Copper-Catalyzed Oxidative Electrophilic Carbofunctionalization of Acrylamides for the Synthesis of Oxindoles

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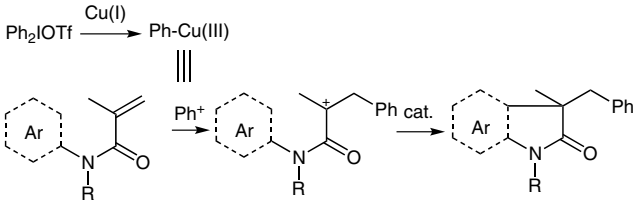
Abstract: A novel and efficient copper-catalyzed tandem oxidative cyclization of arylacrylamides with diaryliodonium salts is reported. This reaction provides a novel approach for the synthesis of oxindoles and various functional groups were well tolerated.

Key words: copper-catalyzed, acrylamides, diphenyliodonium triflate, oxindoles, electrophilic arylation

The synthesis of oxindoles has attracted much interest not only because of their significant biological activities[1] but also because they are important intermediates in the synthesis of heterocyclic compounds.[2] Thus, the development of new methods for their synthesis has been a major focus of study.[3] Among them, difunctionalization reaction of alkenes through a radical process provided an appealing approach for the synthesis of functional oxindoles. To date, various radicals such as aryl, CF_3 and NO_2 have been successfully introduced into the oxindoles skeleton.[4]

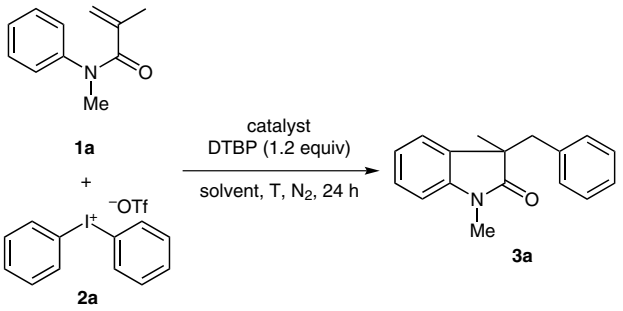
On the other hand, diaryliodonium salts have emerged as powerful electrophilic arylation reagents in metal-catalyzed or metal-free cross-coupling reactions.[5] Since the seminal work of Gaunt,[6] the combined use of copper and diaryliodonium salts to form a Cu(III)-aryl intermediate has been extensively studied.[7] Various heterocyclic compounds such as oxazine[8] and quinazoline[9] have been successfully built by using diaryliodonium salts as coupling partner.

Inspired by the above works and in connection with radical-mediated cyclizations of arylacrylamides, we envi-



Scheme 1 Strategy for the synthesis of oxindoles

Table 1 Optimization of Reaction Conditions[a]



Entry	Catalyst	Solvent	T (°C)	Yield (%)[b]
1[c]	CuI	1,4-dioxane	70	32
2	CuI	1,4-dioxane	70	60
3	$CuCl_2$	1,4-dioxane	70	62
4	CuCl	1,4-dioxane	70	72
5	CuBr	1,4-dioxane	70	35
6	$Cu(OAc)_2$	1,4-dioxane	70	56
7	$Cu(OTf)_2$	1,4-dioxane	70	70
8	CuCl	DCE	70	Trace
9	**CuCl**	**CH_2Cl_2**	**70**	**82**
10	CuCl	toluene	70	65
11	CuCl	THF	70	55
12	CuCl	MeCN	70	23
13	CuCl	DMF	70	34
14	CuCl	CH_2Cl_2	60	82
15[d]	**CuCl**	**CH_2Cl_2**	**60**	**81**
16	–	CH_2Cl_2	60	0

[a] Reaction conditions: catalyst (0.06 mmol), **1a** (0.30 mmol), **2a** (0.36 mmol), under N_2 in a Schlenk tube with screw caps, 24 h, oil-bath temperature.
[b] Isolated yield.
[c] The reaction was performed without DTBP.
[d] The amount of CuCl used was 0.045 mmol.

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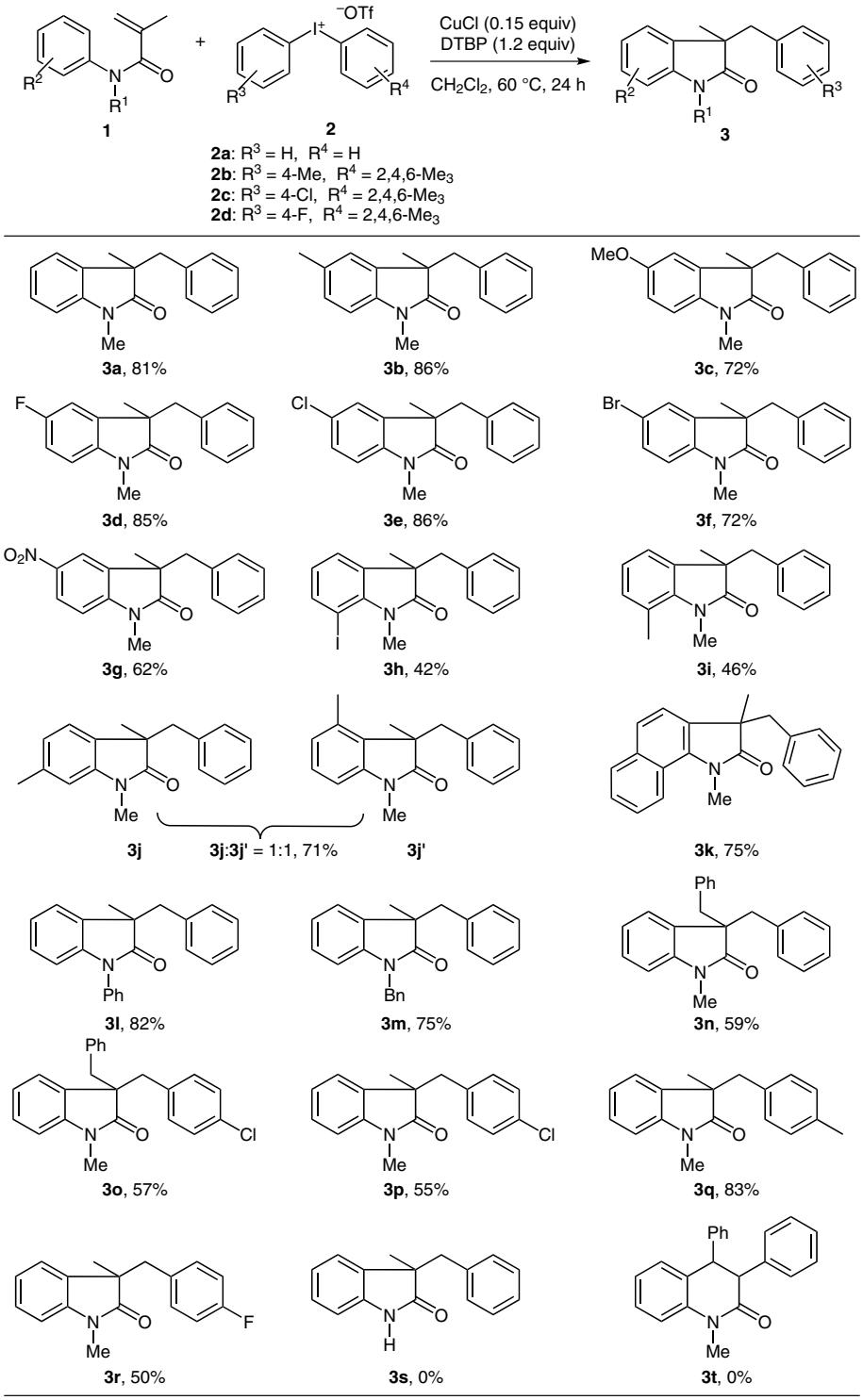
sioned that diaryliodonium salts might react with *N*-arylacrylamides to form the oxindole (Scheme 1).

Initially, we examined the reaction of arylacrylamide **1a** with diphenyliodonium triflate (**2a**) in the presence of CuI in dioxane at 70 °C under N_2. To our delight the desired product **3a** was obtained in 32% yield (Table 1, entry 1). 2,6-Di-*tert*-butylpyridine (DTBP) has often been used as a base in this type reaction. When DTBP (1.2 equiv) was introduced as a base, **3a** was obtanied in 60% yield (entry 2). Screening of a few other copper salts, such as $CuCl_2$, CuCl, CuBr, $Cu(OAc)_2$ and $Cu(OTf)_2$ revealed that CuCl was the best choice and the yield could reach 72% (Table 1, entries 2–7). The solvents were crucial for this transformation. Among the solvents screened, CH_2Cl_2 was optimal, providing **3a** in 82% yield (entry 9).



Scheme 2 Synthesis of oxindoles from acrylamides and iodonium salts

Other solvents such as toluene, THF, DMF, provided moderate to low yields, whereas DCE gave a only trace amount of **3a** (Table 1, entries 4 and 8–13). $NaHCO_3$ was an efficient base in Zhou's report.[5b] In our system, some inorganic bases such as Na_2CO_3 and $NaHCO_3$ gave 20% and 30% yields, respectively. When the reaction temperature was lowered to 60 °C (Table 1, entry 14) or the loading of CuCl was reduced to 15 mol% (Table 1, entry 15), the yield remained almost the same. The reaction did not occur at all in the absence of a copper salt (Table 1, entry 16). Thus, the optimized reaction conditions for this copper-catalyzed coupling reaction was: **1a** (0.5 mmol), **2a** (0.6 mmol), CuCl (15 mol%), in CH_2Cl_2 at 60 °C under N_2 for 24 hours.

Subsequently, we evaluated the scope of substituted arylacrylamides **1** with diphenyliodonium salt **2a** and the results are summarized in Scheme 2. In general, a variety of functional groups on the phenyl ring of arylacrylamides were compatible under this procedure, affording the desired products in moderate to good yields. The substituted arylacrylamides with electron-donating groups, such as methoxy and methyl reacted with diphenyliodonium salt **2a** efficiently and gave the desired products **3b**, **3c** in 86% and 72% yields, respectively. Halo-substituted acrylamides worked well to afford the corresponding products in good yields (**3d**–**3f**), which could allow for further synthetic transformations. The *ortho*-substituted arylacrylamides exhibited a particularly distinct steric hindrance effect, and the corresponding oxindoles **3h**, **3i** were obtained in low yields. As expected, when the *meta*-substituted arylacrylamides were used as the substrate, a mixture of the products **3j** and **3j′** were obtained in 71% yield with poor regioselectivity (1:1). More bulky substrates such as naphthalene acrylamide also efficiently reacted with **2a** and gave the product **3k** in 75% yield. Different N-protection groups such as phenyl and benzyl were tolerated, leading to the corresponding products in good yields (**3l**, **3m**). 2-Benzyl-*N*-methyl-*N*-phenylacrylamide also exhibited a distinct steric hindrance effect to afford **3n** in 59% yield. Unfortunately, unprotected N–H acrylamide did not yield the product under the reaction condition, giving small amount of N-arylation by-products. When *N*-methyl-*N*-phenylcinnamamide was used, the desired six-membered ring **3t** was not obtained.

Next, we examined the chemoselectivity of unsymmetrical diaryliodonium salts. Observations suggested that more bulky aryl groups did not transfer into the products.[5j] When 4-methylphenyl(2,4,6-trimethylphenyl)iodonium triflate (**2b**) was used, steric control resulted in substitution of the less hindered 4-methylphenyl ring as the only product **3q** in 83% yield. The less hindered phenyl ring with electron-withdrawing 4-chloro- (**2c**) and 4-fluoro- (**2d**) reacted with arylacrylamides to give the expected products **3o**, **3p**, and **3r** in 57%, 55%, and 50% yields, result in substitution of the less hindered phenyl ring as the only product, too.

In conclusion, we have developed a Cu-catalyzed approach for the assembly of the biologically important oxindole derivatives.[10] A broad scope of *N*-arylacrylamides and diphenyliodonium salt coupling partners has been defined. The studies of the reactions of diaryliodonium salts with other coupling partners are currently in progress.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(10) **Typical Procedure**: An oven-dried 10-mL Schlenk tube containing CuCl (4.5 mg, 15 mol%), *N*-arylacrylamide **1a** (90.3 mg, 0.3 mmol), and diphenyliodonium triflate (**2a**; 154.8 mg, 0.36 mmol) was evacuated and purged with nitrogen three times. DTBP (68.8 mg, 0.36 mmol) in freshly distilled CH_2Cl_2 (2.0 mL) was added to the system at r.t. The reaction mixture was heated with stirring at 60 °C for 24 h. The reaction mixture was allowed to cool to ambient temperature, and then transferred to a round-bottom flask. Silica gel (3.0 g) was added, and the solvent was removed under reduced pressure to afford a free-flowing powder. This powder was then dry-loaded onto a silica gel column and purified by flash chromatography using petroleum ether–EtOAc (20:1) as the eluent to give the product **3a**. Yield: 75 mg (81%). MS (ESI): *m/z* = 274.0 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.03–7.18 (m, 6 H), 6.83–6.85 (m, 2 H), 6.62 (d, *J* = 7.7 Hz, 1 H), 3.12 (d, *J* = 13.0 Hz, 1 H), 3.01 (d, *J* = 13.0 Hz, 1 H), 2.98 (s, 3 H), 1.47 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.9, 142.9, 136.0, 132.9, 129.7, 127.6, 126.3, 123.2, 121.9, 107.6, 50.0, 44.4, 26.7, 22.6.

