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Efficient Copper-Catalysed Synthesis of Carbazoles by Double *N*-Arylation of Primary Amines with 2,2′-Dibromobiphenyl in the Presence of Air

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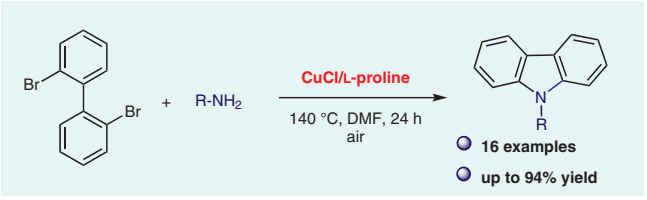

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Abstract An efficient Cu-catalyzed synthesis of carbazole derivatives is reported, which proceeds by double C–N coupling reactions of 2,2′-dibromobiphenyl and amines in the presence of air. The reaction is robust, proceeds in high yields, and tolerates a series of amines including neutral, electron-rich, electron-deficient aromatic amines and aliphatic amines.

Key words Cu catalysis, carbazole synthesis, C–N coupling, carbazole alkaloids, sustainable process

Carbazole derivatives are present in the core structure of many important natural products and pharmaceutically active molecules.[1] Carbazole was first isolated by Graebe and Glaser from the anthracene fraction of coal tar in 1872.[2] In 1987, nearly a century later, Bhattacharyya announced for the first time that carbazole was isolated from a plant *Glycosmis pentaphylla*.[3] During the past four decades, a number of carbazole alkaloids has been isolated from various natural sources (Figure 1).[4] Most carbazole alkaloids are derived from higher plants of the genus *Clausena*, *Murraya*, and *Glycosmis*, all of which belong to the *Rutaceae* family.[5] Moreover, a significant number of natural carbazoles has been found to have biological activities, including antitumor, anti-inflammatory, antihistamine, antibiotic, anti-HIV, antiepileptic, anti-Alzheimer, psychotropic, neuroprotection, and antioxidative functions.[6] Due to the excellent bioactivities of natural carbazoles, the carbazole core structure is also present in important synthetic drugs, such as carprofen (a nonsteroidal anti-inflammatory drug), carvedilol (a congestive heart failure drug), or potential agents, such as Go-6976, an anti-HCMV agent.[7] Carbazole derivatives are not only important structures in pharmaceutical compounds, but are also used in the development of organic light-emitting devices (hole-transporting, luminescent, and host materials).[8] For example, Brunner et al. have reported a variety of carbazole compounds as host materials for triplet emitters in OLEDs.[8] The excellent photorefractive properties and fluorescent nature of the carbazole system were also explored in the development of OLED materials, such as **Bcz1** and **CzCbPy** (Figure 1).[8]

Due to the importance of carbazoles in medicinal and material chemistry, a series of synthetic methods has been reported for the preparation of the carbazole framework.[9] Conventional methods to prepare carbazoles rely on Fischer–Borsche, Graebe–Ullmann and Cadogan reactions.[9] Carbazole derivatives can also be formed by Diels–Alder reactions of pyrano[3,4-*b*]indoles with alkynes.[10] Knölker et al.

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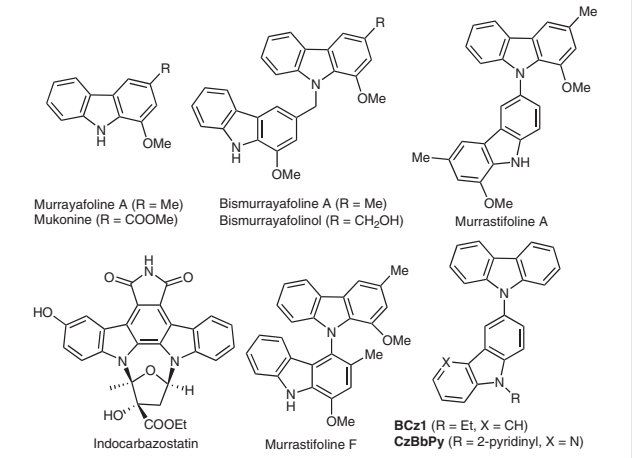
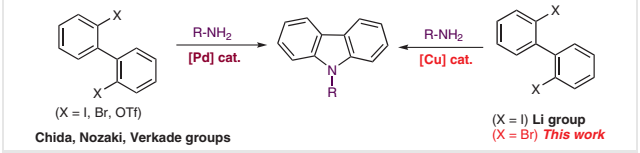


Figure 1 Several natural alkaloids and organic materials containing the carbazole core

described an interesting method to access carbazoles via Fe-mediated oxidative cyclization.[11] In recent years, a series of methods for the preparation of carbazoles relying on Pd-catalyzed cyclizations has been developed.[12] The Larock group reported a one-pot Pd-catalyzed domino process to approach carbazoles using cross-coupling reactions of iodoanilines with silylated aryl triflates.[12a] Langer et al. demonstrated the synthesis of carbazoles by domino 'two-fold Heck/6π-electrocyclization' reactions of 2,3-dibromoindoles with alkenes.[12b] Carbazoles have also been successfully synthesized by transition-metal catalyzed C–H activation reactions.[13] For example, Ackermann et al. developed an efficient access to carbazoles from aniline and 1,2-dihalobenzene derivatives via a domino Pd-catalyzed N–H/C–H activation process.[13a,b] Carbazoles can also be prepared by oxidative Pd-catalyzed cyclizations of diaryl amines.[13c] Fagnou et al. reported an intramolecular Pd(II)-catalyzed oxidative C–C bond formation using pivalic acid as a solvent in the presence of air.[13d] In 2014, we successfully applied this method in a practical synthesis of biscarbazole derivatives.[13e] The Xu group developed the synthesis of N-substituted carbazole derivatives by Rh-catalyzed direct amination of boronic acids with aryl azides via a domino C–H activation and Rh–nitrene migratory insertion process.[13f] The Verma group described a direct Pd-catalyzed transformation of indoles to form carbazoles using alkenes via domino oxidative Heck coupling/cyclization reactions.[13g] Recently, several cycloaddition reactions have been applied for the synthesis of carbazoles derivatives.[14] In 2019, Wang and coworkers reported a Rh-catalyzed [4+2] cycloaddition of indoles with 1,3-dienes to form carbazole derivatives.[14b] Interestingly, carbazoles derivatives can also be prepared by a domino process involving C–H activation and [2+2+2] cyclization of N-protected indoles with alkynes in the presence of Rh (or Mn) catalysts.[14c,d] Electrophilic cyclizations can also be used as an efficient strategy to construct carbazole derivatives by activation of alkynes in the presence of transition metals (or Lewis acids) as catalysts.[14] Au, Pt, Ag salts and Lewis acids (BF_3, $BiCl_3$, $InCl_3$) have also been employed as efficient catalysts.[14] However, these synthetic approaches are often complicated, low yielding, require expensive catalysts or need several steps to prepare the starting materials.

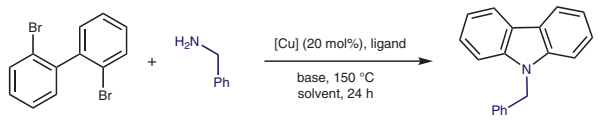
A straightforward approach to prepare carbazoles is based on Pd-catalyzed double arylation of 2,2′-dihalobiphenyls with amines.[15] The groups of Nozaki and Chida independently reported Pd-catalyzed twofold C–N coupling reactions of 2,2′-dihalobiphenyls with amines to form carbazoles.[15a–c] Due to the importance of this approach for the preparation of carbazoles, the Verkade and Ageshina groups designed highly efficient ligands for Pd-catalyzed double N-arylation of primary amines with 2,2′-dihalobiphenyls (Scheme 1).[15d,e] Recently, we successfully applied this strategy as a key step in the synthesis of biscarbazoles in high yields.[16] In order to find cheaper catalysts for this transformation, Li et al. developed a convenient Cu-catalyzed double C–N bond-forming reaction using diiodides and primary amides (Scheme 1).[14e] However, this procedure only worked with diiodides and primary amides and could not be applied to more challenging dibromide or dichloride substrates. Therefore, the development of new procedures to use cheaper dibromides in Cu-catalyzed C–N coupling reactions is of considerable current interest. Herein, we wish to report an efficient and practical method for the Cu-catalyzed synthesis of carbazole derivatives with the tolerance of many functional groups from readily available starting materials such as 2,2′-dibromobiphenyl and amines.



Scheme 1 Approaches to prepare carbazoles by double N-arylation of primary amines with 2,2′-dihalobiphenyls

For the optimization we chose 2,2′-dibromodiphenyl (**1a**) and benzylamine (**2a**) to give the corresponding carbazole **3a** (Table 1). As a starting point we employed 1.5 equivalents of **2a**, 20 mol% of CuI, and 24 mol% of a ligand (*vide infra*) at 150 °C. Several parameters, including the copper source, ligand, solvent, and temperature, were investigated in detail. First, we chose K_2CO_3 as the base and DMSO as the solvent for optimizing ligands. Our initial optimizations started with the use of phosphine and carbene ligands. However, BINAP, Xantphos, and IPr only gave **3a** in low yields (Table 1, entries 1, 2). Subsequently, bipyridine ligands, frequently used in copper catalysis, were screened which, however, also did not give satisfactory results. Recently, amino acids were found to be useful bidentate li-

Table 1 Optimization for the Synthesis of Carbazole

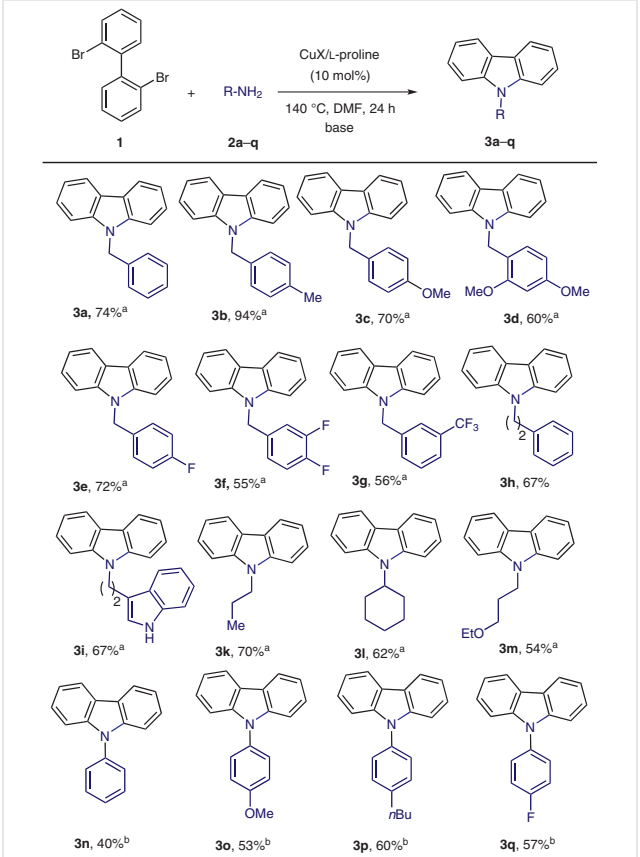


Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[a,b]
1	CuI	BINAP	K_2CO_3	DMSO	25
2	CuI	Xantphos	K_2CO_3	DMSO	5
3	CuI	IPr·HCl	K_2CO_3	DMSO	8
4	CuI	1,10-phenanthroline	K_2CO_3	DMSO	15
5	CuI	bipyridine	K_2CO_3	DMSO	14
6	CuI	L-proline	K_2CO_3	DMSO	30
7	CuI	L-proline	K_3PO_4	DMSO	40
8	CuI	L-proline	KOAc	DMSO	14
9	CuI	L-proline	Cs_2CO_3	DMSO	70
10	CuCl	L-proline	Cs_2CO_3	DMSO	72
11	CuBr	L-proline	Cs_2CO_3	DMSO	34
12	$CuCl_2$	L-proline	Cs_2CO_3	DMSO	45
13	$Cu(OAc)_2$	L-proline	Cs_2CO_3	DMSO	52
14	$Cu(OTf)_2$	L-proline	Cs_2CO_3	DMSO	40
15	CuCl	L-proline	Cs_2CO_3	NMP	55
16	CuCl	L-proline	Cs_2CO_3	DMF	74
17	CuCl	L-proline	Cs_2CO_3	toluene	56
18	CuCl	L-proline	Cs_2CO_3	dioxane	48
19	CuCl	L-proline	KO*t*Bu	DMF	51
20	CuCl	L-proline	KOH	DMF	81
21	CuCl	L-proline	KOH	DMF	79[c]
22	CuCl	L-proline	KOH	DMF	78[c]

[a] Yields were calculated by ^{1}H NMR analysis.
[b] **2a** (1.5 equiv), base (3 equiv), [Cu] catalyst (20 mol%), ligand (24 mol%), 150 °C, 24 h.
[c] **2a** (1.5 equiv), base (3 equiv), [Cu] catalyst (20 mol%), ligand (24 mol%), 140 °C, 24 h.
[d] **2a** (1.5 equiv), base (3 equiv), [Cu] catalyst (10 mol%), ligand (12 mol%), 140 °C, 24 h.

gands in combination with copper salts for C–N coupling reactions.[17] Basing on successful procedures using copper catalysts in the combination with amino acids,[16] thus, L-proline was employed which gave **3a** in 30% yield (Table 1, entry 6). Then, a screening using different bases was carried out, which gave a promising result of 70% yield when Cs_2CO_3 was employed (Table 1, entries 7–9). In order to examine the effect of the copper source, we studied several copper salts, such as CuBr, CuCl, $CuCl_2$, $Cu(OAc)_2$, $Cu(OTf)_2$ (Table 1, entries 10–14). In fact, the yield could be slightly improved to 72% by the use of CuCl. This result led us to evaluate other solvents, for example, NMP, DMF, toluene, and dioxane under the same conditions (Table 1, entries 15–18). The product was formed in 74% yield when the reaction was carried out in DMF. Then, stronger bases, such as KOH and KO*t*-Bu, were examined (Table 1, entries 19, 20). Interestingly, we achieved 81% yield of the desired product with employment of KOH. When the reaction was performed at a lower temperature (140 °C), we still obtained a satisfactory yield (79%). The last screening with reduction of the CuCl loading to 10 mol% was also examined under 140 °C. We realized that this reaction still worked well and **3a** was formed in 78% yield (Table 1, entry 22).

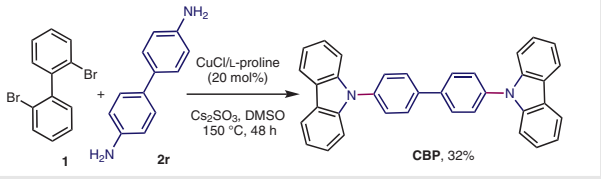
With our optimized conditions in hand, we continued to investigate the substrate scope using different amines. A variety of carbazoles **3a–q** were isolated in moderate to excellent yields (Scheme 2). In general, both aromatic and aliphatic amines could be successfully employed. In the case of benzylamine derivatives containing electron-donating groups (methyl and methoxy) equally good yields were obtained. In the presence of electron-withdrawing groups the yields were lower, presumably due to the lower nucleophilicity of the amines. A carbazole bearing an indole substituent was effectively prepared in 67% isolated yield (**3i**). Aliphatic amines were also used in double C-N coupling reactions, which gave moderate yields of corresponding car-



Scheme 2 Synthesis of carbazoles **3a–q**. Yields of the isolated products are given. [a] Reaction conditions: 140 °C, CuCl/L-proline catalyst (10 mol%), KOH, DMF, 24 h. [b] Reaction conditions: 150 °C, CuI catalyst/L-proline (15 mol%), Cs_2CO_3, DMSO, 24 h.

bazole products (**3k–m**). The reaction of **1** with aniline gave **3n**, albeit, in only 25% yield. The yield could be improved to 40% using 150 °C, 15 mol% of CuI/L-proline, Cs_2CO_3, and DMSO (Table 1, entry 10). Likewise, carbazoles **3o–q**, also derived from anilines, were prepared under these conditions.

We were successful in finding an application of our procedure for the synthesis of commercially available 4,4′-bis(*N*-carbazolyl)-1,1′-biphenyl (CBP), an OLED material, by double Cu-catalyzed cyclization of **1** with diamine **2r** (Scheme 3). Indeed, CBP has been known as one of the most popular host materials for efficient fluorescent and phosphorescent OLEDs with excellent hole mobility.[18] Interestingly, CBP OLED material was successfully prepared in 32% yield using our one-pot procedure.



Scheme 3 Synthesis of biscarbazole OLED material

In conclusion, we have developed a practical and convenient one-pot synthesis of carbazole derivatives in the presence of air from commercially available chemicals. This strategy is based on Cu-catalyzed C–N coupling reactions of 2,2′-dibromobiphenyl with amines and tolerates several functional groups.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706641.

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