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Efficient copper-catalyzed intramolecular N-arylation for the synthesis of oxindoles

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ABSTRACT

An efficient copper-catalyzed intramolecular N-arylation was performed by using substituted 2-(2-bromoaryl)acetamide with small amount of Cu_2O and benzene-1,2-diamine as catalytic system under aerobic conditions, which provided good to excellent yields of oxindoles with tolerance of a wide variety of substrates.

Oxindoles are very important compounds for organic synthesis because of their wide application in natural alkaloids,[1] bioactive compounds[2] and pharmaceuticals.[3] Numerous well-established methods were applied to access this structure motif, and the palladium catalysis[4–8] have been often chosen as a main strategy for the synthetic approach. Although the palladium-catalyzed cyclization is the most powerful method to establish elaborated structures, the high cost and air-sensitive nature make other methods worth developing.

A copper-catalyzed coupling reaction is an alternative pathway to synthesize oxindoles, which possesses the advantages of large scale synthesis and could be conducted under aerobic conditions.[9] However, only few literatures are related to the copper-mediated construction of oxindoles. In 2006, Ma reported copper-catalyzed intramolecular arylation of β-keto amides for the synthesis of 3-acyloxindoles.[10] Later, Kündig built oxindole subunits by the copper-mediated C–H functionalization.[11] More recently, Taylor first realized the copper-catalyzed C–H activation to synthesize oxindoles.[12] The intramolecular N-arylation was utilized for the formation of some specific oxindoles as well.[13] In those former reports; however, the installation of protecting groups on the nitrogen atom is always necessary to facilitate the construction of oxindoles. To address this limitation, we recently disclosed the synthesis of oxindoles via copper-catalyzed domino coupling reaction, which was successfully applied as a key step to the total synthesis of (±)-coerulescine and (±)-horsfiline (Scheme 1).[14] This method provides a shortest synthetic route and highest overall yields for the synthesis of these two alkaloids.

Based on the preliminary result and our previous experience in the catalytic coupling reactions,[15] we then tried to explore the possibility for the synthesis of oxindoles via the copper-catalyzed N-arylation without pre-installing N-protecting groups.

Our previous condition was used for the initial test; thus, 2-(2-bromophenyl)-2-methylpropanamide (**1a**) was treated with 5 mol % CuI, 10 mol % *N*-acetylglycine (**L1**) and 3.0 equiv NaOH in *t*-BuOH at 100 °C for 24 h, affording 3,3-dimethyloxindole (**2a**) in 75% NMR yield (Table 1, entry 1). To optimize this reaction, we first explored the influence of different ligands. Therefore, some other amino acids were selected as ligands to study the effect for this intramolecular N-arylation (entries 2–4). When the 1*H*-imidazole-4-carboxylic acid (**L2**) and 2-(methylamino)acetic acid (**L3**) were employed as ligands, the desired product **2a** was obtained in 67% and 74% yields, respectively (entries 2 and 3), which shows no further improvement comparing to entry 1. Similar result was found when L-proline (**L4**) was used as ligand (entry 4). Because no improvement was exhibited, we then turned to test the aniline and phenanthroline type ligands.

Accordingly, 1,10-phenanthroline (**L5**), 8-aminoquinoline (**L6**), 2-aminophenol (**L7**) and benzene-1,2-diamine (**L8**) were employed for screening (entries 5–8). It was found that 1,10-phenanthroline (**L5**) is almost functionless, but aniline type ligands performed very well. Among the various aniline ligands, **L8** exhibited the best performance and gave good yield of **2a**.

With the best ligand in hand, we further optimized the reaction conditions and the results are summarized in Table 2. Both polar

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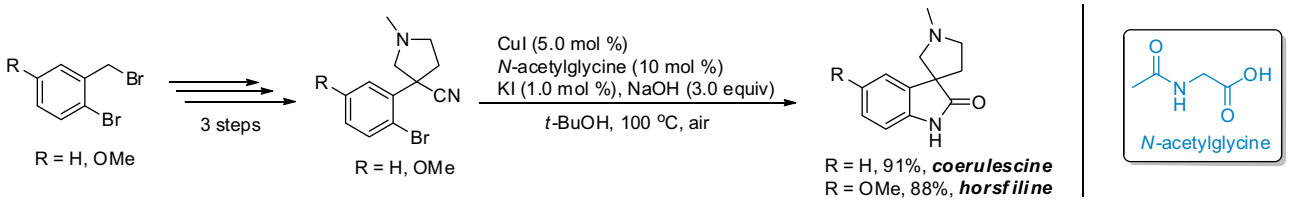
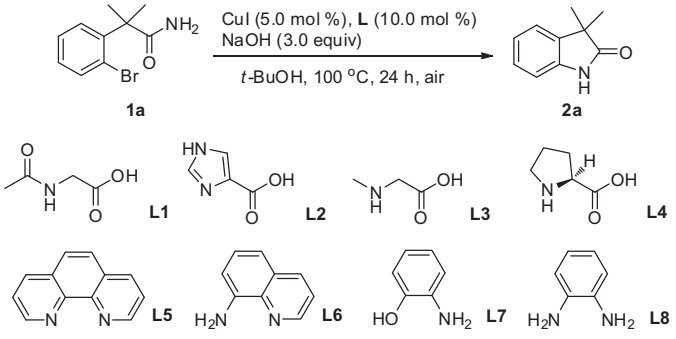


Scheme 1. Total synthesis of (±)-coerulescine and (±)-horsfiline.

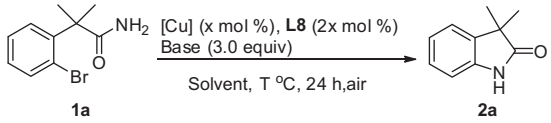
Table 1
Comparison of various ligands in the coupling reaction[a]



Entry	L	Yield[b] (%)
1	**L1**	75
2	**L2**	67
3	**L3**	74
4	**L4**	64
5	**L5**	16
6	**L6**	65
7	**L7**	71
8	**L8**	82

[a] Reactions were carried out using 0.1 mmol 2-(2-bromophenyl)-2-methylpropanamide (**1a**) with 5 mol % CuI, 10 mol % ligand and 3.0 equiv NaOH in 1.0 mL *t*-BuOH at 100 °C for 24 h (under air).
[b] ^{1}H NMR yield based on internal standard mesitylene.

Table 2
Optimization of reaction conditions[a]



Entry	*x*	[Cu]	Solvent	Base	*T* (°C)	Yield[b] (%)
1	5	CuI	*t*-BuOH	NaOH	100	82
2	5	CuI	Dioxane	NaOH	100	64
3	5	CuI	DMF	NaOH	100	42
4	5	CuI	DME	NaOH	100	51
5	5	CuI	DMSO	NaOH	100	69
6	5	CuI	Benzene	NaOH	100	37
7	5	CuI	Toluene	NaOH	100	76
8	5	CuI	CH_3CN	NaOH	100	23
9	5	CuI	*t*-BuOH	NaOMe	100	91
10	5	CuI	*t*-BuOH	NaO^{t}Bu	100	99
11	5	CuI	*t*-BuOH	K_2CO_3	100	11
12	5	CuI	*t*-BuOH	Cs_2CO_3	100	8
13	1	CuI	*t*-BuOH	NaO^{t}Bu	100	87
14	1	CuSCN	*t*-BuOH	NaO^{t}Bu	100	64
15	1	$Cu(OAc)_2$	*t*-BuOH	NaO^{t}Bu	100	78
16	1	$Cu(OTf)_2$	*t*-BuOH	NaO^{t}Bu	100	81
17[c]	1	Cu_2O	*t*-BuOH	NaO^{t}Bu	100	99
18	1	Cu_2O	*t*-BuOH	NaO^{t}Bu	80	18
19	1	Cu_2O	*t*-BuOH	NaO^{t}Bu	60	0
20	1	Cu_2O	*t*-BuOH	NaO^{t}Bu	rt	0

[a] Reactions were carried out using 0.1 mmol 2-(2-bromophenyl)-2-methylpropanamide (**1a**) with copper source, ligand and 3.0 equiv base in 1.0 mL solvent for 24 h (under air).
[b] ^{1}H NMR yield based on internal standard mesitylene.
[c] 18 h.

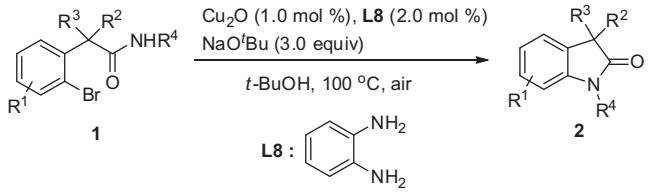
and non-polar solvents afforded desired product **2a** (Table 2, entries 1–8); among them, *t*-BuOH provided better yields than others. Therefore, *t*-BuOH was chosen for further examination of this intramolecular N-arylation. The performance of this reaction also strongly depends on the selection of base (entries 9–12); we found that only the strong base could smoothly promote the reaction and provide product **2a** in excellent yield. Next, we reduced the loadings of catalyst and employed different copper sources (entries 13–17). Among the various copper sources employed as catalysts, Cu_2O was found to be the most effective one, providing excellent yield of **2a** (entry 17). In addition, lower temperature significantly diminished the yield of desired product or shut down the reaction (entries 18–20), and the desired product was not obtained in the absence of Cu_2O. The reaction proceeded well under either nitrogen atmosphere or air, and both provided excellent yields of **2a**.

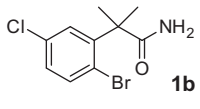
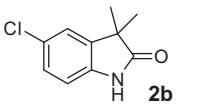
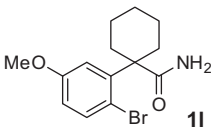
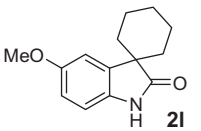
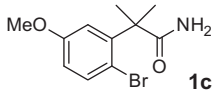
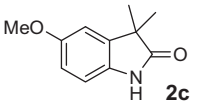
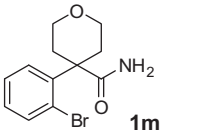
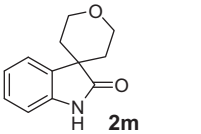
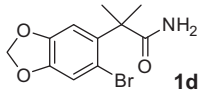
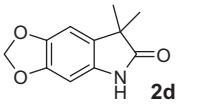
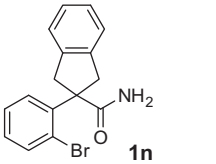
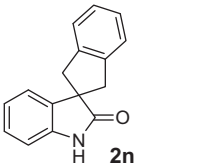
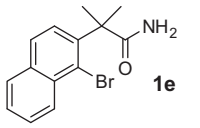
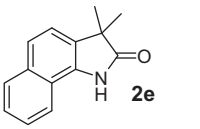
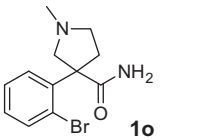
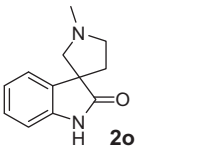
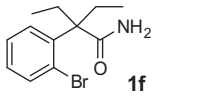
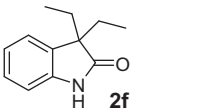
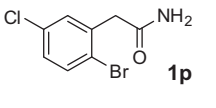
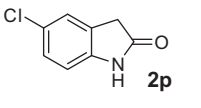
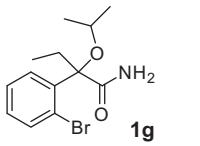
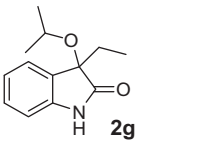
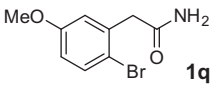
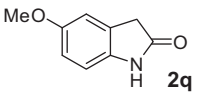
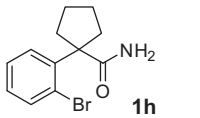
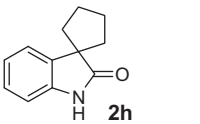
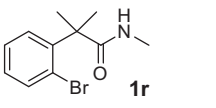
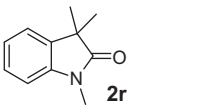
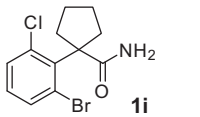
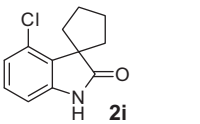
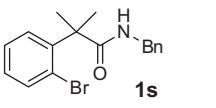
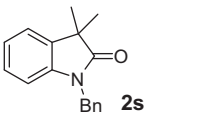
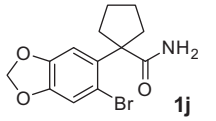
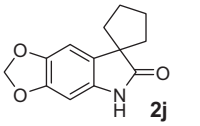
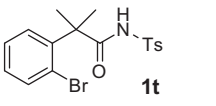
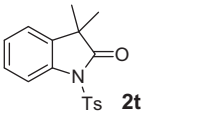
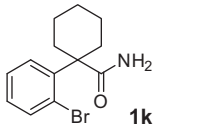
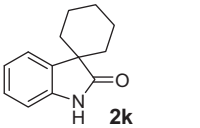
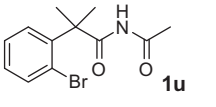
The Cu-catalyzed intramolecular N-arylation was successfully extended to various substrates **(1)**; the results are listed in Table 3. The electronic density on the arene moiety slightly affected the reaction (entries 1–3). Thus, substrates with electron-withdrawing group in the *para* position of bromide (**1b**) provided better yield of the desired product than those with electron-donating group in the same position (**1c**, **1d**). Naphthyl moiety is also tolerated to give the corresponding product **2e** in 91% yield (entry 4). A wide variety of substituents and spiro rings on the 3,3-position of oxindole could also be well tolerated (**2f**–**2o**). It was observed that the steric effect of the substituents on the 3,3-position of the oxindole dominated the yields of the reactions (entries 5 and 6). Thus, the yields of the corresponding products decreased along with the larger substituents.

Oxindoles with a spiro ring on the 3,3-position were also obtained in good to excellent yields (entries 7–14). For the same spiro ring on the 3,3-position of oxindoles, the yields depended only on the electronic effect of the arene moiety (**2h** vs **2i** vs **2j**, **2k** vs **2l**). The larger size of the spiro ring provided lower yields of the desired products (**2h** vs **2m** vs **2n**). Moreover, a natural alkaloid (±)-coerulescine (**2o**) could be obtained by this method in good yield (entry 14) as well. Not only the quaternary carbon on the 3-position, but also the products with secondary carbon of 3,3-unsubstituted oxindoles (**2p**, **2q**) can be successfully generated. The N-protected substrates were well processed and gave desired products in good to excellent yields (entries 17–20); however, cyclization of the substrate with *N*-acetylamide (entry 20, **1u**) accompanied unexpected deprotection to furnish an unprotected oxindole (**2a**) in excellent yield.

Various substrates with *N*-acetylamide were further examined by using the same protocol, and the results indicate that all the substrates provided the surprisingly deprotected oxindoles (Table 4). Reactions for those substrates bearing various substituents on the arene moiety and with different groups *alpha* to the amide carbonyl all proceeded well and gave desired products in excellent yields. Comparing with the substrates without N-substituents,

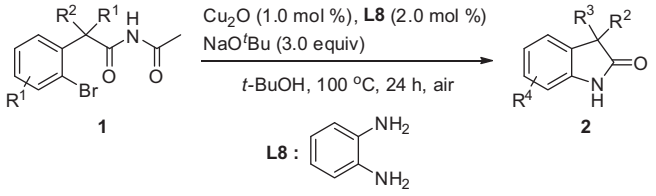
Table 3
Copper-catalyzed intramolecular N-arylation to form oxindoles[a]

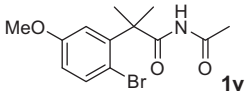
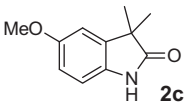
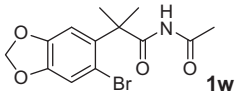
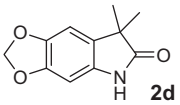
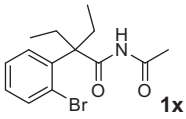
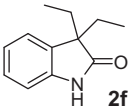
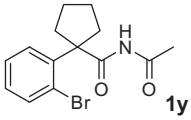
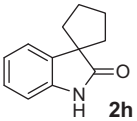
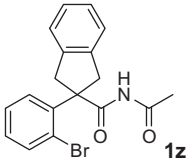
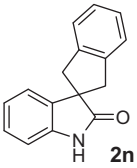


Entry	1	2	t (h)	Yield[b] (%)	Entry	1	2	t (h)	Yield[b] (%)
1	 1b	 2b	18	85 (84)[c]	11	 1l	 2l	24	74
2	 1c	 2c	24	76	12	 1m	 2m	24	46
3	 1d	 2d	24	69	13	 1n	 2n	36	84 (68)[c]
4	 1e	 2e	24	91	14	 1o	 2o	24	87
5	 1f	 2f	18	99 (99)[c]	15	 1p	 2p	24	81
6	 1g	 2g	24	80	16	 1q	 2q	24	70
7	 1h	 2h	18	95 (97)[c]	17	 1r	 2r	48	92 (76)[c]
8	 1i	 2i	18	86 (84)[c]	18	 1s	 2s	36	87 (74)[c]
9	 1j	 2j	24	55	19	 1t	 2t	18	89 (91)[c]
10	 1k	 2k	24	88	20	 1u	2a	18	99 (99)[c]

[a] Reactions were carried out using 0.5 mmol (**1**) with 1.0 mol % Cu_2O, 2.0 mol % benzene-1,2-diamine and 3.0 equiv NaO^tBu in 5.0 mL *t*-BuOH at 100 °C for the specific time (*t*) of various substrates (under air).
[b] Isolated yield after column chromatography.
[c] Yield for 24 h.

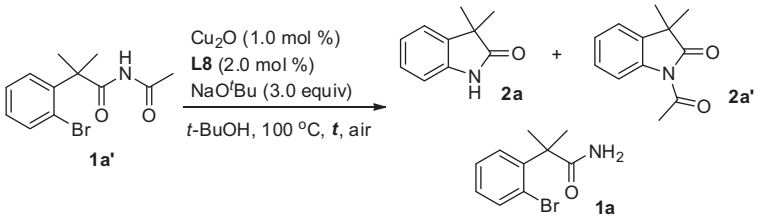
Table 4
Formation of oxindoles from protected *N*-acetylamide[a]



Entry	1	2	Yield[b] (%)
1	 **1v**	 **2c**	88
2	 **1w**	 **2d**	94
3	 **1x**	 **2f**	89
4	 **1y**	 **2h**	97
5	 **1z**	 **2n**	93

[a] Reactions were carried out using 0.5 mmol (**1**) with 1.0 mol % Cu_2O, 2.0 mol % benzene-1,2-diamine, and 3.0 equiv NaO^tBu in 5.0 mL *t*-BuOH at 100 °C for 24 h (under air).
[b] Isolated yield after column chromatography.

Table 5
Time-controlled formation of **2a**



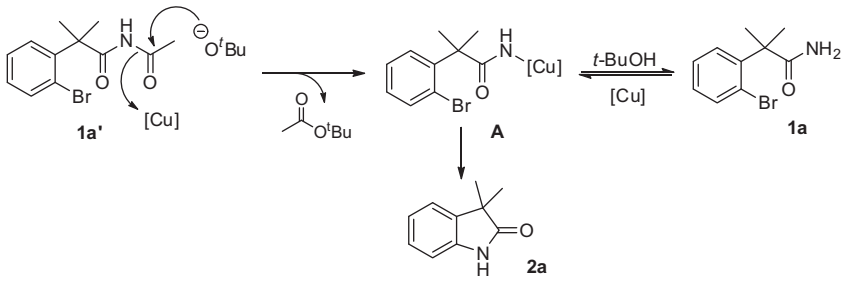
Entry	*t* (h)	**1a′**[a]	**2a**[a]	**2a′**[a]	**1a**[a]
1	**4**	74	21	0	5
2	**8**	37	49	0	14
3	**12**	16	75	1	12
4	**16**	3	94	0	3

[a] Ratios were determined by GC–MS.

substrates with *N*-acetylamide provided better isolated yields of the corresponding oxindoles (entries 1, 2 and 5).

To understand the reason why the substrates with *N*-acetylamide caused higher yields of desired oxindoles, a control experiment was carried out to probe the reaction pathway (Table 5). We found that almost no **2a′** was detected in the reaction and the formation of **1a** was observed during the reaction period, which means deprotection occurred before the intramolecular N-arylation. A small amount of **1a** was found along with the formation of **2a**, which made us propose the reaction pathway (Scheme 2).

The reaction is likely to proceed by the nucleophilic substitution of *tert*-butoxide to **1a′**, followed by the subsequent coordination to the copper complex affording complex **A**. Cyclization of complex **A** generates product **2a**, and the protonation of complex **A** by *tert*-butanol produces compound **1a**.



Scheme 2. Proposed reaction pathway.

In conclusion, we have developed an effective method for the synthesis of oxindoles via Cu_2O/benzene-1,2-diamine catalytic condition for the intramolecular N-arylation. This method efficiently provided poly-substituted oxindoles in moderate to excellent yields with good tolerance of various substrates and only required very small amount of catalyst under aerobic conditions; thus, increased its potential for industrial applications. Further studies to extend the application of this catalytic system are currently underway.

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Supplementary data

Supplementary data associated (experimental procedure, ^1H and ^{13}C NMR spectra and spectral data for all the new compounds) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.082.

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