aldehydes.

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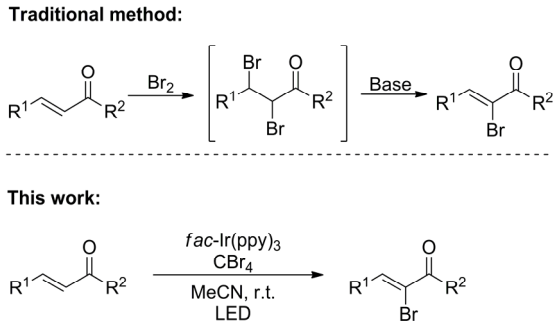


Scheme 2 Different approaches to α-bromo-α,β-unsaturated ketones or aldehyde.

only saturated α-bromo ketones can be formed, to get this work further, we then tried to explore visible light-mediated synthesis of α-bromo-α,β-unsaturated ketones or aldehydes (Scheme 2).

2 Experimental

2.1 General experimental section

All reagents were purchased from commercial sources unless otherwise noted. Solvents were dried according to the standard procedures prior to use.

The chemical shifts in the ^{1}H NMR (600 MHz or 400 MHz) and ^{13}C NMR (150 MHz) spectra are reported in parts per million, with tetramethylsilane (TMS) or solvent resonance (e.g., $CDCl_3$) as the internal standard. HR-MS spectra were recorded on LC mass spectrometer using electrospray ionization (ESI, TOF).

2.2 General procedure for the synthesis of α-bromo-α,β-unsaturated aldehydes 1b

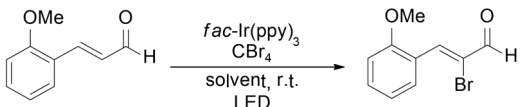
A 10 mL Schlenk flask was equipped with a magnetic stir bar and was charged with substrate **1a** (33 mg, 0.20 mmol), CBr_4 (198.2 mg, 0.60 mmol), CH_3CN (2.0 mL) and *fac*-Ir(ppy)$_3$ (6.6 mg, 0.01 mmol). The reaction mixture was degassed three times by Freeze-Pump-Thaw cycles and then irradiated by blue LEDs (1 W) for 76 h at room temperature under N_2 protection. After reaction, the solvent was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc=50:1) to afford the desired product **1b** (40.1 mg, 83% yield). The characterizations of α-bromo-α,β-unsaturated ketones or aldehydes listed in the Supporting Information online.

3 Results and discussion

We commenced our research on subjecting the electron-rich α,β-unsaturated aldehyde **1a** and CBr_4 in MeCN to visible light irradiation (blue LEDs, λ_{max}=435 nm) in the presence of $Ru(bpy)_3Cl_2$ (5.0 mol%), but no reaction occurred (Table 1, Entry 1). Then the photocatalyst $Ru(bpy)_3Cl_2$ was changed to *fac*-Ir(ppy)$_3$. To our delight, α-bromo-α,β-unsaturated aldehyde **1b** was formed in 93% yield after reaction for 76 h (Entry 2). Notably, the reaction did not happen in the absence of either visible light (Entry 3) or photocatalyst (Entry 4). It seems that light source plays a very important role in this reaction, when changed to 5 W fluorescence blub, only 37% desired product was obtained (Entry 15). The screen on the solvents indicated that the yield was dramatically decreased to 30% in dimethylformamide (DMF, Entry 5), and no reaction was observed in Dimethyl sulfoxide (DMSO), tetrahydrofuran (THF) or dichloromethane (DCM, Entries 6–8). In addition, additives were not necessary for the reaction (Entries 9–13). It was worth mentioning that the reaction was characterized by its high regioselectivity that all the brominated products were *Z* isomers [19] for the olefins, and no *E* isomers were detected.

We then investigated the scope of this photocatalytic reaction by submitting a series of substituted α,β-unsaturated aldehydes to the optimized conditions. As shown in Scheme 3, it can be seen that different kinds of functional groups on the β-aryl substituent were tolerant with the reaction conditions. Substrates with electron-donating group on benzyl ring afforded the corresponding α-brominated products in high yields (**1b**, **3b**). When the substrates bear an electron-withdrawing group, such as NO_2 (**8b**, **9b**) or halogen

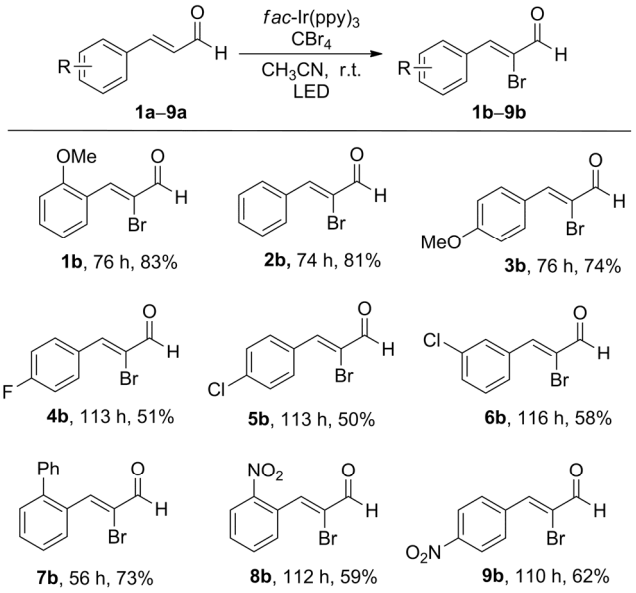
Table 1 Optimization of experimental parameters (I) [a]



1a **1b**

Entry	Light	Catalyst	Solvent	Additive	Yield [b]
1	on	$Ru(bpy)_3Cl_2$	CH_3CN	–	N.R.
2	on	*fac*-Ir(ppy)$_3$	CH_3CN	–	93%
3	off	*fac*-Ir(ppy)$_3$	CH_3CN	–	N.R.
4	on	null	CH_3CN	–	N.R.
5	on	*fac*-Ir(ppy)$_3$	DMF	–	30%
6	on	*fac*-Ir(ppy)$_3$	DMSO	–	N.R.
7	on	*fac*-Ir(ppy)$_3$	THF	–	N.R.
8	on	*fac*-Ir(ppy)$_3$	DCM	–	N.R.
9	on	*fac*-Ir(ppy)$_3$	CH_3CN	K_2HPO_4	27%
10	on	*fac*-Ir(ppy)$_3$	CH_3CN	$AcONH_4$	N.R.
11	on	*fac*-Ir(ppy)$_3$	CH_3CN	Imidazole	19%
12	on	*fac*-Ir(ppy)$_3$	CH_3CN	DMP	70%
13	on	*fac*-Ir(ppy)$_3$	CH_3CN	Na_2CO_3	N.R.
14	on	*fac*-Ir(ppy)$_3$ [c]	CH_3CN	–	56%
15 [d]	on	*fac*-Ir(ppy)$_3$	CH_3CN	–	37%

a) Reaction conditions: **1a** (1.0 equiv.), CBr_4 (3.0 equiv.), *fac*-Ir(ppy)$_3$ (5 mol%), solvent (0.1 mol/L), blue LEDs (1 W), additive (3 equiv.); b) yield: all detected by GC; c) *fac*-Ir(ppy)$_3$=2 mol%; d) fluorescence bulb (5 W).



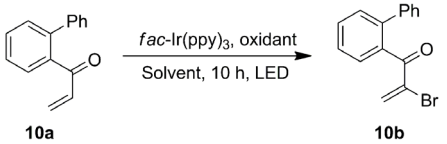
Scheme 3 Substrate scope of α-bromination of aldehydes. Reaction conditions: **a** (1.0 equiv.), CBr_4 (3.0 equiv.), *fac*-Ir(ppy)$_3$ (5 mol%), solvent (0.1 mol/L), blue LEDs (1 W), no additive; yield: isolated yield at complete conversions.

(**4b**, **5b**, **6b**) on the aromatic ring, the reaction proceeded smoothly to yield the desired products in moderate yield, but longer reaction time was needed. Additionally, steric effect on the aryl group is also tolerant with the reaction conditions (**7b**).

Our continuous investigation revealed that this protocol was also suitable for α-bromination of α,β-unsaturated ketones. Therefore, the representative substrate **10a** was subjected to the standard reaction conditions, and anticipated product **10b** was obtained in 56% yield (Table 2, Entry 1). To optimize the reaction conditions, alternative photocatalysis, $Ru(bpy)_3Cl_2$ was tested under the same conditions, however a lower yield was observed (Entry 2). Then we tried to examine some other oxidative quenchers, which provided little or no product (Entries 3 and 4). To our delight, the addition of Na_2CO_3 could improve the reaction efficiency and yield when screening the influence of additives (Entry 6). However, no reaction was observed when the reaction was conducted in other solvents such as DMSO, DMF, and THF (Entries 7–9). Notably, control experiment revealed that both visible light and photocatalyst were essential to this α-bromination reaction.

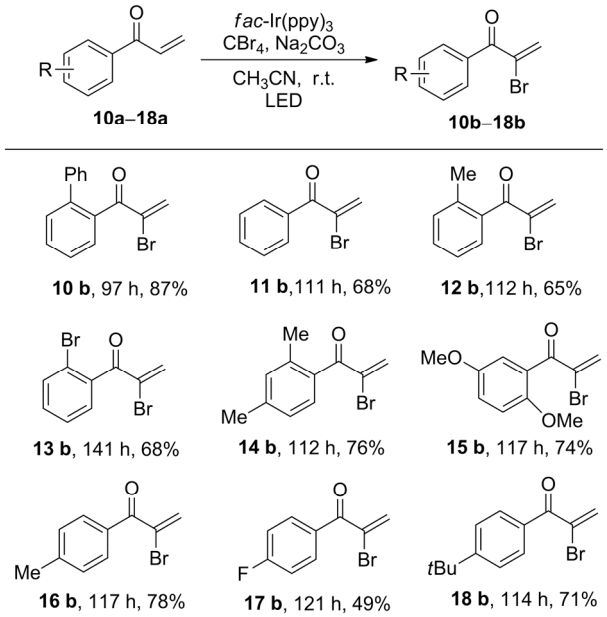
Next, a variety of α,β-unsaturated ketones bearing different substituents were tested, and the results are summarized in Scheme 4. It was found that both electron-withdrawing and -donating functional groups such as –H (**11b**), –Me (**12b**), –Br (**13b**), and –F (**17b**) were well tolerated, giving the corresponding products in good yields. Moreover, some other substituents on different positions of the aryl group were also tested to produce desired products in good yields (Scheme 4, **14b–16b**, **18b**).

Table 2 Optimization of experimental parameters (II) [a]



Entry	Solvent	Additive	Oxidant	Yield [b]
1	CH_3CN	–	CBr_4	56%
2	CH_3CN	–	CBr_4	32%
3	CH_3CN	–	$BrCH_2COOEt$	N.R.
4	CH_3CN	–	$BrCH(CH_2CO_2Et)_2$	5%
5	CH_3CN	K_2HPO_4	CBr_4	43%
6	CH_3CN	Na_2CO_3	CBr_4	68%
7	DMSO	–	CBr_4	N.R.
8	DMF	–	CBr_4	N.R.
9	THF	–	CBr_4	N.R.

a) Reaction conditions: **10a** (1.0 equiv.), oxidative quencher (3.0 equiv.), *fac*-Ir(ppy)$_3$ (5 mol%), solvent (0.1 mol/L), blue LEDs (1 W), additive (3 equiv.); b) yield: all detected by GC.



Scheme 4 Scope of α-bromination of ketones. Reaction conditions: **10a–18a** (1.0 equiv.), CBr_4 (3.0 equiv.), *fac*-Ir(ppy)$_3$ (5 mol%), solvent (0.1 mol/L), blue LEDs (1 W), Na_2CO_3 (3.0 equiv.); yield: isolated yield at complete conversions.

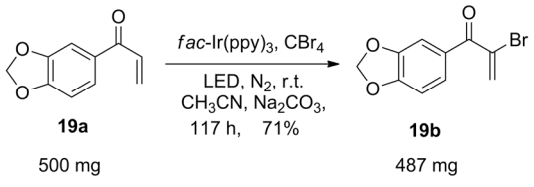
To elucidate the mechanism of the reaction, a number of controlled experiments were carried out using **10a** as the substrate (Table 3). When TEMPO was added to the reaction, **10b** was obtained in high yield (Entry 10) which indicated that the simple free radical pathway might be excluded. Interestingly, when $Na_2S_2O_8$ served as the oxidant and LiBr was employed as an additive, the desired product **10b** was formed in 78% yield, which implied that bromide ion might be involved as nucleophilic reagent (Entry 9). In addition, the amount of CBr_4 ranging from 0.5 to 4 equiv. was

accompanied by the yields changing from 12% to 83% (Entries 1–5). Furthermore, the addition of LiBr improved the yield to 37% in the case of 0.5 equiv. of CBr_4 (Entry 6). The above results showed that CBr_4 served as not only an oxidant. Other oxidative quenchers gave no or little products (Entries 7, 8).

It was documented that the resulting Br^- ($E_{1/2}^{red}$=1.087 V vs. SCE, in CH_3CN) [20] is more oxidizing than *fac*-Ir(ppy)$_3$ ($E_{1/2}^{IV/III}$=0.77 V vs. SCE, in CH_3CN) [17], which means that molecular bromine could not be generated *in situ* from oxidation of Br^- by Ir^{IV}. To map out the reaction mechanism, the oxidation potentials of two representative substrates **1a** and **10a** were therefore tested and shown as 0.65 V vs. SCE, in CH_3CN for **1a** and 0.70 V vs. SCE, in CH_3CN for **10a** which could be oxidized by *fac*-Ir(ppy)$_3$ ($E_{1/2}^{IV/III}$=0.77 V vs. SCE, in CH_3CN). Based on the above results, a tentative reaction mechanism was proposed as shown in Scheme 5.

As shown in Scheme 5, the photoexcited state of *fac*-Ir(ppy)$_3$ was oxidized by CBr_4 to generate Br^- and Ir^{IV} which then accepted one electron from the starting material to form the radical cation intermediate **A**. Nucleophilic addition of Br^- to **A** led to a radical intermediate **B** which was then oxidized by Ir^{IV} to form the cation **C**. The final products **1b–18b** were formed after the elimination of a proton from **C**. Based on the high regioselectivity of the reaction that only the α-bromination product was obtained, we speculate that the stability of the cation intermediate **C** might play an important role in the product distributions.

Finally, to demonstrate the utility of this protocol, a scale of 500 mg of substrate **19a** was subjected to the standard reaction conditions and the corresponding product **19b**, an intermediate for synthesis of natural product (−)-Wodeshiol [21], was successfully prepared in 71% yield (Eq. (1)).

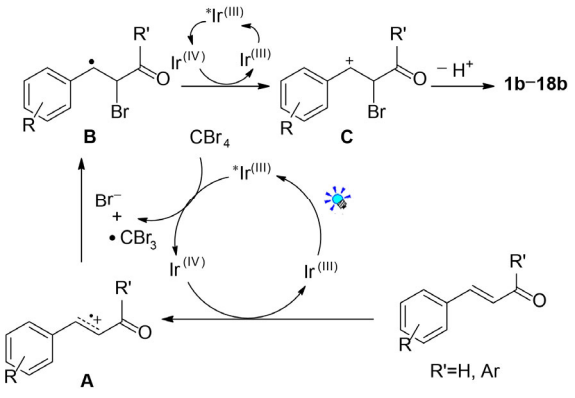


(1)

Table 3 Controlled experiments [a]

Entry	Oxidant	Additive	Yield [b]
1	4 equiv. CBr_4	–	81%
2	3 equiv. CBr_4	–	83%
3	2 equiv. CBr_4	–	65%
4	1 equiv. CBr_4	–	38%
5	0.5 equiv. CBr_4	–	12%
6	0.5 equiv. CBr_4	5 equiv. LiBr	37%
7	3 equiv. $BrCH(CO_2Et)_2$	–	5% [b]
8	3 equiv. $BrCH_2CO_2Et$	–	0%
9	5 equiv. $Na_2S_2O_8$	5 equiv. LiBr	78%
10	3 equiv. CBr_4	4.5 equiv. Tempo	81%

a) *fac*-Ir(ppy)$_3$ as catalyst; b) yield were detected by GC.



Scheme 5 Proposed mechanism.

4 Conclusions

In summary, we have developed a photocatalytic protocol for the α-bromination of different kinds of α,β-unsaturated ketones or aldehydes under mild reaction conditions. Compared with previous procedures, this method is highlighted by operational simplicity, high regioselectivity, and the employment of environmentally friendly brominating reagent. Meanwhile, further experiments were conducted to provide a clear understanding of the reaction mechanism.

Acknowledgments This work was supported by the National Natural Science Foundation of China (21002018, 21072038, 21472030, 21302029), the State Key Laboratory of Urban Water Resource and Environment (2015DX01), the Fundamental Research Funds for the Central Universities (HIT.BRETIV.201310).

Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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