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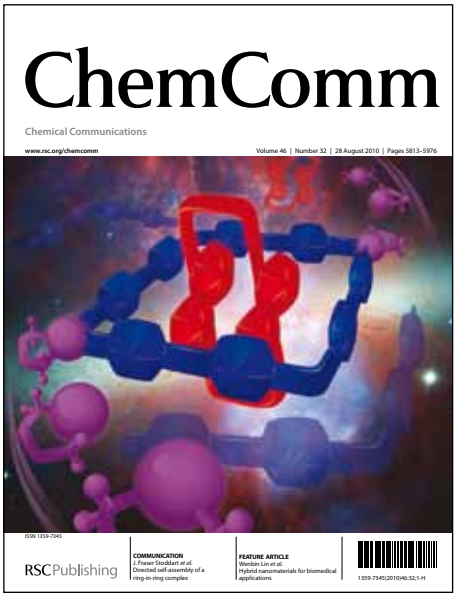

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COMMUNICATION

Cu(I)-Catalyzed Intramolecular Oxidative C–H Amination of 2-Aminoacetophenones: a Convenient Route toward Isatins

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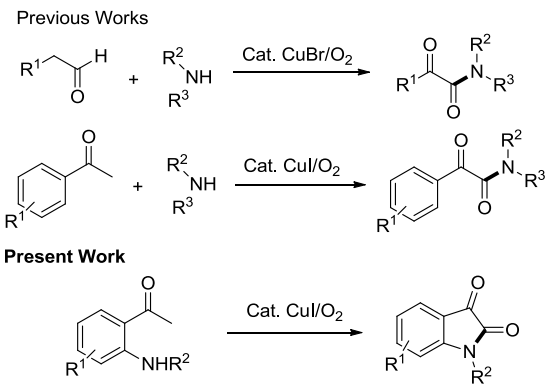
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

2-Aminoaryl methyl ketones undergo intramolecular oxidative C–H amination to give the corresponding substituted isatins under an oxygen atmosphere in the presence of [CuI(bpy)]$_2$.

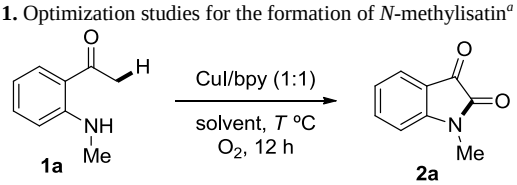
Transition-metal-catalyzed construction of C–C and C–heteroatom bonds has become a proven method for the synthesis of bioactive compounds and advanced materials.[1] In recent years, great effort has been made toward the direct functionalization of C–H bond rather than the pre-functionalized carbon-halogen or carbon-pseudohalogen bond of which additional steps are required for preparation.[2] However, most of these reactions require the use of expensive Pd-, Rh-, Ru- and Ir-complexes as catalysts. Lately, copper-catalyzed C–H functionalization reactions have gained great attention due to their cost effectiveness, availability, low toxicity and wide functional group tolerances.[3] Copper-catalyzed cross dehydrogenative coupling (CDC) transformations *via* a single electron transfer (SET) mechanism allow the access of complex structures in a single step and can be applied to the C–C, C–N, C–O, C–halogen, and C–P bond formations.[4] Recently, Jiao and Ji groups had independently developed an attractive method for the formation of *α*-ketoamides from phenyl acetaldehydes or aryl methyl ketones with amines.[5] In this reaction, both the oxygen atoms of *α*-ketoamides are deduced from the molecular oxygen. Our recent success in the transition metal-catalyzed C–H activation and heterocyclic compound synthesis[6] prompt us to explore the possibility of direct oxidative synthesis of isatins from *ortho*-aminoaryl methyl ketones (Scheme 1).



Scheme 1

Isatins are an important class of heterocyclic compounds due to their biological activity and wide applications in the synthesis of heterocyclic compounds.[7] They were also known as anticonvulsant, antidepressant, antiinflammatory, antimicrobial, antipox virus, and cytotoxic agents.[8]

Table 1. Optimization studies for the formation of *N*-methylisatin[a]



entry	CuI/bpy, mol%	solvent	*T* °C	yield %[b]
1	10	DMF	140	68
2	5	DMF	140	22
3	20	DMF	140	67
4	20	DMF	140	59[c]
5	10	DMF	120	31
6	10	DMAc	140	65
7	10	*o*-DCB	140	47
8	10	*o*-xylene	140	26
9	**10**	**DMSO**	**140**	**91 (89)[d]**
10	---	DMSO	140	---

[a] Unless otherwise mentioned, all reactions were carried out using **1a** (0.3 mmol), CuI (0.03 mmol) and bpy (0.03 mmol) in 0.6 mL solvent for 12 h under O_2 atmosphere. [b] Yields were determined by the ^{1}H NMR integration method using CH_2Br_2 as the internal standard. [c] 1.2 mL DMF was used. [d] Isolated yield. bpy = 2,2'-bipyridine. DMAc = *N*,*N*-dimethylacetamide. *o*-DCB = 1,2-dichlorobenzene.

The most commonly used method for the preparation of isatin is the Sandmeyer procedure by treating a substituted aniline with chloral hydrate and hydroxylamine hydrochloride (or other hydroxylamine salt) in an aqueous sodium sulfate medium.[9] Another frequently used method developed by Stollé involves the treatment of an aniline with oxalyl chloride followed by a Friedel-Crafts intramolecular acylation in the presence of a strong Lewis acid.[10] Since both methods involves intramolecular electrophilic aromatic cyclization, the reactions are highly limited

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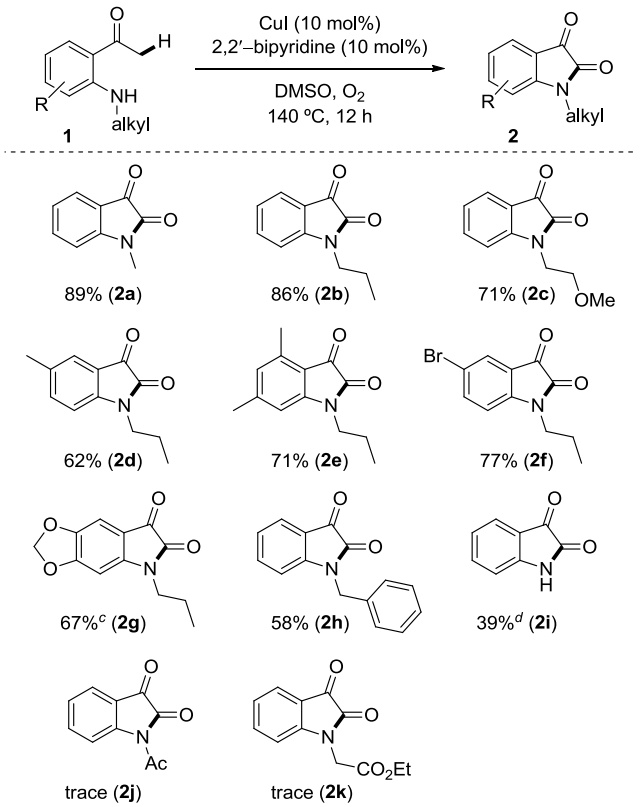
to substrates with electron-donating substituents on the aromatic rings. Other traditional methods[11] also have some drawbacks such as the requirement of strong acid or base condition and the availability of starting materials. Recent report by Li *et al*. involving the $CuCl_2$-catalyzed intramolecular cyclization of formyl-*N*-arylformamides to give isatins appears to be the only method available using transition metal complex as the catalyst.[12] A drawback of this reaction is the formation of inseparable regioisomers for *meta* substituted substrates. Due to wide applications of isatins in organic synthesis and medicinal chemistry, the development of new and effective routes for their synthesis is still highly desirable. Herein, we report a convenient method for the synthesis of isatins from 2-aminoacetophenones *via* copper-catalyzed intramolecular oxidative C–H amination.

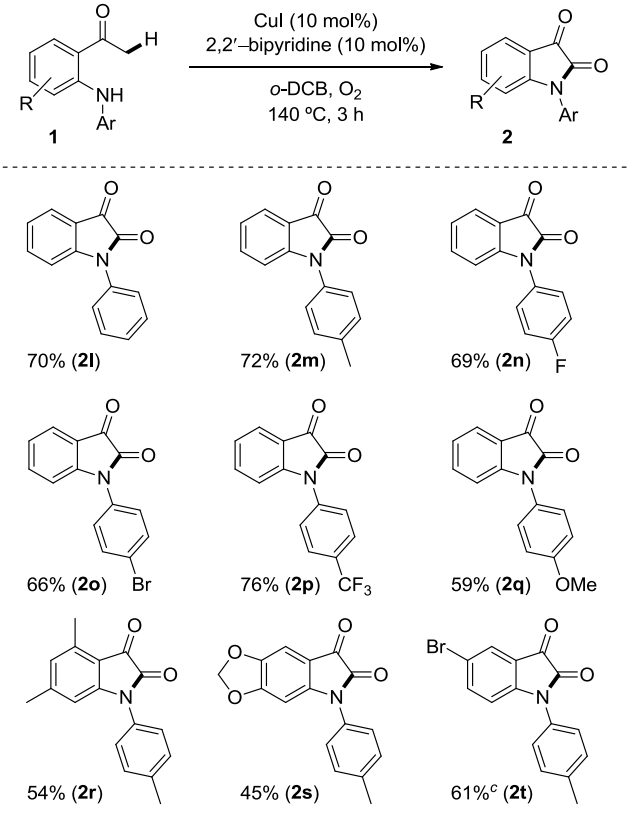
Treatment of 1-(2-(methylamino)phenyl)ethanone (**1a**) in the presence of 10 mol% CuI/bpy in DMSO at 140 °C for 12 h under an oxygen atmosphere gave *N*-methylisatin (**2a**) in 89% isolated yield (Table 1, entry 9). Product **2a** was thoroughly characterized by its ^{1}H and ^{13}C NMR and mass data. The solvent employed is vital to the catalytic reaction. Other solvents such as DMF, DMAc, *o*-DCB also gave **2a** in 68, 65 and 47% yields, respectively (see Supporting Information for detailed studies). It is important to mention that controlled experiment showed that in the absence of CuI, no desired product **2a** was obtained (Table 1, entry 10).

Table 2. Scope of CuI-Catalyzed *N*-alkylisatins synthesis [a,b]



[a] Unless otherwise mentioned, all reactions were carried out using *N*-alkyl 2-aminoacetophenones **1** (0.30 mmol), CuI (0.03 mmol) and bpy (0.03 mmol) in 0.6 mL DMSO at 140 °C for 12 h under O_2 atmosphere. [b] Isolated yields. [c] 120 °C. [d] 130 °C.

Table 3. Scope and results of CuI-catalyzed *N*-arylisatins synthesis[a,b]



[a] Unless otherwise mentioned, all reactions were carried out using *N*-aryl 2-aminoacetophenones **1** (0.3 mmol), CuI (0.03 mmol) and bpy (0.03 mmol) in 0.6 mL *o*-DCB at 140 °C for 3 h under O_2 atmosphere. [b] Isolated yields. [c] 120 °C, 12 h.

By using the standard reaction conditions, various substituted 1-(2-(alkylamino)aryl)ethanone were converted to *N*-alkylisatins in good to excellent yields (Table 2). Thus, *N*-methyl, propyl, 2-methoxyethyl substituted isatins (**2a-2c**) were synthesized in 89, 86 and 71% yields respectively. 5-Methyl and 4,6-dimethyl substituted isatin derivatives **2d** and **2e** are obtained in 62 and 71% yields respectively. The catalytic reaction is compatible nicely with the halo substituents on the aromatic ring to form corresponding isatins. Thus, bromo-substituted isatin **2f** was produced in 77% yield. Similarly, 5,6-methylenedioxy isatin **2g** is formed in 67% yield at 120 °C. *N*-Benzyl substituted isatin **2h** is formed from the corresponding 2-aminoacetophenone in 58% yield. 2-Acetylaniline underwent the transformation to give isatin **2i** in moderate yield. Electron withdrawing groups on the amino group failed to give desired products (**2j** and **2k**).

The copper-catalyzed intramolecular oxidative C–H amination reaction was successfully extended to *N*-aryl 2-aminoacetophenones (Table 3), but the reaction conditions were modified. The solvent used was changed from DMSO to 1,2-dichlorobenzene (*o*-DCB) leading to completion of the reaction in 3 h. Thus, *N*-phenylisatin **2l** is obtained in 70% yield using the standard reaction conditions. Similarly, substrates **1** with *N*-aryl group containing Me, F, Br, CF_3, and OMe substituents gave the corresponding isatins (**2m-2t**) in good yields. This reaction also provided 5,6-methylenedioxy- and bromo substituted isatins **2s** and **2t** from the corresponding substrates **1** in 45 and 61% yields

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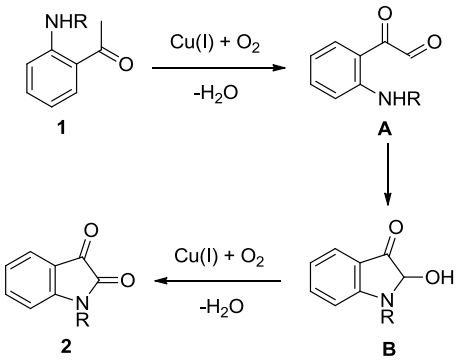
respectively.

The mechanism for the present catalytic reaction is not yet clear. Based on the present results and the known copper chemistry in literature,[5,13] we propose a possible pathway for this CuI-catalyzed isatin formation as shown in Scheme 2. Under the reaction conditions, 2-aminoglyoxal **A** is expected to be formed from 2-aminoaryl methyl ketone **1**.[5b] The intramolecular addition of amino group to the aldehyde group of glyoxal **A** results in the formation of 2-hydroxyindolin-3-one derivative **B** which is further oxidized by Cu(I)/O_2 to form the final product **2**.[5b,13,15]



Scheme 2

In conclusion, we have successfully developed a convenient Cu(I)-catalyzed intramolecualr oxidative C–H amination reaction of 2-aminoacetophenones for the synthesis of isatins. This reaction allows the synthesis of various *N*-alkyl or aryl substituted isatins in good to excellent yields. Further application of this method to other substrates and the detailed mechanistic investigation are in progress.

We thank the National Science Council of Republic of China (NSC-100-2119-M-007-002) for support of this research.

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