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Copper powder-catalyzed chelation-assisted cascade reaction of *o*-chloroarylacetic acids with amines under solvent- and ligand-free conditions: synthesis of oxindoles†

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An efficient method to construct oxindole scaffolds from *o*-chloroarylacetic acids/esters with amines has been explored. This cascade protocol involves the *in situ* generation of *o*-aminoarylacetic acid derivatives by the copper powder catalyzed and weak O-chelation assisted Ullmann amination of unactivated C–Cl bonds under air, and solvent-/ligand-free conditions followed by annulative *N*-acylation.

Oxindoles are privileged heterocycles prevalent in naturally occurring products and pharmacologically active compounds (Fig. 1),[1] and they also serve as important precursors in drug design and organic synthesis.[1b] Over the past few decades, an array of efficient methods have been developed to access oxindoles. Basically, these methods involve the derivatization of three types of starting materials: anilide derivatives,[2] isatins[2g,3] or indoles,[2g,4] and arylacetic acid derivatives.[2g,5] One of the most remarkable features is the pre-installation of a nitrogen-containing functional group on the precursors. Among them, the use of anilide derivatives is predominate in contemporary organic synthetic methodologies, whereas arylacetic acid derivatives are far less used. The methods documented include the nitro reduction/intramolecular cyclization of *o*-nitrophenylacetic acid,[2g] the intramolecular oxidative amidation of *N*-acetoxy-2-phenylacetamides,[2g] and the intramolecular Ullmann-type *N*-arylation of *o*-halophenylacetamides.[2g,5] The former two limit to the preparation of free NH oxindoles. The latter provides a powerful strategy for the construction of oxindoles functionalized at *N*-, *C*3-positions. For instance, Turner's group has reported the access to oxindoles *via* sequential amide formation/palladium-catalyzed intramolecular amidation in two steps (Scheme 1a),[5] wherein the expensive noble metal catalyst, toxic phosphine ligand, and strong base are required besides the high temperature of 150 °C. To our knowledge, the direct construction of oxindole scaffold by the introduction of amino group to the benzene ring of *o*-haloarylacetic acids, especially *o*-chloroarylacetic acids, is yet unexplored.

Copper catalyzed Ullmann-type reaction of arylic C-halo bonds has emerged as a fundamental tool for C–N bond

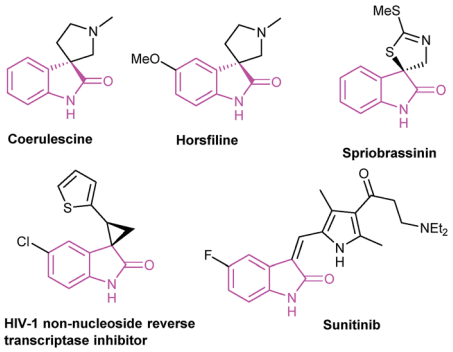
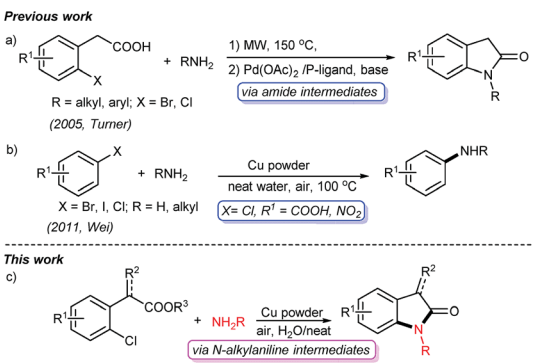


Fig. 1 Naturally occurring and pharmaceutical oxindoles.



Scheme 1 The representative C–N bond formation and access to oxindoles from *o*-haloarylacetic acids.

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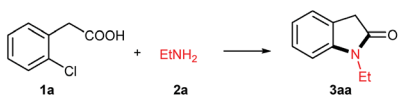
formation in academic and industrial fields.[6] These protocols usually require ligands, and in particular hardly avoid using organic solvents such as DMSO, DMF, and NMP. Later on, Wei reported a copper powder catalyzed amination of aromatic C-halo bonds without ligands in water,[7] which allows efficient access to C–N bonds from C–I, C–Br bonds, and some C–Cl bonds (Scheme 1b). However, the substrates without electron-withdrawing groups (*e.g.* chlorobenzene and *p*-chloroanisole) are inert in such a transformation. Consequently, the transformation of simple arylic C–Cl bonds remains a challenge.[6a]

In the realm of C–H activation, a carboxyl group acts as an effective directing group to promote coupling reactions by weak *O*-coordination with the metal centers of catalysts.[8] Yu reported some elegant transformations of arylacetic acids C–H bonds directed by carboxyl groups.[8b–i] We speculated that the COOH group will also facilitate copper powder catalyzed Ullmann amination through the activation of C–Cl bond, and then subsequent intramolecular cyclization will give oxindole scaffolds. Following our continuous interest in the synthesis of heterocycles,[9] herein, we present a facile and efficient cascade protocol for the construction of oxindole derivatives from readily available *o*-chlorophenylacetic acids with amines catalyzed by copper powder under air and neat conditions (Scheme 1c).

o-Chlorophenylacetic acid **1a** and ethylamine **2a** were chosen as prototype substrates for this cascade reaction (Table 1). The reaction proceeded smoothly in water with a small amount of air sealed in the tube when copper powder (10 mol%) was used as the catalyst in the absence of any additive, and the cyclized product oxindole **3aa** was obtained in 77% yield (entry 1). This positive result suggested that the carboxyl group tethered at *ortho* position did facilitate the C–Cl Ullmann reaction *via ortho* chelating effect,[10] just like acting as a directing group in C–H activation. Reducing the water volume, the **2a** equivalent or the catalyst loading resulted in lower efficiency (entries 2, 3, 6). Prolonging the reaction time or elevating the reaction temperature enhanced the yield while shortening the time or lowering the temperature diminished the efficiency (entries 4 *vs.* 5, 7 *vs.* 8). It is worthwhile to note that the activated copper powder delivered a comparable yield of 78% (entry 9). Interestingly, the higher yield of 85% resulted under solvent-free condition (entry 10). As expected, no reaction occurred under N_2 atmosphere (entry 11), which further confirmed that the small amount of O_2 is essential in the copper powder catalyzed transformation as pointed out by Wei.[7] Other copper sources such as cuprous salts (CuCl, CuBr) or oxide (Cu_2O) could also catalyze this cascade reaction under N_2 atmosphere, providing the similar yields (entries 12–14). The cupric species ($CuCl_2 \cdot 2H_2O$, CuO) were ineffective in water and N_2 systems (entries 14 & 15). Intriguingly, they could trigger the current transformation with less efficacy (58% & 65%) under the solvent-free and N_2 conditions.[11] These results revealed that the catalytically active species is Cu(I).[7] Thus, the optimum conditions for this cascade reaction were summarized as follows: **1a** (2 mmol), **2a** (10 mmol), Cu powder (10 mol%) all sealed in a 15 mL reaction tube under air atmosphere, stirring at 100 °C for 16 h, affording *N*-ethyl indolin-2-one **3aa** in 85% yield.

With the optimized reaction conditions in hand, we set out to investigate the scope of amines **2** for this copper powder catalyzed C–Cl amination and the results are compiled in Table 2. In general, all the tested aliphatic primary amines are effective substrates with *o*-chlorophenylacetic acid **1a**, providing the corresponding 3-unsubstituted oxindoles in moderate to

Table 1 Screening optimal conditions for cascade cyclization[a]

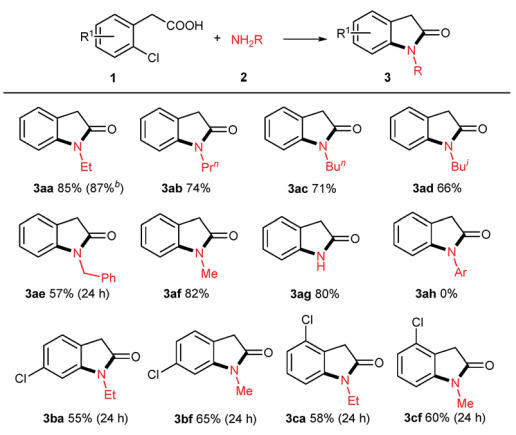


1a 2a 3aa

Entry	Cat. (mol%)	Temp. (°C)	Time (h)	Yield[b] (%)
1	Cu (10)	100	16	77
2[c]	Cu (10)	100	16	70
3[d]	Cu (10)	100	16	66
4	Cu (10)	100	12	73
5	Cu (10)	100	24	82
6	Cu (5)	100	16	66
7	Cu (10)	80	16	67
8	Cu (10)	120	16	80
9[e]	Cu (10)	100	16	78
10[f]	Cu (10)	100	16	85
11[f,g]	Cu (10)	100	16	N. R.
12[g]	CuCl (10)	100	16	67
13[g]	CuBr (10)	100	16	67
14[g]	Cu_2O (5)	100	16	80
15[g]	CuO (10)	100	16	N. R.
16[g]	$CuCl_2$ (10)	100	16	Trace

[a] Reaction conditions: **1a** (2 mmol), **2a** (10 mmol), Cu powder or other copper catalyst, H_2O (2 mL, not degassed) added to a 15 mL sealed tube under air atmosphere, 100 °C unless otherwise stated. [b] Isolated yields. [c] H_2O (1 mL, not degassed). [d] 3 equiv. of **2a**. [e] Cu powder activated by I_2 in acetone. [f] Without water. [g] Under N_2. N. R. means no reaction.

Table 2 Substrate scope for 3-unsubstituted oxindoles[a]



1 2 3

3aa 85% (87%[b]) **3ab** 74% **3ac** 71% **3ad** 66%

3ae 57% (24 h) **3af** 82% **3ag** 80% **3ah** 0%

3ba 55% (24 h) **3bf** 65% (24 h) **3ca** 58% (24 h) **3cf** 60% (24 h)

[a] Reaction conditions: **1** (2 mmol), **2** (10 mmol), Cu powder (10 mol%) in a 15 mL sealed tube, 100 °C for 16 h unless otherwise stated. Isolated yields based on the acids. [b] The use of *o*-bromophenylacetic acid as the precursor.

good yields (entries **3aa–3af**). The amines with longer chains gave relatively lower yields (**3aa**, **3ab**, **3ac**). The straight-chain amine **2c** was preferred over the branched-chain one **2d**. Benzyl amine **2e** delivered the desired product only in 57% yield when the reaction time was fixed at 24 h (**3ae**). Noteworthy, aqueous methyl amine **2f** afforded oxindole **3af** in 82% yield, and aqueous ammonium gave free NH oxindole **3ag** in 80% yield. Besides, the *o*-bromophenylacetic acid instead of **1a** generated a comparable yield of 87%.

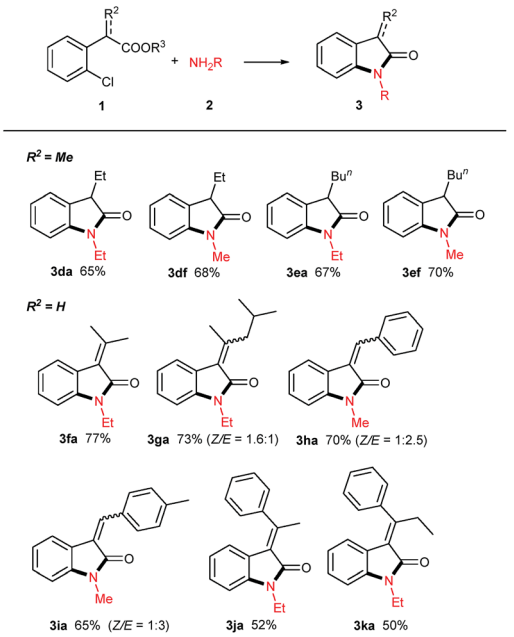
When aromatic amines were used instead, for example, aniline, *o*/*p*-toluidines, *o*/*p*-anisidines, and *p*-chloroaniline, no obvious *N*-arylated oxindoles were observed (**3ah**), even in the case of strong nucleophilic *p*-anisidine, but their corresponding amides **4ah** were verified based on NMR and MS analysis (please see ESI†). The additional bases (*e.g.* NaOH 2.0 equiv., *t*-BuONa 2.0 equiv.) could not trigger Ullmann-type C–N bond formation, even in higher temperature (120 °C or 130 °C). This failure might be ascribed to the weaker nucleophilicity of aromatic amines than that of aliphatic amines.

When 2,4-dichlorophenylacetic acid **1b** and 2,6-dichlorophenylacetic acid **1c** were used in this transformation, their corresponding oxindoles were obtained. It is worth noting that in the former case the Ullmann-type amination reaction occurred selectively at the *ortho* C–Cl bond of carboxylates (**3ba** & **3bf**). In both cases, no sequential Ullmann-type amination process re-occurred at the other C–Cl bond. These results suggested that the tethered carboxyl group presumably plays an essential role in this cascade reaction. Besides, it should be noted that further oxidation products such as 3-hydroxyloxindoles or isatins were not observed although oxindole *C*3–H bonds are very reactive to O_2 in all the cases of the aforementioned 3-unsubstituted oxindoles.

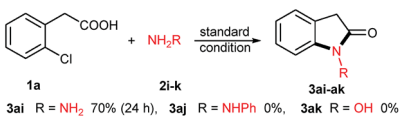
The synthesis of 3-monosubstituted oxindoles remains a challenge. Because 3-unsubstituted oxindoles are reactive enough to alkylation, sequential double alkylation usually occurs. Normally, they are produced *via* post-functionalization, for example, by the condensation of 3-unsubstituted indolin-2-ones with carbonyl compounds followed by reduction. As such, we attended to extend this cascade reaction to the synthesis of 3-monosubstituted oxindoles. Delightedly, 2-alkylated *o*-chlorophenylacetic acid esters can be smoothly converted into 3-alkylated oxindoles in moderate yields (**3da**, **3df**, **3ea**, **3ef**, Table 3). In these cases, it is not necessary to use the acetic acids as precursor. Additionally, the use of 2-(2-chlorophenyl)acrylic acids **1f–k** were attempted, and the desired 3-methyleneindolin-2-ones were furnished in acceptable yields (**3fa–3ka**). In the cases of **1g–I**, the products were mixtures of *Z*/*E* isomers, which can readily be isolated by preparative thin-layer chromatography. Interestingly, as for the acids **1j** & **1k**, only the *E*-isomers were isolated in yields of 52% & 50%, respectively. The configurations of all the isomers were assigned based on the documented reports including the results of Studer.[12] Noteworthy, no aza-Michael adducts resulted under standard conditions, although **3fa–ka**, especially **3ha** and **3ia**, are good Michael acceptors.

After the investigation of amines, their analogues hydrazines or hydroxylamine were attempted (Scheme 2). Interestingly,

Table 3 Substrate scope for 3-substituted oxindoles[a]



[a] Reaction conditions: **1** (2 mmol), **2** (10 mmol), Cu powder (10 mol%) in a 15 mL sealed tube, 100 °C for 24 h. Isolated yields based on the substrates **1**. *Z*/*E* ratios were calculated from the isolated isomer yields.

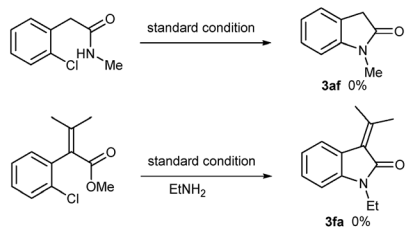


Scheme 2 Tandem cyclization from hydrazines or hydroxylamine.

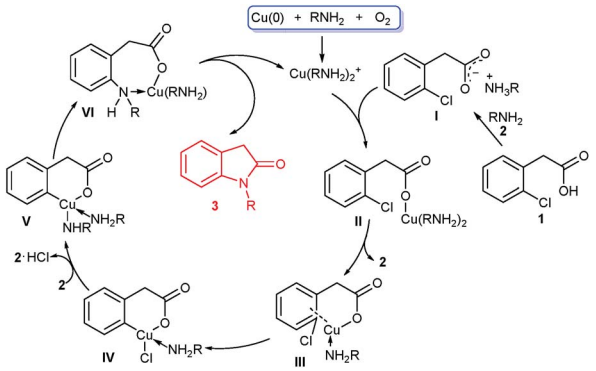
aqueous hydrazine **2i** is an effective coupling partner, and its desired product *N*-amino oxindole **3ai** was obtained in 70% yield after 24 h of reaction. However, *N*-phenyl hydrazine **2j** gave a negative result. Hydroxylamine hydrochloride **2k** was used, even in combination with equivalent base (*e.g.* NaOH, Et_3N), and no product was detected except with the starting acid **1a** recovered.

To explore the application possibility of this chemistry in industry or organic synthesis, the scale-up experiment was carried out. When 10 mmol of **1a** was used to react with ethylamine **2a** in a 48 mL sealed tube under the standard conditions, the reaction proceeded smoothly, providing 80% yield of **3aa** with a small amount of **1a** detected after 16 h.

To gain an insight into the mechanism of this cascade reaction, simple experiments were carried out to unveil the cascade process. When methyl 2-chlorophenylacetamide was used as cyclization precursor under the standard conditions, intramolecular cyclization to indolin-2-one did not occur with the amide almost fully recovered (Scheme 3). This result excluded the possibility of a sequential amide formation/intramolecular Ullmann-type *N*-arylation process. When the ester of **1f** reacted with ethylamine **2a**, no reaction also



Scheme 3 Control experiments.



Scheme 4 Plausible mechanism for oxindoles formation from the acids.

occurred. This suggests that the existence of benzyl C–H, which enables the formation of an enolate, is essential for the esters to realize the present cascade reaction.

Based on our experimental results and previous reports,[6,7,10] a tentative mechanism was proposed in Scheme 4. Initially, Cu(0) powder is oxidized to Cu(I) species such as $Cu(RNH_2)_2^+$ in the presence of a small amount of O_2 and amines *via* a complicated process. Reaction of the acetic acid **1** with amine **2** affords the ammonium carboxylate **I**,[13] which exchanges with $Cu(RNH_2)_2^+$ to generate the cuprous carboxylate **II**. Intramolecular ligand exchange of **II** produces coordinated **III** along with the release of amine **2**, and further oxidative addition of **III** furnishes **IV**. Then **IV** undergoes chloride/amine ligand exchange with the aid of second amine **2** to form **V**, followed by reductive elimination to generate coordinated **VI**. Finally, intramolecular cyclization of **VI** forms the target product **3** and reactive Cu(I) species.

Conclusions

We have disclosed a ligand- and solvent-free catalytic approach to access oxindoles from *o*-chloroarylacetic acids with amines using copper powder *via* one pot sequential Ullmann type amination, and annulative *N*-acylation. The *ortho* chelating effect of a carboxyl/ester group and the presence of a small amount of O_2 both play essential roles in the C–Cl activation and catalytic activity of copper powder. In view of its efficiency and operational simplicity, this cascade protocol will find its wide application in academic and industrial fields relating to the oxindole chemistry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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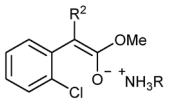
13 In the case of the esters **1d** & **1e**, their corresponding enolates **I′** could be formed as the intermediates.



I′