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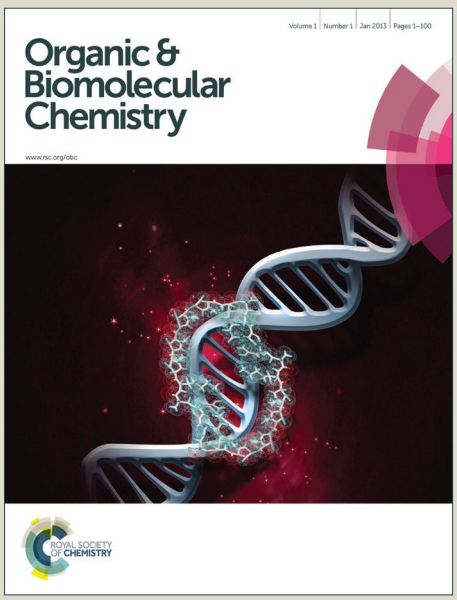

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Brønsted acid cocatalysis in photocatalytic intramolecular coupling of tertiary amines: efficient synthesis of 2-arylindols

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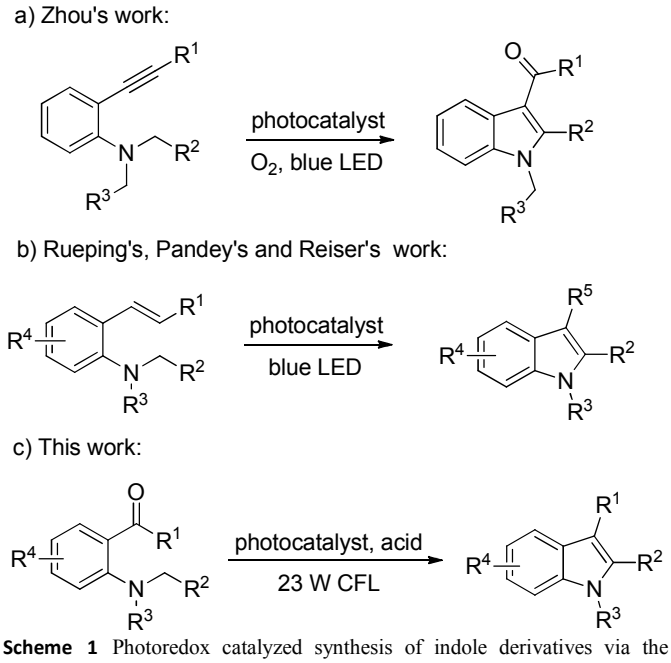
We report herein a highly efficient intramolecular coupling reaction of tertiary amines and ketones (α,β-unsaturated ketones) by using Brønsted acid as a cocatalyst, affording 2-arylindols in good to excellent yields (up to 92%) under visible light irradiation at room temperature.

Indole derivatives have been found in a variety of biologically active heterocyclic compounds, which are abundant in natural products, pharmaceuticals, and materials.[1] Therefore, seeking more efficient and convenient methods for the preparation of indoles attracts great attentions. Numerous classical methods for the synthesis of indoles have been developed during the past decades.[2, 3] The direct functionalization of an sp^3 C-H bond adjacent to the N atom of amines, which is one of the most important methods for atom-economic synthesis of indole derivatives, has been a challenge to synthetic chemists in recent years. Recently, Yan and co-workers reported an elegant method for synthesizing indole derivatives promoted by KO-*t*-Bu/DMF at high temperature.[4] However, in order to develop more mild condition protocols, further exploration in this area is still in high demand.

Recently, visible-light photocatalysis[5] was recognized as an ideal approach to generate reactive radicals from tertiary amines under mild reaction conditions with good functional-group compatibility. But most of these transformations proceed via the in situ generation of iminium intermediates, which are further attacked by a wide range of nucleophiles.[6] Successful examples of the α-amino alkyl radicals formed by single electron oxidation of amines are quite limited, because they are rapidly oxidized to iminium ions in the presence of a stoichiometric amount of oxidants.[7] MacMillan's group demonstrated visible-light induced α-amino C-H arylation reaction for the construction of benzylic amines.[8] Zhou and co-workers reported the application of visible light to generate α-amino alkyl radicals in situ and their subsequent radical addition to alkynes followed by C-O bond formation to produce 3-acylindoles (Scheme 1a).[9] Rueping and co-workers described a photoredox catalyzed synthesis of indole-3-carbaldehydes derivatives through domino reactions via the formation of α-amino alkyl radical intermediates (Scheme 1b).[10] A similar protocol was also realized by Pandey and Reiser et al. using inter- and intramolecular addition of α-amino alkyl radicals to α,β-unsaturated carbonyl compounds (Scheme 1b).[11] To the best of our knowledge, directly trapping nucleophilic α-amino alkyl radicals with carbonyl groups through photocatalysis has never been reported.

To further develop our exploration on visible-light photoredox radical chemistry[12], we now report α-amino alkyl radicals react with carbonyl groups for synthesizing indole derivatives under mild reaction conditions with visible light as the only energy source (Scheme 1c).



Scheme 1 Photoredox catalyzed synthesis of indole derivatives via the formation of α-amino alkyl radical intermediates.

Initially, we examined the reaction of 1-(2-(3,4-dihydroisoquinolin-2(1H)-yl)phenyl)ethan-1-one **1a** in acetonitrile with trifluoroacetic acid (20 mol%) at room

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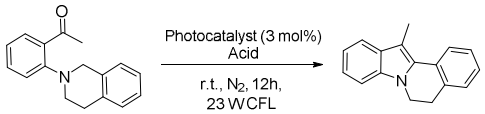
temperature in the presence of 3 mol% $Ru(bpy)_3Cl_2·6H_2O$ using a 23 W household fluorescent light bulb as the source of visible light. To our delight, 12-methyl-5,6-dihydroindolo[2,1-*a*]isoquinoline **2a** was observed in 32% isolated yield. Encouraged by this promising result, we further optimized the reaction conditions in detail (Table 1). Firstly, different photocatalysts were tested and it was found that a satisfactory yield of 61% could be obtained when $Ir(ppy)_2(dtbbpy)PF_6$ was used (entries 1-6). The choice of photocatalyst was vital to this reaction for organic dyes show low effiency. Considering the noticeable impact of additives, some acids were screened (entries 7-10). Inspiringly, 82% yield was achieved when diphenylphosphoric acid was used as acid (entry 10). Moreover, a change of the solvent to N,N-dimethylformamide increased the yield of **2a** to 92%. When lower loading of catalyst (1 mol%) was used, a decrease in the yield (83%) of product was observed (entry 14). Meanwhile, control experiments showed that photocatalysts and light were essential to the success of this reaction (entries 15-16). The presence of diphenylphosphoric acid had a significant impact on the reaction, and in the absence of this Brønsted acid essentially no product was formed (entry 17). It was found that the optimal reaction should be catalyzed by 3 mol% $Ir(ppy)_2(dtbbpy)PF_6$ with 40 mol% diphenylphosphoric acid and N,N-dimethylformamide by irradiation with visible light at room temperature.

Table 1. Photocatalyzed synthesis of indole derivatives[a]



1a **2a**

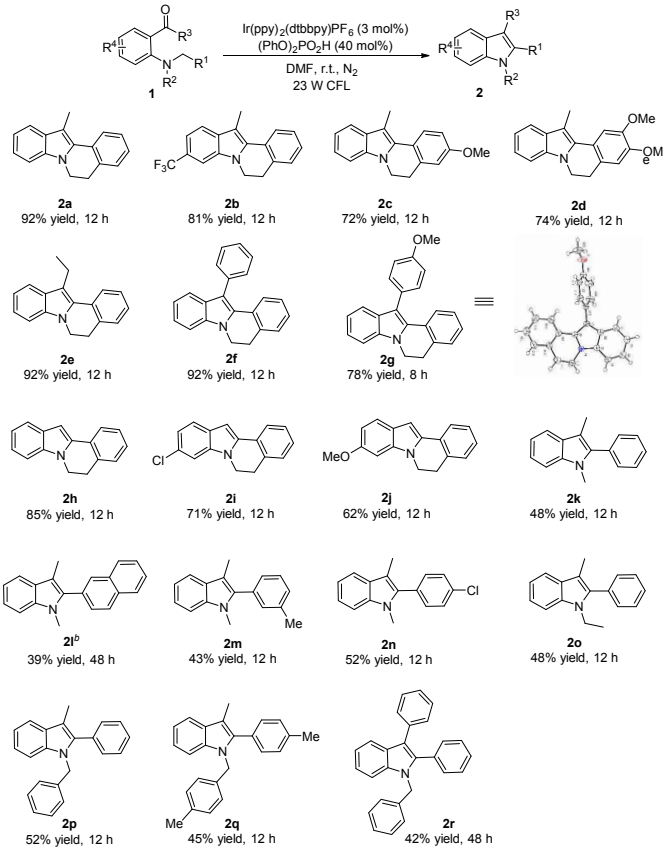
entry	Photocatalyst	Acid	Solvent	yield (%)[b]
1	$Ru(bpy)_3Cl_2·6H_2O$	TFA[d]	CH_3CN	32
2	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	TFA[d]	CH_3CN	57
3	$Ir(ppy)_2(dtbbpy)PF_6$	TFA[d]	CH_3CN	61
4	Mes-AcrClO$_4$	TFA[d]	CH_3CN	25
5	Riboflavin	TFA[d]	CH_3CN	17
6	riboflavin tetraacetate	TFA[d]	CH_3CN	20
7	$Ir(ppy)_2(dtbbpy)PF_6$	*p*-TSA[d]	CH_3CN	43
8	$Ir(ppy)_2(dtbbpy)PF_6$	H_3PO_4[d]	CH_3CN	32
9	$Ir(ppy)_2(dtbbpy)PF_6$	Sc(OTf)$_3$[d]	CH_3CN	51
10	$Ir(ppy)_2(dtbbpy)PF_6$	$(PhO)_2PO_2H$[d]	CH_3CN	82
11	$Ir(ppy)_2(dtbbpy)PF_6$	$(PhO)_2PO_2H$[e]	CH_3CN	86
12	$Ir(ppy)_2(dtbbpy)PF_6$	$(PhO)_2PO_2H$[e]	DMF	92
13	$Ir(ppy)_2(dtbbpy)PF_6$	$(PhO)_2PO_2H$[e]	DMSO	67
14[f]	$Ir(ppy)_2(dtbbpy)PF_6$	$(PhO)_2PO_2H$[e]	DMF	83
15[c]	$Ir(ppy)_2(dtbbpy)PF_6$	$(PhO)_2PO_2H$[e]	DMF	NR
16	None	$(PhO)_2PO_2H$[e]	DMF	NR
17	$Ir(ppy)_2(dtbbpy)PF_6$	None	DMF	NR

[a] All reactions were performed on a 0.3 mmol scale using a 3 mol% photocatalyst, 1.5 mL solvent, and a 23 W CFL as the light source, at room temperature, 12 h. [b] Yield of the isolated product. [c] In the absence of light source. [d] Performed using 20 mol% of acid. [e] Performed using 40 mol% of acid. [f] Performed using 1 mol% of photocatalyst. TFA = trifluoroacetic acid; *p*-TSA = *p*-toluenesulfonic acid; $(PhO)_2PO_2H$ = diphenylphosphoric acid.

To explore the scope of this transformation, a variety of tetrahydroisoquinoline derivatives **1a-j** were examined under the optimized reaction conditions. As shown in Table 2, tetrahydroisoquinolines were particularly well suited to this reaction and afforded the desired indole derivatives **2a-j** in moderate to good yields. Both electron-donating groups and electron-withdrawing groups on the aromatic moieties were tolerated very well. 2-Tetrahydroisoquinolinylpropiophenone **1e** and 2-tetrahydroisoquinolinyl diphenyl ketone **1f** gave **2e** and **2f** in good yields. In addition, we were delighted to find that tetrahydroisoquinoline-derived benzaldehyde **1h-j** was also suitable for the reaction, affording the corresponding product **2h-j** in moderate yields.

The reaction was not limited to tetrahydroisoquinoline derivatives, and it was also applied to benzylamine-derived ketones. N-benzyl substituted ketones led to lower yields, while the reaction of benzylamine-derived ketones gave the debenzylation products. Benzylmethylamine-, 2-naphthylamine-, 3-methylbenzylamine-, and 4-chlorinbenzylaminederived ketones **1k-n** gave products **2k-n** in moderate yields. When the N-substitutent is ethyl or benzyl, the indole products **2o-p** were obtained in moderate yields. Tetrahydroisoquinoline derivative **1q** with 1,2-dimethyl substitution also provided product **2q** in moderate yield. N,N-dibenzylamine-derived diphenyl ketone **1r** also worked well to give the indole product **2r** in moderate yield. Unfortunately, no expected products were obtained, when aliphatic analogues were used.

Table 2. Substrate scope of tertiary amines **1**[a]



[a] Unless otherwise noted, reactions were performed on a 0.3 mmol scale using a 3 mol% $Ir(ppy)_2(dtbbpy)PF_6$, 40 mol% diphenylphosphoric acid, 1.5 mL DMF, and a 23 W CFL as the light source, at room temperature. [b] 60 mmol% TFA, 1.5 mL CH_3CN.

Furthermore, we examined the intramolecular reaction with the coupling of tertiary amines and α,β-unsaturated carbonyl compounds. Irradiation of 2-(5,6-dihydroindolo[2,1-a]isoquinolin-12-yl)-1-phenylethanone **3a** in the presence of catalytic amounts of $Ir(ppy)_2(dtbbpy)PF_6$ (3 mol%) in 1,2-Dichloroethane with trifluoroacetic acid (30 mol%) at room temperature resulted in the desired formation of indole

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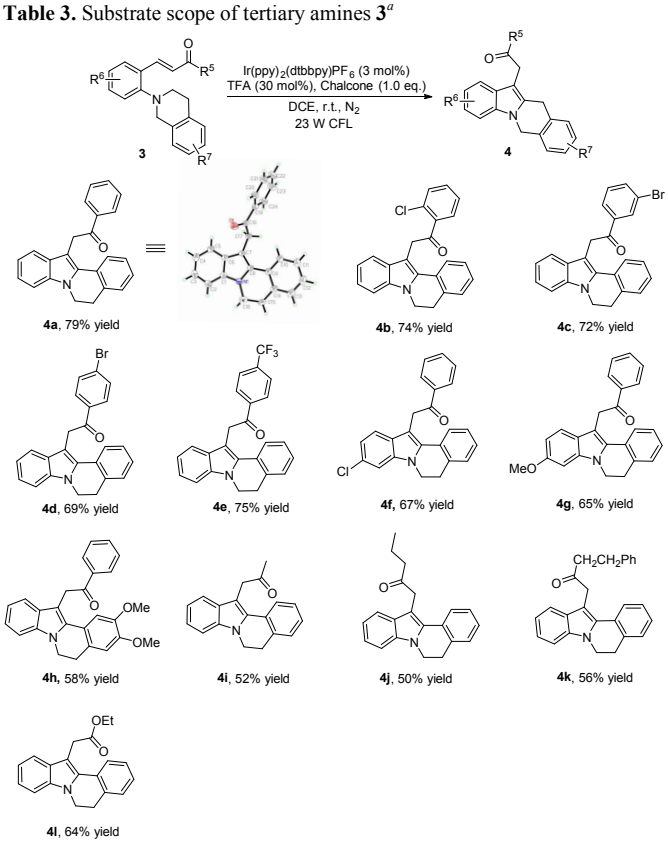
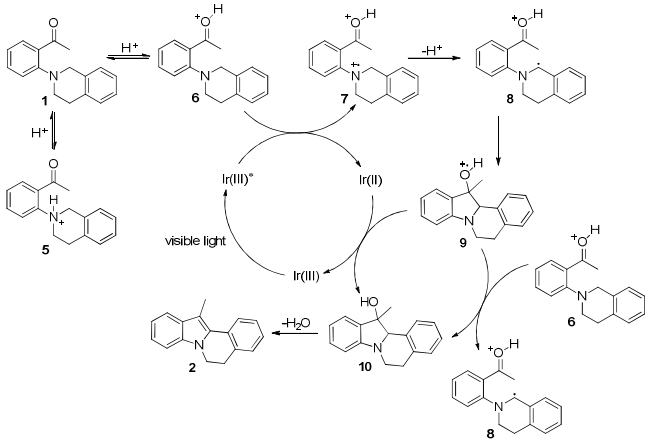
derivatives **4a**. In the process of optimizing for better yields and shorter reaction times, we have discovered that a chalcone additive provides a dramatic improvement in the efficiency of this transformation. (see SI) We surmised that chalcone played the critical role of the proton transfer via abstracting two H atom equivalents from indolines.[13] The benzyl moiety can tolerate both electron-donating substitution such as methoxy and electron-withdrawing substitution such as chloro, bromo, trifluoromethyl. Both aliphatic and aromatic enones **3i-k** gave expected products **4i-k** in moderate yields. Furthermore, acrylate esters **3l** are also reactive and gave a moderate yield of product **4l**.

Table 3. Substrate scope of tertiary amines **3**[a]



[a] Unless otherwise noted, reactions were performed on a 0.3 mmol scale using a 3 mol% $Ir(ppy)_2(dtbbpy)PF_6$, 30 mol% TFA, 1.5 mL DCE, 1.0 equiv of chalcone, and a 23 W CFL as the light source, at room temperature, 12 h.

On the basis of our experiments and the relevant literature, a possible mechanistic pathway is proposed for the photocatalyzed synthesis of indoles in Scheme 2.[7e, 14] The proposed mechanism starts with the reductive quenching of the excited state of Ir(III)* by tertiary amine **6**, generating amine radical cation **7** and the strong reductant Ir(II). Deprotonation of the resultant tetrahydroisoquinoline radical cation **7** affords an α-amino radical **8**, and then adds to the carbonyl group to form radical **9**. Radical **9** is then further reduced either by the Ir(II) photocatalyst to produce the intermediate **10** and complete the catalytic cycle or it is reduced by tertiary amine **6** in a radical chain mechanism. Finally, the intermediate **10** is dehydrated yielding product **2**. When α,β-unsaturated carbonyl compounds **3** participate in this reaction, the key α-amino radical can attack the Michael acceptor and dehydrogenation, affording indoles **4**. Collectively, the use of a stoichiometric amount of Brønsted acids[15] is sufficient to promote the reaction.



Scheme 2 Proposed mechanism of photocatalyzed synthesis of indole derivatives.

In conclusion, we have developed a highly efficient method for synthesizing indole derivatives through intramolecular dehydrated coupling reaction of tertiary amines and ketones. By using Brønsted acid as a cocatalyst, α-amino alkyl radicals can directly react with carbonyl groups for synthesizing indole derivatives in good to excellent yields under visible light irradiation at room temperature. Furthermore, α,β-unsaturated carbonyl compounds are also suitable in this transformation, affording indole derivatives in high yields. Further investigations on the functionalization of an sp^3 C-H bond adjacent to amines are on going in our laboratories.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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