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# Copper-catalyzed synthesis of benzocarbazoles *via* α-C-arylation of ketones†

**Ruilong Xie,[ab] Yun Ling*[b] and Hua Fu*[ac]**

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**A simple and efficient copper-catalyzed method for the synthesis of 11*H*-benzo[*a*]carbazoles has been developed. The protocol uses readily available substituted 2-(2-bromophenyl)-1*H*-indoles and ketones as starting materials and an inexpensive catalyst system. The corresponding 11*H*-benzo[*a*]carbazoles were obtained in moderate to excellent yields.**

Over the past decades, much attention has been paid to transition metal-catalyzed arylation reactions of substrates containing activated $sp^3$-hybridized C–H bonds with aryl halides and pseudohalides, in which the alkyl–aryl bonds are formed at the α-position of electron-withdrawing groups including keto, formyl, alkoxycarbonyl, cyano, nitro, sulfoximino, and sulfonyl groups.[1] Of the previous methods, palladium-catalyzed α-C-arylations are very efficient and commonly used,[2] and this strategy has been applied to the synthesis of cyclic compounds.[3] However, palladium-catalyzed methods need expensive Pd catalysts, and often employ expensive, patented phosphine ligands. Although nickel-catalyzed α-C-arylations are also effective, the high toxicity of Ni catalysts greatly limits their use in industrial applications.[4] Recently copper catalysts have become popular and widely used due to their low cost and low toxicity, and great achievements have been made in this area.[5] Copper-catalyzed α-C-arylations have been investigated,[6] and some heterocycles have been constructed using this strategy by us[7] and other groups.[8] Unfortunately, copper-catalyzed α-C-arylations were only effective for substrates bearing two electron-withdrawing moieties linked at a methylene group, and those containing one electron-withdrawing group did not work. To the best of our knowledge, the copper-catalyzed α-C-arylation of simple ketones has not been reported thus far.

Benzocarbazole derivatives show various biological functions although they are rarely found as natural products. For example, they exhibit antitumor (leukemia, renal, colon)[9] and anti-inflammatory activities,[10] and some benzocarbazoles can bind to estrogen receptors and inhibit the growth of mammary tumors in rats.[11] In addition, benzocarbazole derivatives have found extensive application as photographic materials.[12] Some methods for the synthesis of benzocarbazole derivatives have been developed,[13] but these methods usually suffer from the need to synthesize complex starting materials, harsh reaction conditions and low yields. Therefore, it is highly desirable to develop a simple, efficient and practical approach to benzocarbazole derivatives. Herein, we report a novel and efficient copper-catalyzed synthesis of benzocarbazoles *via* α-C-arylation of ketones.

The reaction of 2-(2-bromophenyl)-1*H*-indole (**1a**) with acetophenone (**2a**), leading to 6-phenyl-11*H*-benzo[*a*]carbazole (**3a**) was used as the model to optimize conditions including the catalysts, ligands, bases, solvents and temperature under a nitrogen atmosphere. As shown in Table 1, six copper catalysts were tested using L-proline as the ligand, $Cs_2CO_3$ as the base and DMSO as the solvent at 80 °C (entries 1–6). CuBr exhibited the highest activity (entry 4). No target product was observed in the absence of a copper catalyst (entry 7). The effect of the solvent was investigated (compare entries 4, 8–11), and DMSO was found to be the most suitable (entry 4). Other ligands were screened (entries 12–14), and they were inferior to L-proline. We investigated other bases (entries 15–18), and $Cs_2CO_3$ provided the highest yield (entry 4). The effect of reaction temperature was also explored (compare entries 4, 19 and 20), and 80 °C was the best choice (entry 4). The ratio of the substrates and $Cs_2CO_3$ was investigated (entries 21–23), and the use of 2 equiv. of **2a** and 2 equiv. of $Cs_2CO_3$ relative to **1a** was optimal (entry 22). The solvent was removed from the reaction mixture of entry 22 and the residue was examined using inductively coupled plasma mass spectroscopy (ICP-MS). Only trace amount of Ni (5 ppm), Pd (<10 ppm), Rh (<10 ppm) and Ru (<10 ppm) were found, eliminating the possibility of involvement of other transition metals in the reaction.

As shown in Table 2, the substrate scope of the reaction was investigated using substituted 2-(2-bromophenyl)-1*H*-indoles and ketones under the optimized conditions, *i.e.* 10 mol% CuBr as the catalyst, 20 mol% L-proline as the ligand, $Cs_2CO_3$ as the base and DMSO as the solvent at 80 °C under a nitrogen atmosphere (minor changes to the conditions were made for several substrates), and the examined substrates afforded the products in moderate to excellent yields. For substituted

[a] *Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing, 100084, P. R. China. E-mail: fuhua@mail.tsinghua.edu.cn; Fax: +86 10-62781695*
[b] *Key Laboratory of Pesticide Chemistry and Application, Department of Applied Chemistry, College of Science, Ministry of Agriculture, China Agricultural University, Beijing, 100193, P. R. China*
[c] *Key Laboratory of Chemical Biology (Guangdong Province), Graduate School of Shenzhen, Tsinghua University, Shenzhen, 518057, P. R. China*

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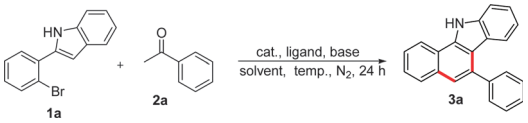
**Table 1** Copper-catalyzed synthesis of 6-phenyl-11*H*-benzo[*a*]carbazole (**3a**) *via* coupling of 2-(2-bromophenyl)-1*H*-indole (**1a**) with acetophenone (**2a**): optimization of conditions[a]



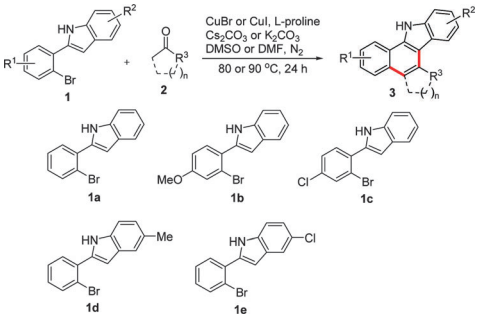

| Entry | Cat. | Ligand (mol%) | Base | Solvent | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | Cu | L-Proline | $Cs_2CO_3$ | DMSO | 45 |
| 2 | $Cu_2O$ | L-Proline | $Cs_2CO_3$ | DMSO | 60 |
| 3 | CuCl | L-Proline | $Cs_2CO_3$ | DMSO | 61 |
| 4 | CuBr | L-Proline | $Cs_2CO_3$ | DMSO | 63 |
| 5 | CuI | L-Proline | $Cs_2CO_3$ | DMSO | 62 |
| 6 | $CuCl_2$ | L-Proline | $Cs_2CO_3$ | DMSO | 60 |
| 7 | — | L-Proline | $Cs_2CO_3$ | DMSO | 0 |
| 8 | CuBr | L-Proline | $Cs_2CO_3$ | DMF | 46 |
| 9 | CuBr | L-Proline | $Cs_2CO_3$ | NMP | 2 |
| 10 | CuBr | L-Proline | $Cs_2CO_3$ | Toluene | 16 |
| 11 | CuBr | L-Proline | $Cs_2CO_3$ | Dioxane | 38 |
| 12 | CuBr | DMEDA | $Cs_2CO_3$ | DMSO | 44 |
| 13 | CuBr | 1,10-phen | $Cs_2CO_3$ | DMSO | 53 |
| 14 | CuBr | PCA | $Cs_2CO_3$ | DMSO | 57 |
| 15 | CuBr | L-Proline | $Na_2CO_3$ | DMSO | 12 |
| 16 | CuBr | L-Proline | $K_2CO_3$ | DMSO | 45 |
| 17 | CuBr | L-Proline | $K_3PO_4$ | DMSO | 45 |
| 18 | CuBr | L-Proline | KOAc | DMSO | Trace |
| 19 | CuBr | L-Proline | $Cs_2CO_3$ | DMSO | 10[c] |
| 20 | CuBr | L-Proline | $Cs_2CO_3$ | DMSO | 61[d] |
| 21 | CuBr | L-Proline | $Cs_2CO_3$ | DMSO | 71[e] |
| 22 | CuBr | L-Proline | $Cs_2CO_3$ | DMSO | 77[f] |
| 23 | CuBr | L-Proline | $Cs_2CO_3$ | DMSO | 73[g] |

[a] Reaction conditions: nitrogen atmosphere, 2-(2-bromophenyl)-1*H*-indole (**1a**) (0.5 mmol), acetophenone (**2a**) (0.75 mmol), catalyst (0.05 mmol), ligand (0.1 mmol), base (1.5 mmol), solvent (2.0 mL), reaction temperature 80 °C. [b] Isolated yield. [c] Reaction temperature 60 °C. [d] Reaction temperature 100 °C. [e] **2a** (1.0 mmol), base (1.5 mmol). [f] **2a** (1.0 mmol), base (1.0 mmol). [g] **2a** (1.0 mmol), base (0.75 mmol). NMP = *N*-methylmorpholine. DMEDA = *N*,*N*-dimethylethylenediamine. 1,10-phen = 1,10-phenanthroline. PCA = piperidine-2-carboxylic acid.

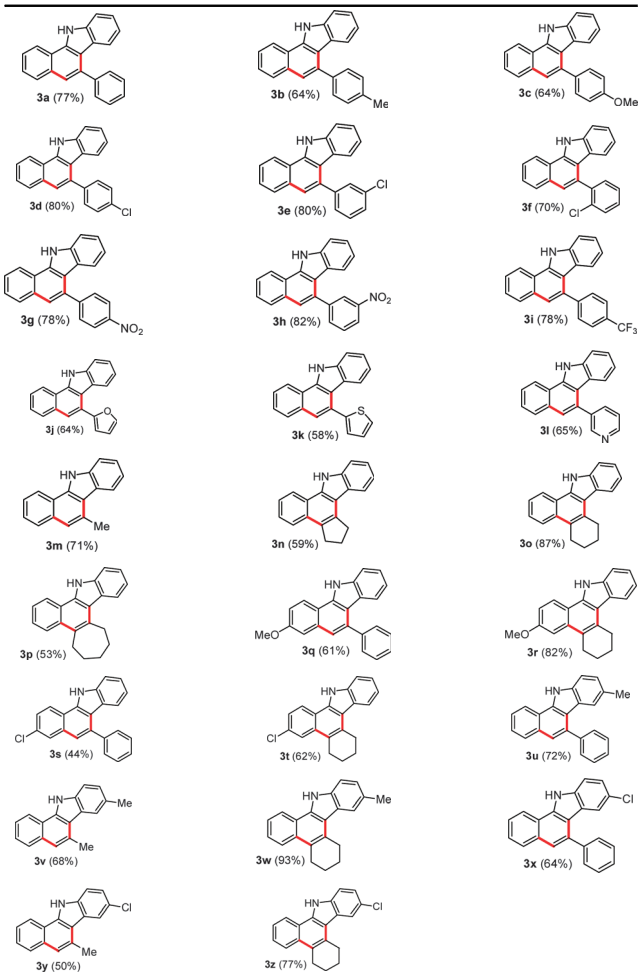
2-(2-bromophenyl)-1*H*-indoles, in general, no significant difference in reactivity was observed for the examined substrates with varied electronic properties, including electron-rich, electron-poor and neutral groups. For aromatic ketones, substrates containing electron-withdrawing groups displayed higher reactivity than those containing electron-donating and neutral groups. For aliphatic ketones, cyclohexanone afforded higher yields than propan-2-one, cyclopentanone and cycloheptanone. Substrates with various functional groups were tolerated under the reaction conditions, including ethers (**3c**, **3q** and **3r**), C–Cl bonds (**3d–f**, **3s**, **3t**, **3x–z**), nitro (**3g** and **3h**), $CF_3$ (**3i**), nitrogen heterocycles (**3a–z**), oxygen heterocycles (**3j**) and sulfur heterocycles (**3k**). Interestingly, the indole NH group of **1** was retained in the reactions above.

We explored the mechanism of the copper-catalyzed synthesis of 11*H*-benzo[*a*]carbazoles. Treatment of 2-(2-bromophenyl)-1-methyl-1*H*-indole (**1f**) with acetophenone (**2a**) was investigated under the standard conditions, and no reaction was observed (Scheme 1a). Treatment of 2-phenyl-1*H*-indole (**1g**) with acetophenone (**2a**) did not lead to **4** (Scheme 1b). In order to compare the reactivity of aryl bromide (**1a**) and aryl iodide (**1h**), the reaction temperature was decreased from 80 °C to 60 °C, and **1b** provided higher yield than **1a** (Scheme 1c).

**Table 2** Copper-catalyzed synthesis of 11*H*-benzo[*a*]carbazoles[a]

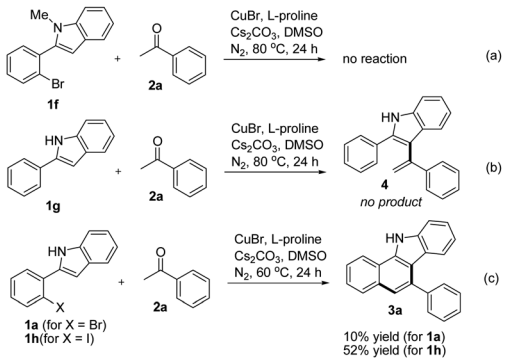



**3** (Yield[b])

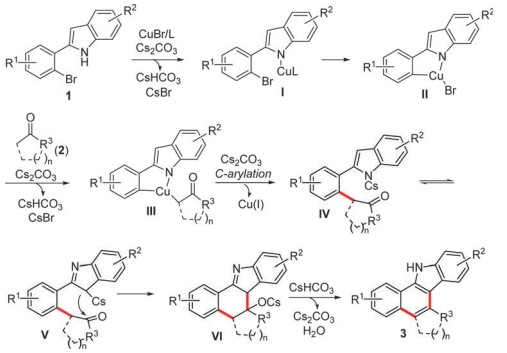



[a] Reaction conditions: nitrogen atmosphere, **1** (0.5 mmol), **2** (1.0 mmol), CuI (0.05 mmol) for **3n**; CuBr (0.05 mmol) for other compounds, L-proline (0.1 mmol), $K_2CO_3$ (1.0 mmol) for **3g** and **3h**; $Cs_2CO_3$ (1.0 mmol) for other compounds, DMF (2.0 mL) for **3s**; DMSO (2.0 mL) for other compounds, temperature (90 °C for **3s**; 80 °C for other compounds), reaction time 24 h. [b] Isolated yield.

This result shows that the domino reaction could start from C-arylation of ketones in the synthesis of 11*H*-benzo[*a*]-carbazoles. Therefore, a possible mechanism for the copper-catalyzed synthesis of 11*H*-benzo[*a*]carbazoles is proposed in Scheme 2. Treatment of **1** with CuBr (or CuI) and a ligand in the presence of $Cs_2CO_3$ (or $K_2CO_3$) provides **I**, and oxidative addition of **I** leads to **II**. In the presence of base, coordination




**Scheme 1** (a) Treatment of 2-(2-bromophenyl)-1-methyl-1*H*-indole (**1f**) with **2a**. (b) Treatment of 2-phenyl-1*H*-indole (**1g**) with **2a**. (c) Reaction of 2-(2-bromophenyl)-1*H*-indole (**1a**) or 2-(2-iodophenyl)-1*H*-indole (**1h**) with **2a** at 60 °C.




**Scheme 2** Possible mechanism for the synthesis of 11*H*-benzo[*a*]-carbazoles.

of **II** to the ketone affords **III**, and reductive elimination of **III** (*C-arylation*) gives **IV**, regenerating the copper catalyst. Isomerization of **IV** provides **V**, and intramolecular nucleophilic attack leads to **VI**. Finally, dehydration and isomerization of the C=N bond to a C=C bond gives the target product (**3**) in the presence of $CsHCO_3$.

In conclusion, we have developed a simple and efficient copper-catalyzed method for the synthesis of 11*H*-benzo[*a*]-carbazoles. The protocol uses readily available substituted 2-(2-bromophenyl)-1*H*-indoles and ketones as starting materials, CuBr or CuI as the catalyst, L-proline as the ligand, $Cs_2CO_3$ or $K_2CO_3$ as the base, and DMSO or DMF as the solvent, and 11*H*-benzo[*a*]carbazoles were obtained in moderate to excellent yields. The method could tolerate various functional groups in the substrates. This is the first example of copper-catalyzed C-arylation of ketones and construction of cyclic compounds using this strategy thus far. Therefore, this method will find many applications in organic chemistry and medicinal chemistry.

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