Synthesis Design

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Copper-Catalyzed C–C Bond Formation through C–H Functionalization: Synthesis of Multisubstituted Indoles from *N*-Aryl Enaminones**

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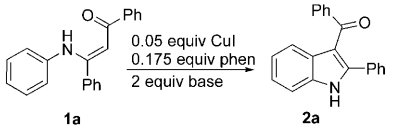
Because of the economic attractiveness and good functional tolerance of copper-catalyzed methods and hence their potential in large-scale applications, during the past few years there have been remarkable advances in the use of copper catalysis in organic synthesis. An impressive number of Ullmann coupling reactions have been described starting from aryl halides and suitable reagents.[1] Recent reports[2] have shown that copper catalysis can also be used in the formation of C–heteroatom and C–C bonds through selective catalytic activation of aryl C–H bonds, a topic of intense current interest that, for the most part, has witnessed the use of palladium-, rhodium-, and ruthenium-based catalysts.[3] In particular, intramolecular copper-catalyzed *ortho* C–H functionalizations through C–N and C–O bond-forming reactions have been shown to form benzimidazoles[2c] and benzoxazoles[2d] from amidines and anilides, respectively. Herein, we disclose a new synthesis of multisubstituted indoles from *N*-aryl enaminones that involves an intramolecular copper-catalyzed aryl C–H functionalization through C–C bond formation.[4] The indole moiety is prevalent in a vast array of biologically active natural and nonnatural compounds. Consequently, despite the existence of numerous methods for the synthesis of indole derivatives,[5] the development of new, more efficient procedures is a subject of great importance.

N-Aryl enaminones **1** were readily prepared through Sonogashira cross-coupling of terminal alkynes with aroyl chlorides,[6] followed by the conjugate addition of anilines with the resultant α,β-ynones.[7]

We initiated our study by examining whether the enaminone **1a** could be converted into the corresponding indole **2a**. Reactions were usually carried out under an atmosphere of air. After an initial screen of copper catalysts ($CuSO_4$, $CuCl_2$, CuI), we found that **2a** could be isolated in 63% yield by using CuI, Li_2CO_3, and 1,10-phenanthroline (phen) in dimethyl acetamide (DMA) after 48 h (Table 1, entry 1). Optimization studies were then performed that varied the nature of solvents, bases, temperature, and the excess phen. These investigations revealed that the utilization of dimethyl sulfoxide (DMSO) gave a similar yield but in half the time (Table 1, entry 2), whereas 1,4-dioxane led to the recovery of the starting enaminone in almost quantitative yield (Table 1, entry 3). A satisfactory result was obtained when dimethylformamide (DMF) was used as solvent: **2a** was isolated in 80% yield (Table 1, entry 4). The use of K_2CO_3 (Table 1, entry 5) or Cs_2CO_3 (Table 1, entry 6) resulted in lower yields, as did decreasing the reaction temperature (Table 1, entry 7) or the excess phen (Table 1, entry 8). No indole formation was observed upon omitting CuI (Table 1, entry 9) or phen even after increasing the amount of CuI to 30 mol% and the reaction temperature to 120°C (Table 1, entry 10). Interestingly, compound **2a** was isolated in only 50% yield when the reaction was carried out under an atmosphere of oxygen (Table 1, entry 11) and was formed in good yield under an argon atmosphere (Table 1, entry 12).

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



1a **2a**

Entry	Base	Solvent	*T* [°C]	*t* [h]	Yield of **2a** [%][b]
1	Li_2CO_3	DMA	100	48	63
2	Li_2CO_3	DMSO	100	24	66
3[c]	Li_2CO_3	1,4-dioxane	100	24	–
4	Li_2CO_3	DMF	100	24	80
5	K_2CO_3	DMF	100	96	48
6	Cs_2CO_3	DMF	100	24	51
7[d]	Li_2CO_3	DMF	80	48	42
8[e]	Li_2CO_3	DMF	100	30	61
9[f]	Li_2CO_3	DMF	100	24	–
10[g]	Li_2CO_3	DMF	120	24	–
11[h]	Li_2CO_3	DMF	100	24	50
12[i]	Li_2CO_3	DMF	100	24	73

[a] Unless otherwise stated, reactions were carried out on a 0.25 mmol scale in 2.5 mL anhydrous solvent under an air atmosphere. [b] Yields of isolated products. [c] **1a** was recovered in 94% yield. [d] **1a** was recovered in 44% yield. [e] With 5 mol% phen. [f] Without CuI; **1a** was recovered in 91% yield. [g] Without phen, in the presence of 30% CuI; **1a** was recovered in 90% yield. [h] Under oxygen (balloon). [i] Under argon (balloon).

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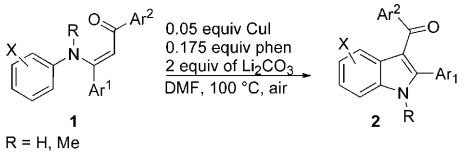
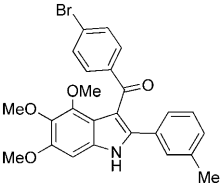
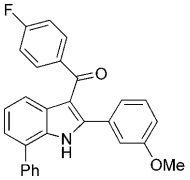
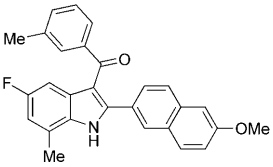
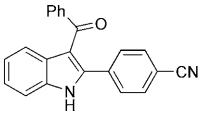
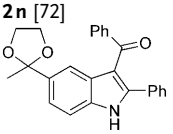
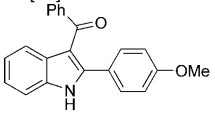
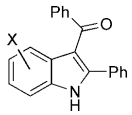
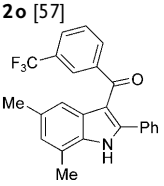
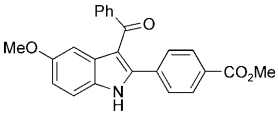
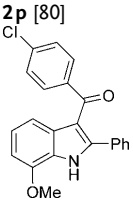
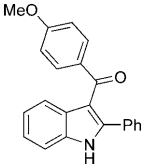
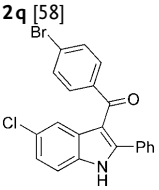
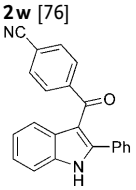
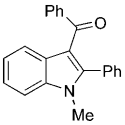
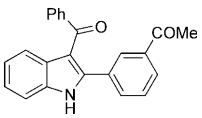
The scope and generality of the process was next explored under the optimized conditions (Table 1, entry 4).[8] As shown in Table 2, a great variety of enaminones can be converted into the corresponding indoles. Several useful functional groups are tolerated both in the enone and the *N*-aryl fragment, including the whole range of halogen substituents. The ability to incorporate the latter makes this reaction particularly attractive for increasing the molecular complex-

Table 2: Copper-catalyzed synthesis of indoles **2** from enaminones **1**.[a]



1 R = H, Me

2

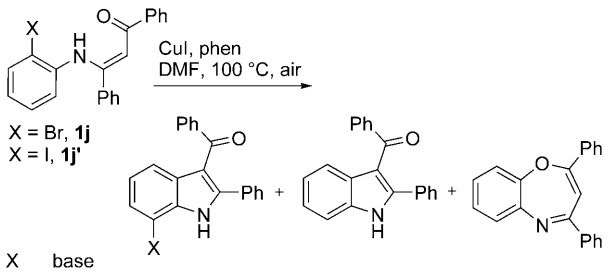
Entry	Product [yield in %][b]	Entry	Product [yield in %][b]	Entry	Product [yield in %][b]
1	H: **2a** [80]	14		21	
2	5-MeO,7-Me: **2b** [84]		**2m** [68]		**2s** [83]
3	5-MeO:**2c** [76]	15		22	
4	5-Me: **2d** [84]		**2n** [72]		**2t** [66]
5	6-MeO/4-MeO 50:50: **2e** [79]	16		23	
6	5-F: **2f** [75]		**2o** [57]		**2u** [75]
7	 X = 5-Cl: **2g** [53]	17		24	
8	5-Br: **2h** [60]		**2p** [80]		**2v** [66]
9	5-I: **2i** [72]	18		25	
10	7-Br: **2j** [51]		**2q** [58]		**2w** [76]
11	4,6-Me_2: **2k** [78]	19		26	
12	6-EtO_2C/4-EtO_2C 64:36: **2l** [82]		**2r** [65]		**2x** [56]
13	5-MeCO: [–]	20		27	
			[–][c]		**2y** [56]

[a] Reactions were carried out on a 0.25 mmol scale. [b] Yields of isolated products. [c] The starting *N*-methyl derivative of **1a** was recovered in 90% yield.

ity, for example by transition-metal-catalyzed coupling reactions. The presence of substituents at both *meta* positions of the aniline fragment does not hamper the reaction (Table 2, entries 11 and 14). However, when there is only one substituent *meta* to the nitrogen atom, the cyclization affords regioisomeric derivatives with both electron-donating (Table 2, entry 5) and electron-withdrawing (Table 2, entry 12) groups. No indole formation was observed with the enaminone containing an acetyl group *para* to the nitrogen atom (Table 2, entry 13). However, the appropriately protected derivative afforded the desired product in good yield (Table 2, entry 16). The cyclization of the *N*-methyl derivative of **1a** was also attempted. However, no indole formation was observed and the starting material was recovered almost unchanged (Table 2, entry 20).

The formation of **2j** from the corresponding *N*-(2-bromophenyl)enaminone **1j** (Table 2, entry 10) is remarkable in that 7-bromoindoles are key intermediates in the preparation of biologically active compounds via Suzuki–Miyaura cross-coupling reactions.[9] Its formation is the result of a C–H activation process that is favored over the possible indole formation through substitution of the C–C bond for the C–Br bond.

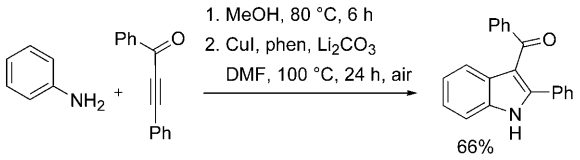
This C–H bond versus C–Br bond selectivity represents a distinct advantage of the present method and was found to depend on a subtle combination of base and halide effects. Control experiments revealed that the cyclization to give the indole derivative occurs preferentially at the carbon atom bound to Br when K_2CO_3 is substituted for Li_2CO_3 (Scheme 1). Under these conditions, no evidence of **2j** was obtained and the dehalogenated indole **3** was isolated in 30% yield. Interestingly, the benzoxazepine product **4** was also isolated in 36% yield. Most probably it is generated by an intramolecular C–Br functionalization involving a C–O bond-forming reaction. When the enaminone **1j′**, which bears an *o*-iodo substituent on the aniline fragment, was used as the starting substrate, only part of the reaction was found to proceed through the C–H functionalization pathway in the presence of Li_2CO_3. The corresponding 7-iodoindole was obtained in only 27% yield and the main product was the dehalogenated indole **3**. Use of K_2CO_3 as the base led to the conversion of **1j′** into **3** in excellent yield and no evidence of benzoxazepine was obtained.



X	base			
Br	Li_2CO_3	**2j** (51%)	–	–
Br	K_2CO_3	–	**3** (30%)	**4** (36%)
I	Li_2CO_3	**2j'** (27%)	**3** (51%)	–
I	K_2CO_3	–	**3** (92%)	–

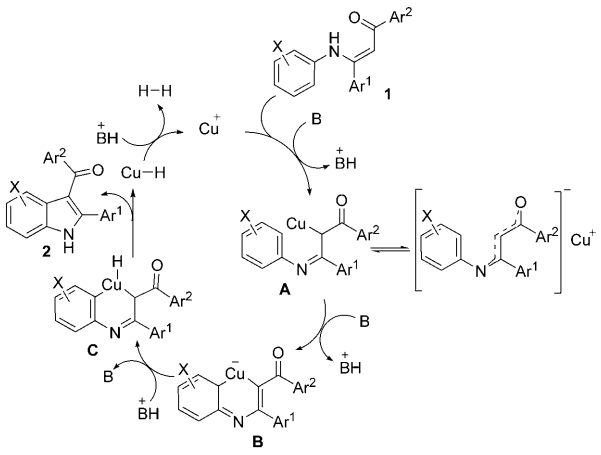
Scheme 1. Influence of halide and carbonate base on the copper-catalyzed cyclization of *N*-(2-halophenyl)enaminones.

To make this overall approach to indoles more attractive from a synthetic standpoint, we explored their formation through a process that omits the isolation of the enaminone intermediates. Addition of DMF and the reagents required for the cyclization step to the crude methanolic mixture resulting from the conjugate addition of the aniline to the α,β-ynone led to moderate yields. For example, **2a** was isolated in only 50% overall yield after 48 h by using this protocol. In addition, no indole product was formed when the overall process was carried out with methanol or DMF as the sole solvents for the two steps. Control experiments revealed that the cyclization does not proceed in methanol and that the enaminone product is not formed in DMF. Finally, we found that good results could be obtained by adding DMF, CuI, phen, and Li_2CO_3 to the crude mixture derived from the reaction of anilines with α,β-ynones after evaporation of the volatile materials. Under these conditions, **2a** was isolated in 66% overall yield (Scheme 2).



Scheme 2. Synthesis of indoles from anilines and α,β-ynones omitting the isolation of enaminone intermediates.

A plausible pathway for this indole synthesis is outlined in Scheme 3. The reaction of **1** with CuI under basic conditions presumably leads to the formation of complex **A**. The ate complex **B** is subsequently formed through nucleophilic attack of the *ortho* carbon atom of the aniline fragment to copper promoted by the extraction of the hydrogen bound to the carbon atom α to the carbonyl group. Protonation of **B** followed by a rearomatization/tautomerization process leads to the formation of **C**. The indole product **2** is generated by reductive elimination of CuH, which reacts with the conjugate acid of the base affording hydrogen and regenerating the active copper catalytic species.



Scheme 3. Possible reaction pathway for the copper-catalyzed cyclization of **1** to **2**.

To probe the action of a mechanism involving the intermediacy of complex **C** and the subsequent reductive elimination to afford CuH, we treated **1a** under standard conditions in the presence of methyl cinnamate. α,β-Unsaturated esters are known to undergo conjugate reduction in the presence of CuH intermediates generated in situ.[10] A slower reaction rate was observed and **2a** was isolated in 30% yield after 24 h (compare with Table 1, entry 4). The starting enaminone was recovered in 60% yield. Methyl 3-phenylpropanoate, derived from the reduction of the carbon–carbon double bond, was isolated in 5% yield. This corresponds to approximately 16% of reduced product that forms through the intervention of CuH generated from **C**. An intramolecular competition experiment using *ortho*-deuterium-labeled **1a** was also performed. This experiment allowed us to determine the absence of an isotope effect ($k_H/k_D = 1.0$; 100 °C),[11] which suggests that a hydrogen-abstraction step does not occur in the rate-limiting step. Both these results, combined with the observation that the reaction does not require the presence of oxygen (reactions were carried out under an atmosphere of air for simplicity), are consistent with the proposed mechanism.

In conclusion, an efficient copper-catalyzed approach to the construction of a multisubstituted indole skeleton from readily available *N*-aryl enaminones has been developed. The new method tolerates a variety of useful functionalities including the whole range of halogen substituents. With *N*-(2-bromophenyl)enaminone a remarkable selectivity was observed that favors C–H functionalization in comparison to C–Br functionalization and affords 7-bromoindoles, key intermediates in the synthesis of biologically active compounds. Indole products can also be prepared from α,β-ynones and primary amines by a sequential process that omits the isolation of the enaminone intermediates. Since multisubstituted indoles are formed by assembling 2-haloaroyl chlorides, terminal alkynes, and primary amines, a wide variety of indole derivatives can be synthesized by using this protocol, which can be particularly useful for the preparation of compound libraries.

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