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Synthesis of Carbazoles by Copper-Catalyzed Intramolecular C−H/N−H Coupling

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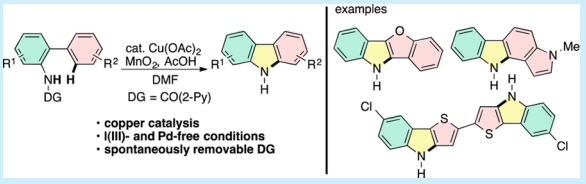
Supporting Information

ABSTRACT: A Cu-catalyzed intramolecular C−H amination for the synthesis of carbazoles has been developed. The key to success is the installation of the picolinamide-based directing group, which is spontaneously removed after the coupling event. The Cu catalysis proceeded smoothly under Pd- and I(III)-free conditions, and its mild oxidation aptitude enables the rapid and concise construction of heteroatom-incorporated carbazole core π-systems.



Carbazole nuclei are frequently occurring heteroaromatic cores in biologically active natural and unnatural products and functional organic materials.[1] Among numerous approaches to this important class of compounds, transition-metal-mediated intramolecular C−H amination of 2-aminobiphenyls has now received significant attention because of its higher step and atom economies. As pioneering work, Buchwald et al. reported a Pd-catalyzed intramolecular C−H amination of anilides in conjugation with a $Cu(OAc)_2$ oxidant, leading to the carbazole directly.[2] Subsequently, Gaunt developed a Pd/$PhI(OAc)_2$ system for similar transformations with *N*-alkyl aminobiphenyls.[3] Around the same time, Matsubara also developed a relevant Pt catalysis under hydrothermal conditions.[4] Additionally, Chang[5] and Antonchick[6] independently found a metal-free, I(III)-mediated carbazole formation from *N*-sulfonyl or -acetyl aminobiphenyls, in which a $Cu(OTf)_2$ additive[5] sometimes facilitated the reaction. Good alternatives involve an Rh-catalyzed intramolecular nitrene insertion reaction of 2-azidobiphenyls[7] and the Cadogan cyclization of 2-nitrobiphenyls[8] in the presence of transition metals such as Pd, Ru, or Mo under high CO pressure. Although these precedents can provide an efficient, facile route to the carbazole core, they rely on the noble catalysts (e.g., Pd, Pt, and Rh) or special hypervalent I(III) reagents. Moreover, the synthesis of heteroatom-containing carbazoles is not trivial, probably due to reaction conditions associated with strong oxidants such as $PhI(OAc)_2$. Thus, great demand still exists for further development of mild C−H amination catalysis for the synthesis of carbazoles. Herein, we disclose a picolinamide-directed, Cu-catalyzed intramolecular C−H amination for the synthesis of carbazole, under Pd- and I(III)-free conditions.[9] The picolinamide directing group is spontaneously removed after the coupling event, giving N−H carbazoles exclusively. Moreover, the catalyst turnover is achieved by a less expensive and abundant co-oxidant MnO_2 of mild oxidation aptitude, which is compatible with the formation of heteroatom-incorporated carbazoles of great interest in material science.[10]

On the basis of our recent studies on Cu-promoted C−H functionalization,[11,12] we initially examined suitable substituents on the nitrogen of 2-aminobiphenyl in *N*,*N*-dimethylformamide (DMF) with a stoichiometric amount of $Cu(OAc)_2$ and PivOH (Piv = *tert*-butylcarbonyl) as promoters (Table 1). Gratifyingly, we found the picolinoyl moiety,[13] which was originally developed by Daugulis,[13a] to be promising, and the desired N−H carbazole (**2a**) was obtained in 89% yield (entry 1). The substrate **1a** was readily accessible from the commercially available 2-bromoaniline and phenylboronic acid via the Suzuki−Miyaura coupling followed by condensation with picolinoyl chloride (see the Supporting Information (SI)). Other starting 2-aminobiphenyl derivatives **1** (vide infra) also can be easily prepared by the same procedure. The control experiments with *N*-benzoyl and N−H analogues (**1a-Bz** and **1a-H**, respectively) revealed the necessity of the coordinating pyridine ring in **1a** (entries 2 and 3). Additional investigation of acidic additives identified AcOH to be optimal, giving **2a** in 97% yield (entries 4 and 5). To render the reaction catalytic in Cu, we then tested a variety of co-oxidants in the presence of 20 mol % of $Cu(OAc)_2$ and 1.0 equiv of AcOH. After the extensive screening, MnO_2 was found to be a good candidate (entry 6), whereas other inorganic and organic oxidants were ineffective (entries 7−9). Unfortunately, an ideal oxidant, molecular oxygen, did not work well, forming **2a** in only 8% GC yield (data not shown). Elevating the temperature to 170 °C and increasing the concentration further improved the yield to 80% (entry 10). However, longer reaction periods (28 h) were essential to obtain good conversion, which caused a *N*-carbamoylation side reaction by DMF to form a significant amount of **2a-CONMe$_2$**. Pleasingly, we found that microwave irradiation (200 °C) dramatically accelerated the reaction much more cleanly, and **1a** was produced in 96% yield within 1 h, without formation of any detectable byproducts (entry 11). The reaction did not proceed at all in the absence of $Cu(OAc)_2$, confirming the Cu catalysis in the C−H amination (entry 12). Additionally notable is that the picolinoyl group on the nitrogen was spontaneously removed during the course of the reaction,

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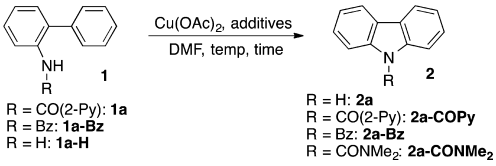
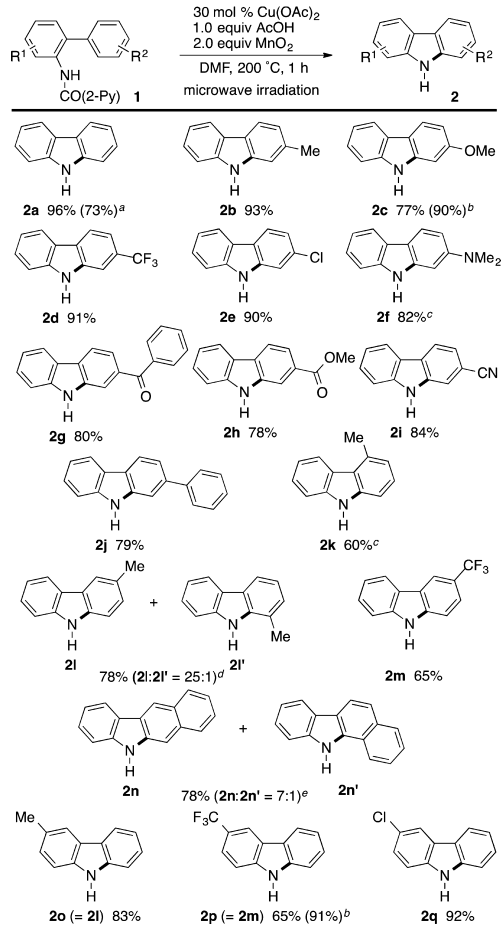
Table 1. Optimization Studies for Cu-Catalyzed Intramolecular C−H Amination of 2-Aminobiphenyls 1[a]



entry	1	$Cu(OAc)_2$ (mol %)	additives (equiv)	temp, time	2, % yield[b]
1	**1a**	200	PivOH (1.0)	150 °C 4 h	**2a**, (89)
2	**1a-Bz**	200	PivOH (1.0)	150 °C 4 h	**2a**, 0; **2a-Bz**, 0
3	**1a-H**	200	PivOH (1.0)	150 °C 4 h	**2a**, 0
4	**1a**	200	AcOH (1.0)	150 °C 4 h	**2a**, (97)
5	**1a**	200	none	150 °C 4 h	**2a**, 89
6	**1a**	20	AcOH (1.0) MnO_2 (2.0)	150 °C 4 h	**2a**, 21
7	**1a**	20	AcOH (1.0) $Na_2S_2O_8$ (2.0)	150 °C 4 h	**2a**, 0
8	**1a**	20	AcOH (1.0) $K_2S_2O_8$ (2.0)	150 °C 4 h	**2a**, 0
9	**1a**	20	AcOH (1.0) (*t*-BuO)$_2$ (2.0)	150 °C 4 h	**2a**, 11
10[c]	**1a**	20	AcOH (1.0) MnO_2 (2.0)	170 °C 28 h	**2a**, 80[d]
11[e]	**1a**	30	AcOH (1.0) MnO_2 (2.0)	200 °C 1 h	**2a**, (96)
12[e]	**1a**	0	AcOH (1.0) MnO_2 (2.0)	200 °C 40 min	**2a**, 0; **2a-COPy**, 0

[a]Reaction conditions: $Cu(OAc)_2$, additives, **1** (0.25 mmol), DMF (1.5 mL), N_2 (entries 1−5) or air (entries 6−12). [b]Yield estimated by GC method. Yield of isolated product given in parentheses. [c]In 0.75 mL of DMF. [d]*N*-Carbamoylcarbazole **2a-CONMe$_2$** was also detected. [e]Under microwave irradiation.

Scheme 1. Carbazole Products by Cu-Catalyzed Intamolecular C−H Amination of Various Aminobiphenyls (Formed C−N Bond Drawn as a Bold Line; Yield of Isolated Product Provided)



[a]Yield on a 2.5 mmol scale in parentheses. [b] Yield estimated by GC method is in parentheses. [c] $Cu(OAc)_2$ (200 mol %) without MnO_2. [d] Isolated as an inseparable mixture. [e] GC yield of a 7:1 mixture. The major isomer **2n** was isolated in 45% yield.

and the carbazole product was obtained almost in a free N−H form. In a few cases of Table 1, a small amount of **2a-COPy** was also detected by GC and GCMS analysis of the crude mixture, but it could be readily and completely transformed into **2a** upon workup with ethylenediamine (see the SI for the detailed procedure). This appears to be beneficial from the synthetic point of view since the removal of such directing groups is sometimes problematic and requires additional operations.

With the optimized conditions in hand, we first evaluated substitution effects on the right phenyl ring, i.e., R^2 (Scheme 1). The Cu catalysis was compatible with electronically diverse functional groups at the 4′ position, including electron-donating Me and OMe (**2b** and **2c**) as well as electron-withdrawing CF_3 and Cl (**2d** and **2e**). In the case of highly electron-donating and strongly coordinating (to Cu) NMe_2, 200 mol % of $Cu(OAc)_2$ was necessary for the completion of the reaction, and the removal of the directing group was accomplished only by additional treatment with aq. NaOH (**2f**; see the SI for the detailed procedure). Additionally, base-labile ketone, ester, and nitrile moieties were also tolerated under reaction conditions to form **2g**, **2h**, and **2i** in good yields. The Ph-substituted substrate underwent the C−H amination smoothly (**2j**). On the other hand, the introduction of the Me substituent at the 2′ position decreased the reaction efficiency, and a stoichiometric amount of $Cu(OAc)_2$ was required for a satisfactory conversion (**2k**). This is probably because the steric hindrance caused by the Me moiety interfered with the planar alignment of the left and right phenyl rings, which is critical in a cyclometalation step (vide infra).[14] When the Me and CF_3 groups were located at the 3′ position, the C−N bond formation predominantly occurred at the less congested position (**2l**, **2l′**, and **2m**). A similar trend was observed in the naphthalene system (**2n** and **2n′**). We subsequently prepared substrates that bear Me, CF_3, and Cl at the 5-position in the left ring and tested their reactivity. Regardless of the electronic nature, the Cu-catalyzed C−H amination proceeded effectively to form the corresponding 3-substituted carbazoles in 83−92% yields (**2o**, **2p**, and **2q**). Additionally notable are that the synthesis of **2a** on a 10-fold larger scale was possible and that the reaction could be set up on the benchtop and conducted without any special precautions related to air and moisture, indicating the good reproducibility and practicality of this catalysis. Moreover, the resultant N−H moiety can be a useful synthetic handle for further manipulations

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such as N-arylation and -vinylation by conventional Pd and Cu catalysts.

We next focused on the synthesis of heteroatom-incorporated condensed carbazoles (Figure 1). To our delight, the Cu catalyst

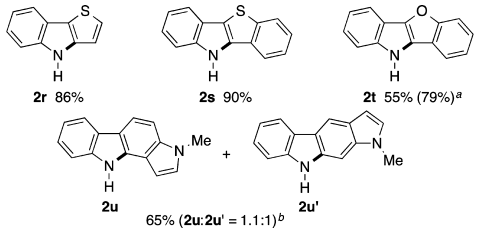
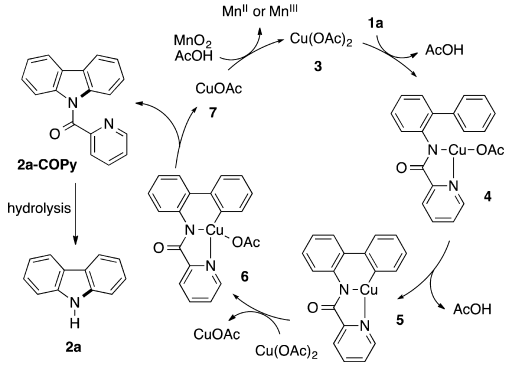


Figure 1. Pyrrole, thiophene, and furan-based *N,S-* *N,O-*, and *N,N-*heteroanthracene and tetracene prepared by the present Cu-catalyzed intramolecular C−H amination. The formed C−N bond was shown in a bold line. Yield of isolated product is shown. [a] The yield in parentheses is when $Cu(OAc)_2$ (200 mol %) is employed without MnO_2. [b] Both regioisomers **2u** and **2u′** were readily separated in 34% and 31% yields, respectively, by silica gel column chromatography.

accommodated the thiophene ring, and the thienoindole **2r** was isolated in 86% yield. Moreover, higher condensed S-, O-, and N-containing carbazole derivatives **2s**, **2t**, and **2u** (**2u′**) were also readily accessible. In the last case, both regioisomers **2u** and **2u′** were formed in a nearly 1:1 ratio but were readily separated by silica gel column chromatography. These results highlight the synthetic utility of this Cu/Mn process of mild oxidation aptitudes and deserve significant attention, because such carbazoles were a challenging substrate class in the precedented intramolecular C−H amination of 2-aminobiphenyl derivatives[2−8] despite their high potential in the field of material chemistry.[1]

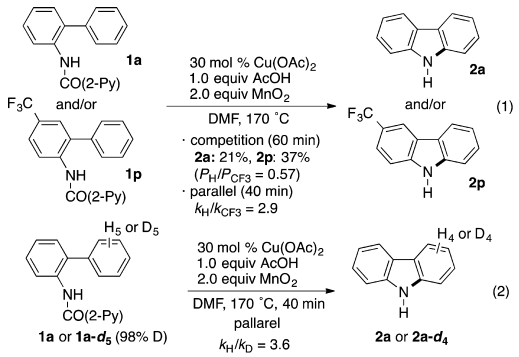
On the basis of our findings and literature, we propose the reaction mechanism of **1a** as illustrated in Scheme 2. Initial

Scheme 2. Plausible Mechanism



neutral and anionic *N,N*-bidentate coordination of the picolinamide moiety to the Cu^{II} **3** center forms the intermediate **4**. The results of control experiments with **1a-Bz** and **1a-H** (Table 1, entries 2 and 3) apparently support this chelation mode. Subsequent C−H cupration[15] (**4** → **5**) is followed by oxidation (disproportionation)-induced reductive elimination via Cu^{III} species **6**[16] to produce the carbazole **2a-COPy** together with a Cu^{I} complex **7**. The catalytic cycle is closed by the reoxidation of Cu^{I} **7** into the starting Cu^{II} **3** by MnO_2 and AcOH.[17] The initially formed **2a-COPy** spontaneously undergoes hydrolysis under the standard conditions to furnish the observed N−H carbazole **2a**. To better understand the above mechanism, the following kinetic studies were performed (Scheme 3).[18] The competition reaction of **1a** and **1p** resulted

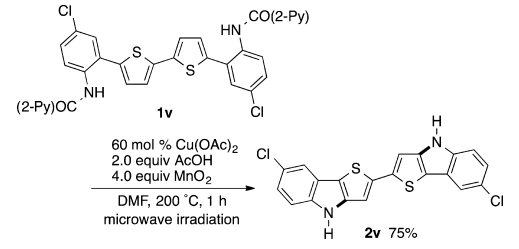
Scheme 3



in the preferable formation of **2p** over **2a**, whereas the parallel system afforded the higher reaction rate of **1a** than that of **1p** (eq 1). These phenomena suggest that the more acidic NH of **1p**[19] is deprotonated and coordinated to the Cu center more readily, but it cannot control the overall reaction rate. Namely, the *N,N*-bidentate coordination step might be the product-determining step but not the rate-determining step.[20] On the other hand, the kinetic experiments with **1a** and **1a-d_5** in the separate reaction vessels provided the major kinetic isotope effect (KIE) value of 3.6 (eq 2).[21] Thus, C−H cleavage would be involved in the rate-determining step. Although the exact role of external AcOH is not clear at present, the acetate-type ligand on the Cu is believed to accelerate the C−H cleavage step.[22] Further studies to reveal the detailed mechanism are ongoing.[23]

Finally, we applied the present Cu catalysis to the double cyclization of **1v** directed toward the bisthienodiindole framework **2v**, which is an intriguing *N,S*-based bisacene for highly performing organic transistors (Scheme 4).[24] Gratifyingly, the

Scheme 4. Synthesis of Bisthienoindole 2v by the Cu-Catalyzed Double C−N Forming Cyclization



reaction took place without any difficulties under identical conditions to deliver **2v** in 75% yield. Additionally, the resultant chloride moiety can be a useful synthetic handle for further expansion of π-systems.

In conclusion, we have developed a copper-catalyzed intramolecular C−H amination of 2-aminobiphenyls, in conjunction with an MnO_2 terminal oxidant, for the synthesis of carbazoles. The reaction is facilitated by the picolinamide-based bidentate directing group, which is spontaneously removed after the coupling event. Moreover, the mild oxidation aptitudes of the Cu/Mn system allow for the otherwise difficult C−H aminative construction of heteroatom-containing carbazole analogues. Further development of relevant Cu-based C−H activation catalysts is now in progress.

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■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) The ^{1}H NMR chemical shifts of NH in **1a** and **1p** are 10.30 and 10.50, respectively ($CDCl_3$, 25 °C).

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