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Cu-Catalyzed Aerobic Oxidative N–N Coupling of Carbazoles and Diarylamines Including Selective Cross-Coupling

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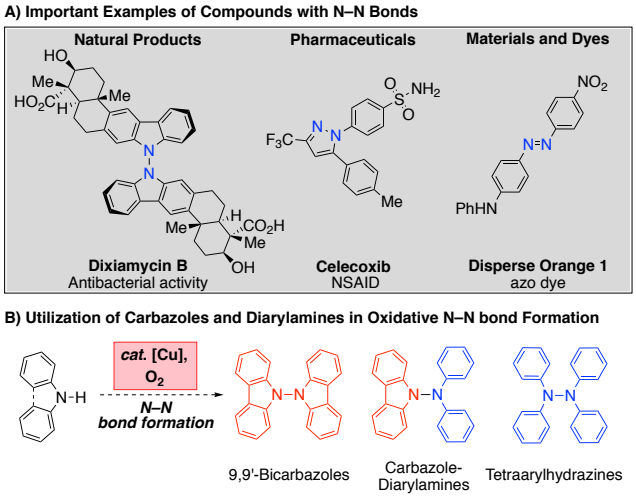
Supporting Information Placeholder

ABSTRACT: A Cu-catalyzed method has been identified for aerobic oxidative dimerization of carbazoles and diarylamines to the corresponding N–N coupled bicarbazoles and tetraarylhydrazines. The reactions proceed under mild conditions (1 atm O_2, 60–80 °C) with a catalyst composed of CuBr·dimethylsulfide and *N,N*-dimethylaminopyridine. Reactions between carbazole and diarylamines show unusually selective cross-coupling, even with a 1:1 ratio of the two substrates. This behavior was found to arise from reversible formation of the tetraarylhydrazine. Formation of this species is kinetically favored, but cleavage of the N–N bond under the reaction conditions leads to selective formation of the thermodynamically favored cross-coupling product.

Nitrogen-nitrogen bonds are prevalent in natural products,[1] pharmaceuticals,[2] and organic materials[3] (Scheme 1A). Various methods are available to prepare these bonds, with classical methods including diazotization of anilines with sodium nitrite and a Brønsted acid, and the use of *N*-chlorinated reagents or related electrophilic nitrogen species.[4] Amidst growing interest in "green" oxidation methods for organic synthesis, catalytic methods have been identified for N–N coupling that are capable of using O_2 as the terminal oxidant.[5] Recent examples include intramolecular reactions for the formation of pyrazoles and related heterocycles[5d,g] and Au- and Cu-catalyzed methods for aerobic oxidative coupling of anilines to azo compounds.[5b,e] These precedents and our interest in Cu-catalyzed aerobic oxidation reactions[6,7] prompted us to consider intermolecular N–N coupling reactions of *N*-substituted anilines, including carbazoles. Homodimeric 9,9'-bicarbazoles, such as Dixiamycin B[8] (cf. Scheme 1A), are found in nature and are also of interest in materials chemistry.[9] Previously reported methods for the preparation of these compounds feature stoichiometric oxidants, such as $KMnO_4$,[10] Ag_2O,[11] or dichromate,[12] in addition to a recent electrolysis method.[13] Here, we report a Cu-catalyzed aerobic oxidation method to access these molecules, as well as tetraarylhydrazines derived from diarylamines. Reactions between carbazole and diarylamine substrates undergo selective cross-coupling to afford unsymmetrical tetrasubstituted hydrazines (i.e., carbazole-diarylamines in Scheme 1B) in preference to the homocoupled dimers. The origin of this unusual selectivity is elucidated.

Scheme 1. A) N–N bonds found naturally and synthetically B) Intermolecular cross-coupling of nitrogen atoms.



We began our studies by using 3,6-di(*tert*-butyl)-carbazole **1a** as a model substrate, and a summary of results obtained from reactions performed with 20 mol% of a copper salt in combination with an ancillary ligand are provided in Table 1. Copper(II) salts were ineffective precatalysts (Table 1, entries 1 and 2), but moderate yields of 9,9'-bicarbazole **2a** were obtained when CuCl or CuBr was used in combination with 1,10-phenanthroline (entries 3 and 4). Use of CuBr·DMS instead of CuBr led to further improvement (entry 5). Assessment of other bidentate ligands revealed improved results with 2,2'-bipyridine (bpy; cf. entries 5-7), but two equivalents of an electron- rich monodentate ligand proved even more effective (entries 8-11), with the best results obtained with *N,N*-dimethylaminopyridine (DMAP) and *N*-methylimidazole (NMI) (entries 10 and 11). Further optimization of the CuBr·DMS/DMAP catalyst system led to formation of bicarbazole **2a** in 85% yield (70% isolated; cf. entry 12), with 10 mol% Cu loading at 60 °C. Good yields were also

observed in other solvents, including 1,2-dichloroethane (78%, entry 13) (see Supporting Information for full screening data).

Table 1. Optimization of carbazole dimerization.

1a **2a**

entry	Cu Source (mol%)	Ligand[a] (mol%)	Conversion (%)[b]	Yield (%)[b]
1	$Cu(OAc)_2$•H_2O (20)	phen (20)	18	2
2	$CuBr_2$ (20)	phen (20)	2	0
3	CuCl (20)	phen (20)	76	26
4	CuBr (20)	phen (20)	70	39
5	CuBr•DMS (20)	phen (20)	64	43
6	CuBr•DMS (20)	TMEDA (20)	63	38
7	CuBr•DMS (20)	bpy (20)	66	50
8	CuBr•DMS (20)	pyridine (40)	41	18
9	CuBr•DMS (20)	4-methoxypyridine (40)	44	33
10	CuBr•DMS (20)	DMAP (40)	87	72
11	CuBr•DMS (20)	NMI (40)	88	71
12[c]	**CuBr•DMS (10)**	**DMAP (20)**	**94**	**85 (70)**
13[c,d]	CuBr•DMS (10)	DMAP (20)	100	78

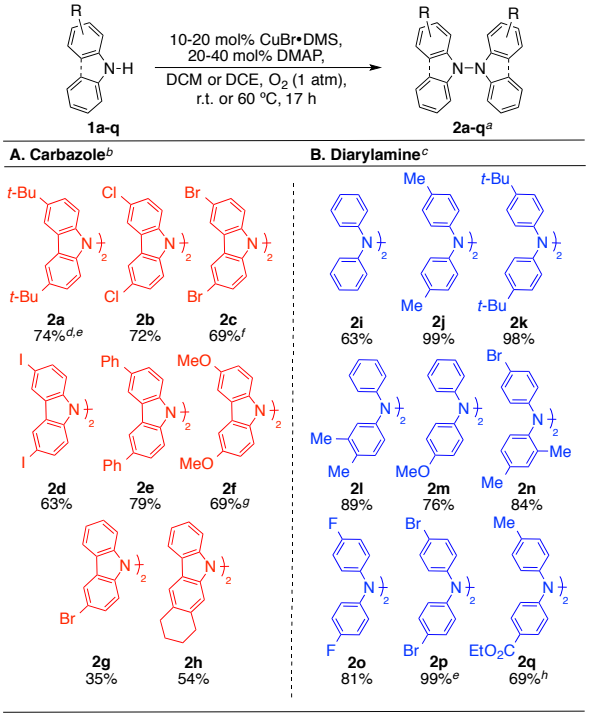
[a] phen = 1,10-phenanthroline, TMEDA = tetramethylethylenediamine, bpy = 2,2'-bipyridine, DMAP = 4-dimethylaminopyridine, NMI = *N*-methylimidazole. [b] Conversion and yield determined by ^{1}H NMR integration, using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield in parentheses. [c] Performed at 60 ºC for 17 h. [d] Performed in DCE.

Application of these catalytic conditions to other substrates showed that good yields of bicarbazoles could be obtained from carbazoles bearing both electron-withdrawing and electron-donating groups in the 3- and 6-positions (i.e., *para* to the nitrogen atom of the carbazole; cf. **2b-f**, Table 2A). 1,2-Dichloroethane proved to be the most effective solvent in these cases. Substrates lacking substitution in one or both of the 3- and 6-positions are susceptible to side reactions leading to C–N and C–C-coupled carbazole dimers and oligomers.[14] For example, the parent bicarbazole was obtained in < 30% yield (See Supporting Information, Table S7). Even in these cases, however, the desired N–N-coupled bicarbazoles could be readily isolated from side products, and products **2g** and **2h** were obtained in moderate yields (35% and 54%, respectively). The latter compound is noteworthy because it represents a structural analog of Dixiamycin B (cf. Scheme 1). The recently reported synthesis of this natural product by Baran and coworkers provides important context for the challenge associated with this type of N–N coupling.[13]

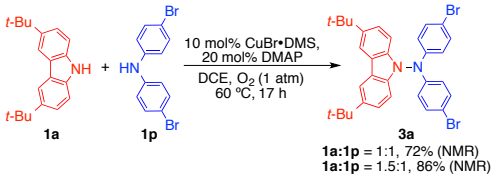
In general, aerobic oxidative dimerization of diarylamines proved to proceed under milder conditions and afford higher yields than the reactions of carbazoles (Table 2B). Precedents for this reaction are limited. Kajimoto et al. showed that N–N coupling of the parent diphenylamine could be achieved under aerobic conditions with stoichiometric CuCl,[15] and Knölker recently described an Fe(phthalocyanin) catalyst for aerobic oxidative N–N coupling of diarylamines.[5h,16,17] The present reactions were conducted at room temperature in DCM with 10 mol% CuBr·DMS and 20 mol% DMAP. Several substrates underwent conversion to the corresponding tetrarylhydrazine in near-quantitative yield (cf. **2j**, **2k**, **2p**), and oxidative coupling of bis(4-*tert*-butylphenyl)amine to **2k** was conducted on 1 g scale without impact on the isolated yield (98%). Good yields were observed with a number of the other substrates, including those with electron-donating and electron-withdrawing substituents (cf. **2j**, **2k** and **2n**, **2o**, **2p**, respectively), and the reactions were less affected by the lack of an aryl substituent *para* to the nitrogen atom (cf. **2i**, **2l**, **2m**). The unsymmetrical diarylamine, **1q**, required elevated temperature (60 °C) to reach completion.

Table 2. Substrate scope of carbazole and diarylamine dimerization.

[a] Numbers below refer to isolated yields. [b] 20 mol% CuBr·DMS, 40 mol% DMAP, DCE, 60 ºC [c] 10 mol% CuBr·DMS, 20 mol% DMAP, DCM, r.t. [d] 10 mol% CuBr·DMS, 20 mol% DMAP, DMF, 60 ºC. [e] Average isolated yield over three runs. [f] 80 ºC. [g] 10 mol% CuBr·DMS, 20 mol% DMAP. [h] 60 ºC, DCE.



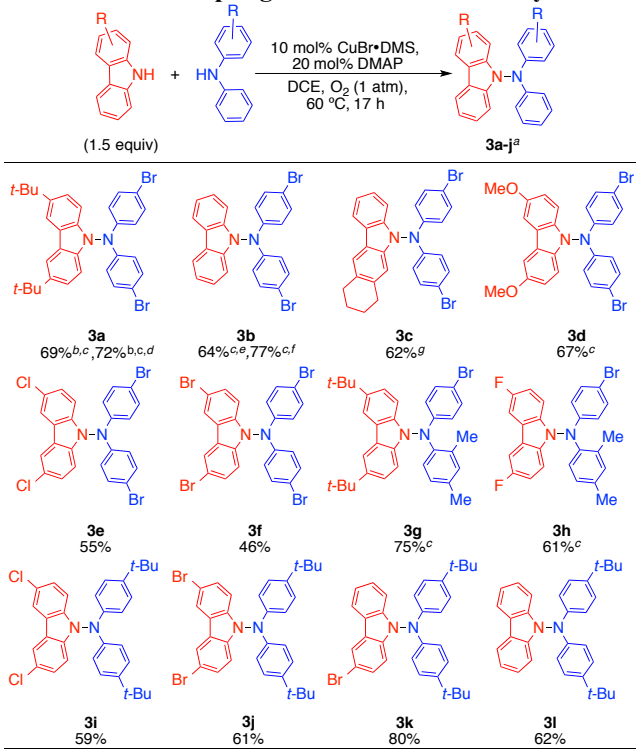
After demonstrating these homocoupling reactions, we evaluated prospects for cross-coupling. N–N cross-coupling reactions are rare, with precedents typically requiring use of one of the reaction partners in large excess to achieve formation of the desired product.[5e] A reaction of carbazole **1a** and diarylamine **1p** was tested in 1:1 stoichiometry under standard conditions (eq 1). A 72% yield of the cross-coupled product **3a** was observed, with a 10% yield of each homocoupled dimer. Use of a small excess of the carbazole (**1a**:**1p** = 1.5:1) led to formation of the cross-coupled product in 86% yield. In both cases, the cross-coupling selectivity far exceeds that expected from statistical product ratios.



(1)

Due to the paucity of synthetic methods available to create N–N cross-coupled products,[18] we explored the substrate scope of this reaction (Table 3). A 1.5:1 ratio of substrates was used to facilitate purification of the cross-coupled product. For example, product **3a** was obtained in a 69% isolated yield when using a 1:1.5 ratio of **1a**:**1p**. The parent carbazole was a poor substrate for oxidative homocoupling (see above), but it performed well as a cross-coupling partner, affording **3b** and **3l** in 64% and 62% yield, respectively. Product **3b** could be isolated in an improved 77% yield when the reaction was performed on a larger scale (1 g, 6 mmol carbazole). Both electron-rich and electron-deficient carbazoles were effective with bis(4-bromophenyl)amine **1p** as the coupling partner (cf. **3c**–**3f**). Halogen substituents are well-tolerated on both coupling partners (**3a**–**3k**), and the unsymmetrical diarylamine **1n** was an excellent cross-coupling partner, affording **3g** and **3h** in a 75% and 61% yields, respectively.

Table 3. Cross-coupling of carbazoles and diarylamines.



[a] Isolated yields. [b] 20 mol% CuBr·DMS, 40 mol% DMAP. [c] 1.5 equiv diarylamine. [d] Reaction performed in air. [e] Average isolated yield over three runs. [f] Isolated yield, 1 g (6 mmol) carbazole scale. [g] 0.1 mmol scale.

The selectivity observed in the carbazole/diarylamine cross-coupling reactions is generally better than that observed from the cross-coupling of two different diarylamines (Figure 1), and much higher than that observed in previously reported reactions of primary anilines.[5e] The latter reactions required a 5:1 ratio of aniline substrates to obtain moderate-to-good yields (42–73%) of cross-coupled azo compounds, ArN=NAr'. More systematic assessment of the different selectivities observed in the present cross-coupling reactions was probed by varying substrate ratios from 5:1 to 1:5 in each case (Figure 1).[19] In the reaction of carbazole **1a** with diarylamine **1p**, the yield of **3a** was relatively insensitive to the ratio of the coupling partners (Figure 1, red trace), showing significantly greater-than-statistical selectivity for cross-coupling under conditions with a 1:1 substrate ratio (73% yield of **3a**; the dashed line in Figure 1 shows the yield expected from a statistical ratio of products). Only a small excess of either substrate was needed to observe 80–90% yield of the cross-coupled product. The reaction of two different diarylamines also achieved greater-than-statistical selectivity (Figure 1, blue trace), albeit not as high as that observed in the carbazole/diarylamine coupling reaction (56% yield of **4a** at 1:1 ratio). Excellent yields of the tetraarylhydrazine cross-coupling product were obtained when excess of either partner was used (i.e., at 1:5 or 5:1 ratio).

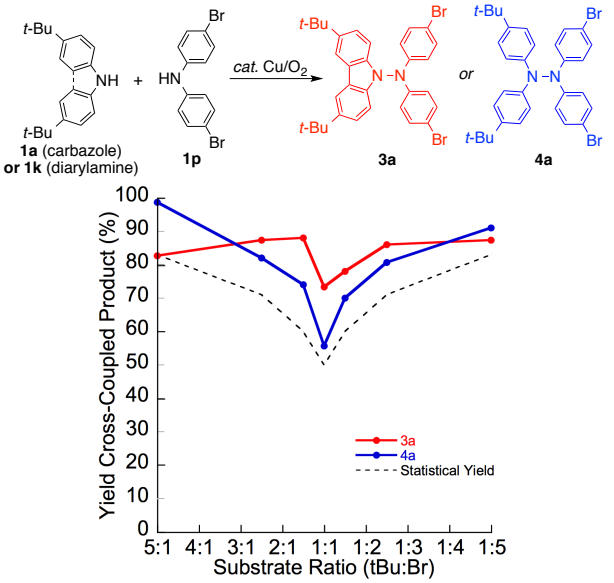


Figure 1. Dependence of cross-coupling yield on substrate stoichiometry. ^{1}H NMR yields, average of three runs. Conditions: (**3a**) 10 mol% CuBr·DMS, 20 mol% DMAP, DCE, O_2 (1 atm) 60 ºC, 17 h; (**4a**) 10 mol% CuBr·DMS 20 mol% DMAP, DCM, O_2 (1 atm) r.t., 17 h.

In order to gain further insight into the origin of the selectivity for **3a** in Figure 1, we analyzed a time course for the reaction between **1a** and **1p** by ^{1}H NMR spectroscopy (Figure 2). The diarylamine **1p** is consumed rapidly, generating the homocoupled tetraarylhydrazine **2p**. Initial formation of **2p** is consistent with the milder reaction conditions observed with diarylamines relative to carbazoles (cf. Table 2). The tetraarylhydrazine **2p** reaches a maximum concentration at ~40 minutes and then disappears with concomitant formation of the cross-coupling product **3a**. This observation indicates that formation of the N–N bond in **2p** is reversible under the reaction conditions, and **2p** is consumed by irreversible formation of the cross-coupled product **3a**. Control experiments reveal that N–N cleavage in **2p** is not promoted by copper and that N–N bond formation in **3a** is irreversible under the reaction conditions (Figure S6). The N–N bond in tetraarylhydrazines is quite weak (e.g., BDE = 23.5 kcal/mol for Ph_2N–NPh_2[20]), and homolytic cleavage of the tetraarylhydrazine N–N bond will generate aminyl radicals[21] capable of undergoing cross-coupling with the carbazole coupling partner. Irrespective of

mechanism, the observations show that preferential formation of the cross-coupled product **3a** over **2p** is thermodyanamically controlled. The cross-coupling selectivity for **4a** obtained from the reaction of **1k** and **1p** reflects an equilibrium preference for formation of the cross-coupled over the homocoupled tetraarylhydrazines.[22]

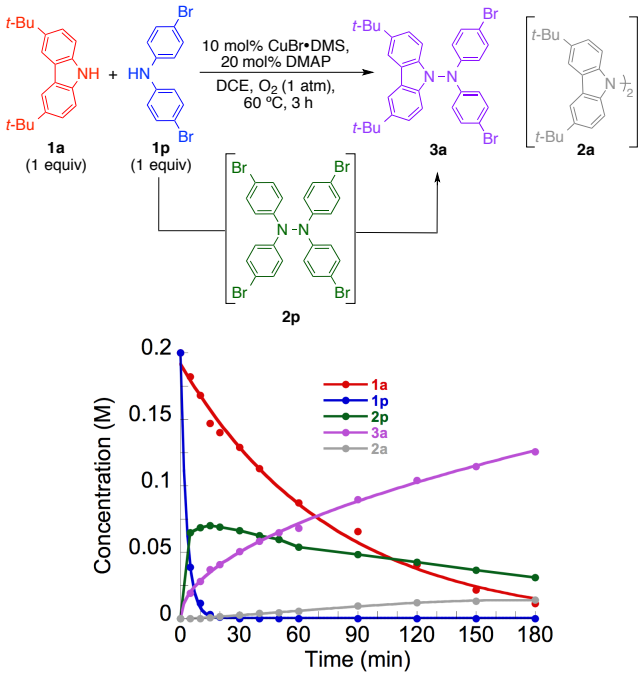


Figure 2. ^{1}H NMR time course of the cross-coupling of carbazole **1a** and diarylamine **1p**.

In conclusion, we have developed the first catalytic method for aerobic N–N coupling of carbazoles to 9,9′-bicarbazoles, and showed that similar conditions may be used for the coupling of diarylamines. Moreover, we have identified selective cross-coupling reactions of carbazoles and diarylamines, wherein the selectivity arises from reversible cleavage of the N–N bond in kinetically favored tetraarylhydrazine intermediates, ultimately generating the more stable carbazole-diarylamine products. The latter compounds have little precedent and warrant attention in medicinal and materials applications.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.
Experimental Procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interests.

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21. Evidence for *N*-centered radical formation under catalytic reaction conditions has been confirmed by EPR spectroscopy. See section X in the Supporting Information.

22. See Section IX in the Supporting Information for equilibration studies.

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