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Copper-Catalyzed C–N, C–O Coupling Reaction of Arylglyoxylic Acids with Isatins

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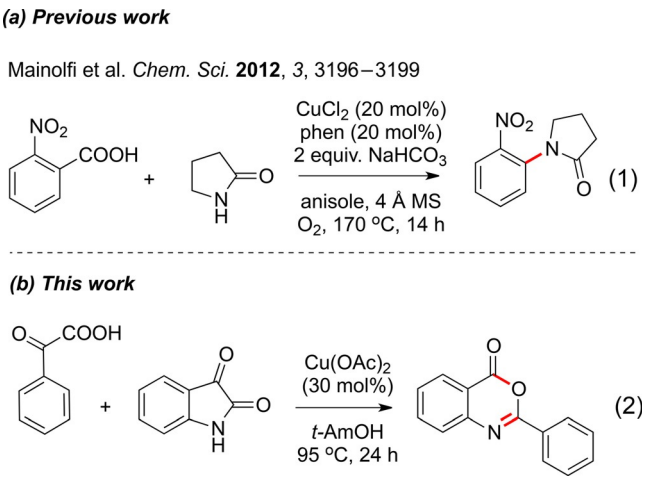
Abstract: The copper(II)-catalyzed decarboxylative coupling reactions of arylglyoxylic acids with isatins afford 4*H*-benzo[*d*][1,3]oxazin-4-ones *via* decarbonylation and concurrent C–N, C–O bond formation.

Keywords: arylglyoxylic acids; benzooxazinones; copper; decarbonylation; decarboxylative C–N coupling

In the past decade, transition metal-catalyzed decarboxylative coupling reactions have attracted considerable interest in C–C bond formation reactions.[1] As the carboxyl group can direct the regioselectivity of the reaction and the only waste material is carbon dioxide, this metal-catalyzed reaction turns out to be a very useful synthetic method for C–C bond formation. Recently, arylcarboxylic acids have been used for the transition metal-catalyzed decarboxylative C–N cross-coupling reactions with N-nucleophiles which afford C–N coupling products [Scheme 1, Eq. (1)].[2] Similarly, α-oxocarboxylic acids have also been successfully utilized as acyl nucleophiles in transition metal-catalyzed decarboxylative coupling reactions for C–C bond formation reactions.[3] Nevertheless, α-oxocarboxylic acids have never been used in metal-catalyzed decarboxylative coupling reactions for C–N bond formation reactions. In continuation of our work on the development of novel metal-catalyzed routes for the syntheses of important heterocycles,[4] herein, we report an unprecedented Cu(II)-catalyzed decarboxylative coupling reaction for the formation of C–N bonds [Scheme 1, Eq. (2)]. This decarboxylative cross-coupling reaction of arylglyoxylic acids with isatins as nucleophiles leads to the formation of C–N and C–O bonds simultaneously, *via* decarbonylation of isatin, to afford a wide range of pharmaceutically important substituted 4*H*-benzo[*d*][1,3]oxazin-4-ones.[5]

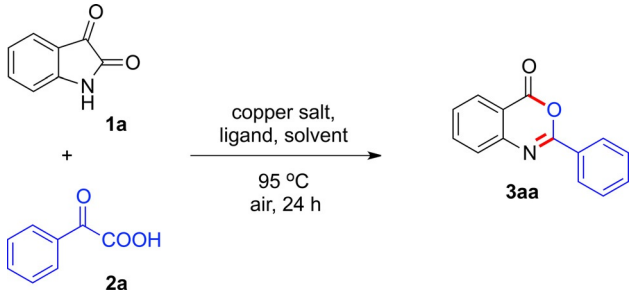


Scheme 1. Decarboxylative C–N coupling reactions.

Initially, isatin **1a** and phenylglyoxylic acid **2a** were chosen as the model compounds to optimize the reaction conditions for the synthesis of **3aa**[5j] (Table 1). Fortunately, in the presence of 20 mol% of $Cu(OAc)_2$, the reaction afforded a 67% yield of **3aa** in *t*-AmOH (entry 1). Increasing the catalyst loading to 30 mol% provided a better yield of **3aa** (entry 2). Among a set of copper sources screened for this reaction, none of them provided better yields than $Cu(OAc)_2$ (entries 3–7). Further screening of solvents showed that *t*-AmOH was superior to other solvents such as NMP, H_2O and toluene (entries 8–10). Performing the reaction under 1 atm of O_2 did not further improve the yield of **3aa** (entry 11). The use of commonly used ligands in copper-catalyzed reactions such as 1,10-phenanthroline, DABCO and 2,2′-bipyridine provided lower yields of **3aa** (entries 12–14).

With the optimized reaction conditions in hand, we first tested its scope in the coupling reaction of phenylglyoxylic acid (**2a**) with representative isatins **1a**–**1j** (Table 2). The isatins substituted with electron-donating groups and electron-withdrawing groups such as

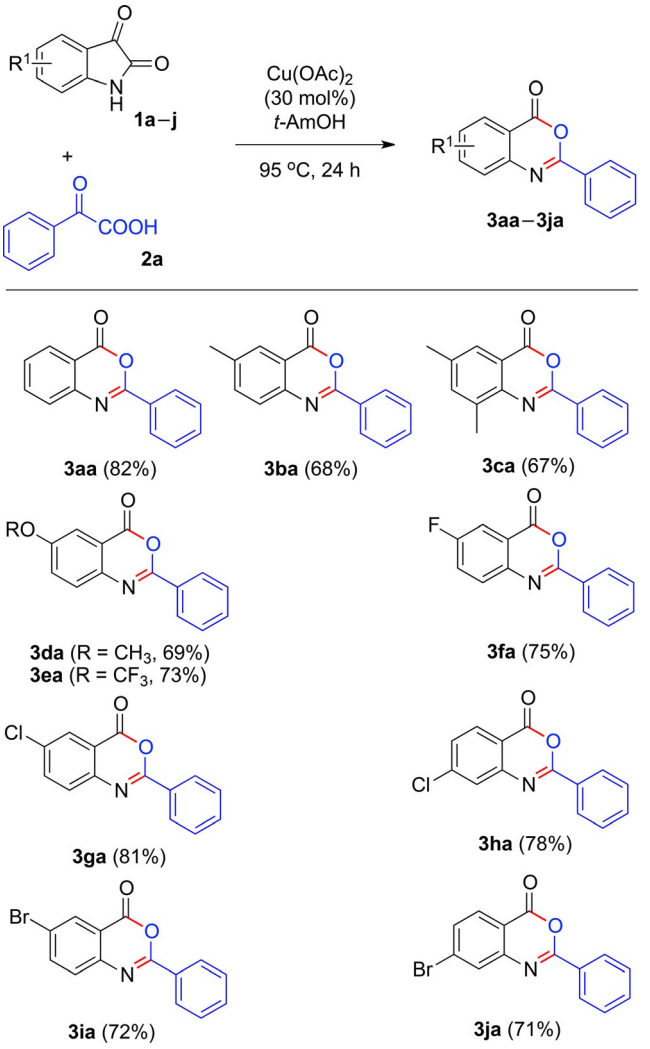
Table 1. Optimization of the reaction conditions.[a]



Entry	[Cu] (30 mol%)	Ligand	Solvent	**3aa** [%][b]
1[c]	$Cu(OAc)_2$	–	*t*-AmOH	67
2	$Cu(OAc)_2$	–	*t*-AmOH	82
3	$CuCl_2$	–	*t*-AmOH	21
4	$CuBr_2$	–	*t*-AmOH	61
5	$Cu(OTf)_2$	–	*t*-AmOH	60
6	CuI	–	*t*-AmOH	58
7	Cu_2O	–	*t*-AmOH	31
8	$Cu(OAc)_2$	–	NMP	72
9	$Cu(OAc)_2$	–	H_2O	57
10	$Cu(OAc)_2$	–	toluene	48
11[d]	$Cu(OAc)_2$	–	*t*-AmOH	77
12	$Cu(OAc)_2$	1,10-Phen	*t*-AmOH	64
13	$Cu(OAc)_2$	DABCO	*t*-AmOH	50
14	$Cu(OAc)_2$	2,2-bipyridine	*t*-AmOH	61

[a] *Reaction conditions:* **1a** (1.0 mmol), **2a** (1.0 mmol), copper salt (30 mol%), ligand (40 mol%) and solvent (4 mL) at 95 °C under air for 24 h; unless otherwise mentioned.
[b] Isolated yields.
[c] 20 mol% catalyst.
[d] Under O_2 (1.0 atm).

Table 2. Scope of substituted isatins (**1a–j**).[a]



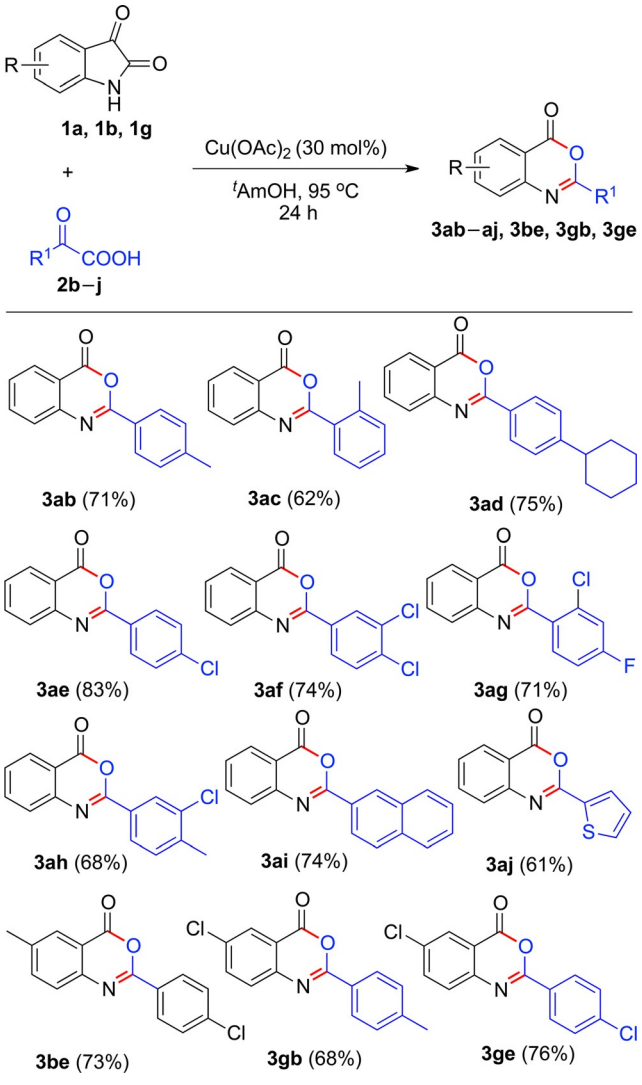
[a] *Reaction conditions:* isatin (1.0 mmol), α-keto acid (1.0 mmol) and Cu catalyst (30 mol%) in *t*-AmOH (4.0 mL) were heated at 95 °C for 24 h under air; isolated yields.

CH_3, OCH_3, OCF_3, F, Cl and Br at different positions of the phenyl ring were well tolerated, providing benzooxazinones **3aa–3ja** in good yields.

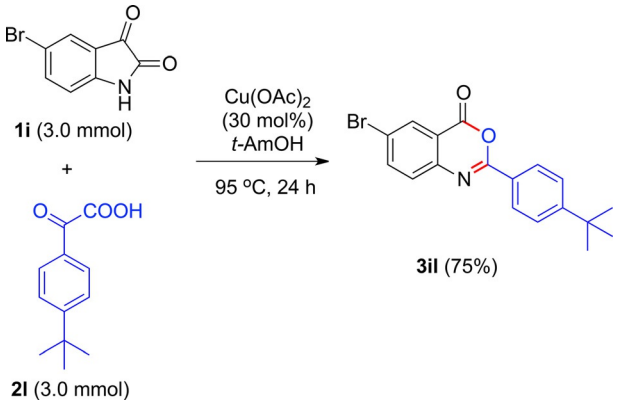
Isatins bearing electron-withdrawing groups on the aromatic ring provided slightly higher yields of benzooxazinones (**3fa–3ja**). The halo-substituted benzooxazinone derivatives thus obtained could be used for further transformations. The position of the substituents on the aromatic ring of isatin had little effect on the yields of products (**3ga–3ja**). However, the reaction between nitro group-substituted isatin and **2a** did not work under the standard conditions.

Next, the coupling reaction of isatin **1a** was tested with various functionalized α-oxocarboxylic acids **2b–j**, which is shown in Table 3. Phenylglyoxylic acids substituted with electron-donating groups (**2b–d**), electron-withdrawing groups (**2e–g**) and both electron-donating and electron-withdrawing groups (**2h**) were found to be good substrates for this cyclization reaction to provide the corresponding benzooxazinones (**3ab–ah**) in good yields. However, *o*-substituted phenylglyoxylic acid **2c** afforded slightly inferior yield of benzooxazinone **3ac**. We were delighted to observe that α-naphthyl- and α-heteroaryl- substituted oxocarboxylic acids (**2i** and **3j**) were also well tolerated to provide benzooxazinones **3ai** and **aj** under the standard conditions. To probe the wide scope of the decarbonylative and decarboxylative coupling reaction, electron-rich isatin (**1b**) was treated with electron-poor α-oxocarboxylic acid (**2e**) to afford a good yield of **3be**. Similarly, the reaction of electron-poor isatin (**1g**) with electron-rich α-oxocarboxylic acid (**2b**) and electron-poor α-oxocarboxylic acid (**2c**) also provided good yields of benzooxazinones **3gb** and **3ge**, respectively. However, under the standard conditions, 3-nitrophenylglyoxylic acid, alkylglyoxylic acids such as pyruvic acid and trimethylpyruvic acid did not react with isatin. Finally, the new methodology was tested for the synthesis of the HDL elevator **3il** (Scheme 2).[5c] To understand the mechanism of this

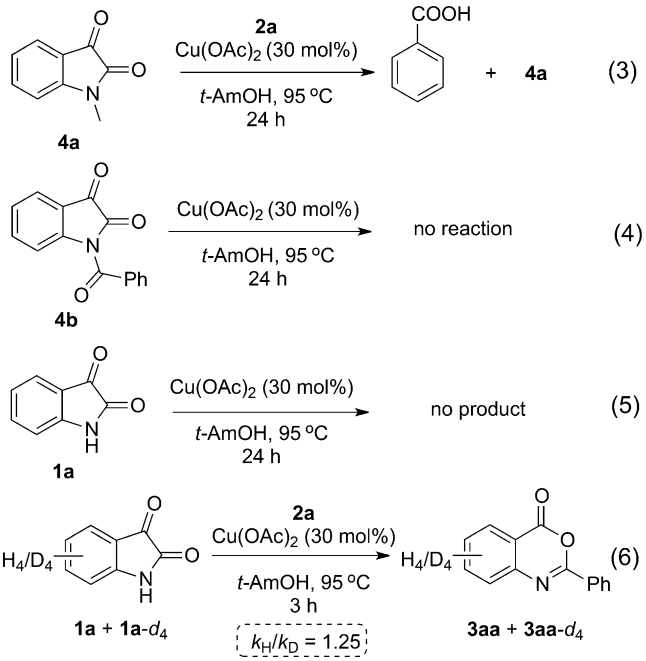
Table 3. Synthesis of various substituted benzooxazinones.[a]



[a] *Reaction conditions:* isatin (1.0 mmol), α-keto acid (1.0 mmol) and Cu catalyst (30 mol%) in *t*-AmOH (4.0 mL) was heated at 95 °C for 24 h under air; isolated yields.



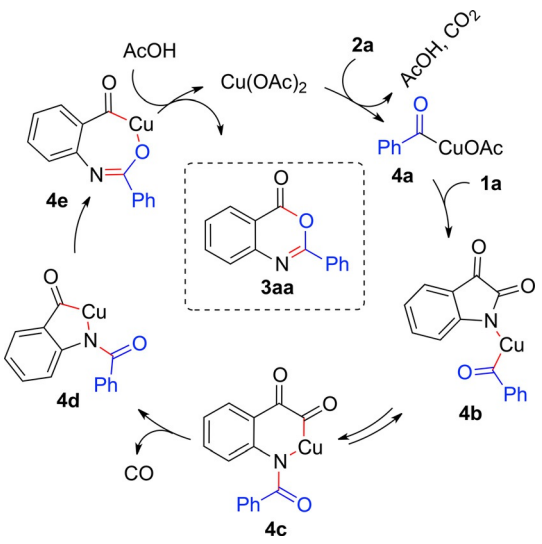
Scheme 2. Synthesis of the HDL elevator **3il**.



Scheme 3. Control and isotope labelling experiments.

reaction, a series of experiments was conducted (Scheme 3). Under the optimized reaction conditions, the reaction of N–H protected isatin (**4a**) and phenylglyoxylic acid **2a** did not proceed; it provided benzoic acid as the sole product [Eq. (3)]. This result indicated the presence of the free N–H group of the isatin ring to be a crucial factor for this reaction. The expected intermediate **4b** of the reaction, which was independently prepared, could not afford either the expected amide bond cleavage products 2-(2-benzamidophenyl)-2-oxoacetic acid/2-benzamidobenzoic acid or the final compound **3aa** under the standard reaction conditions [Eq. (4)]. Similarly, the reaction of isatin alone [Eq. (5)] or the reaction of isatin with benzoic acid could not provide the desired product under the optimized reaction conditions. The intermolecular kinetic isotope effect experiment performed between **1a**+**1a**-d_4 (1:1) and **2a**, displayed a secondary kinetic isotope effect [$k_H/k_D = 1.25$, Eq. (6)].

Although the exact mechanism of the coupling reaction is still not clear, based on our results and literature reports, a plausible mechanism is proposed which is shown in Scheme 4.[6] The copper acetate-catalyzed decarboxylation of α-oxocarboxylic acid (**2a**) generates Cu(II) species **4a**, which further reacts with isatin to generate **4b**. This Cu(II) species **4b** might remain in equilibrium with Cu(II) species **4c** due to migration of Cu into the neighbouring amide bond which, on decarbonylation and subsequent rearrangement, forms seven-membered Cu intermediate **4e**. Finally, reductive elimination of **4e** in presence of air and acetic acid affords the desired product **3aa** and regenerates the Cu(II) catalyst. In the case of Cu(I)-cata-



Scheme 4. Plausible reaction mechanism.

lyzed reactions (entries 6–7, Table 1), initially, air oxidation of Cu(I) to Cu(II) occurs, which catalyzes the decarboxylation of the α-oxocarboxylic acid (**2a**) to generate benzoyl Cu(II) species (**4a**).[6d]

In summary, we have described the first metal-catalyzed decarboxylative cross-coupling reaction of arylglyoxylic acids with N-nucleophiles isatins for the formation of C–N bonds. This unprecedented Cu(II)-catalyzed reaction which proceeds through decarboxylation, decarbonylation, C–N and C–O bond formation affords a wide range of pharmaceutically important 4*H*-benzo[*d*][1,3]oxazin-4-ones efficiently in good yields.

Experimental Section

Typical Experimental Procedure

A solution of isatin **1** (1.0 mmol), α-oxocarboxylic acid **2** (1.0 mmol) and copper acetate (30 mol%) in *tert*-amyl alcohol (4.0 mL) was heated at 95 °C under air for 24 hours. After completion of the reaction, the solvent was removed under vacuum. The crude product obtained was purified by column chromatography over silica gel (100–200 mesh) using EtOAc/hexane (1:9) as the eluant to afford the 4*H*-benzo[*d*][1,3]oxazin-4-one.

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