

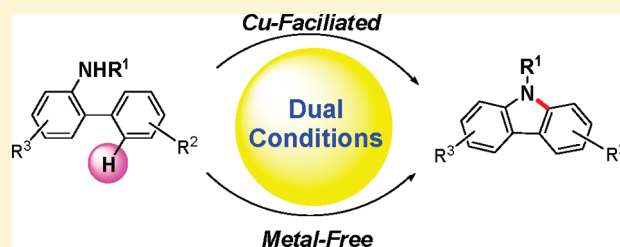
Intramolecular Oxidative C–N Bond Formation for the Synthesis of Carbazoles: Comparison of Reactivity between the Copper-Catalyzed and Metal-Free Conditions

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 Supporting Information

ABSTRACT: New synthetic procedures for intramolecular oxidative C–N bond formation have been developed for the preparation of carbazoles starting from *N*-substituted amidobiphenyls under either Cu-catalyzed or metal-free conditions using hypervalent iodine(III) as an oxidant. Whereas iodobenzene diacetate or bis(trifluoroacetoxy)iodobenzene alone undergoes the reaction to provide carbazole products in moderate to low yields, combined use of copper(II) triflate and the iodine(III) species significantly improves the reaction efficiency, giving a more diverse range of products in good to excellent yields. On the basis of mechanistic studies including kinetic profile, isotope effects, and radical inhibition experiments, the copper species is proposed to catalytically activate the hypervalent iodine(III) oxidants. The synthetic utility of the present approach was nicely demonstrated in a direct synthesis of indolo[3,2-*b*]carbazole utilizing a double C–N bond formation.



INTRODUCTION

Direct installation of nitrogen groups into hydrocarbons, without relying on prefunctionalization of the simple compounds to the corresponding organic (pseudo)halides, is a highly attractive synthetic strategy as an atom-economic and environmentally benign method for C–N bond formation. While an approach based on nitrenoid transfer to C–H bonds was extensively investigated by using Rh, Ru, or Pd catalysts,¹ oxidative amination of alkenes or (hetero)arenes has been scrutinized only in recent years.^{2,3} In this context, Buchwald disclosed an efficient route to carbazoles starting from 2-acetamidobiphenyl under Pd-catalyzed oxidative conditions.⁴ In addition, Gaunt elegantly utilized a postulated Pd(II)/Pd(IV) catalytic cycle for the preparation of carbazoles under mild oxidative conditions,⁵ and its success was attributed to the facile reductive elimination of aminoaryl palladium(IV) intermediates, leading to C–N bond formation (Scheme 1).^{6–8} In this regard, while much effort has been devoted to the development of Pd-catalyzed oxidative C–H/N–H couplings, *alternative and/or complementary methods using more practical metal catalysts such as Cu species or metal-free conditions are less investigated.*

In recent years, copper catalysts have come to be regarded as a promising alternative in metal-catalyzed oxidative coupling reactions to replace costly metal species such as Pd and Rh.^{9,10} A postulated organocopper(III) intermediate in the catalytic cycle of copper species enabled numerous important organic transformations such as arylation, alkenylation, and alkynylation reactions.¹¹ Based on these observations, we initially envisaged that a

proper combination of copper species and oxidants would promote an intramolecular oxidative C–N bond formation of *N*-substituted amidobiphenyls to give carbazoles by taking advantage of the high electrophilicity of presumed Cu(III) intermediates.¹² We herein describe our new finding that *carbazole synthesis can indeed be facilitated by the action of a copper catalyst under oxidative conditions, revealing that the copper species works as an activator of the iodine(III) oxidants employed.* In addition, we also discovered that *oxidative C–N bond formation is possible even in the absence of copper species, although the reaction efficiency is lower under metal-free conditions.*¹³ Since carbazole is an important structural motif having a diverse range of applications, such as bioactive alkaloids (Figure 1)^{14,15} and electronic materials,¹⁶ new practical synthetic methods for the preparation of carbazoles are highly desired.

RESULTS AND DISCUSSION

To test our initial hypothesis of the Cu-catalyzed intramolecular C–N bond formation, *N*-substituted amidobiphenyl derivatives **1a–c** were subjected to various reaction conditions (Table 1). When 2-acetamidobiphenyl (**1a**) was used as a substrate, no conversion was observed under the conventional oxidative conditions using O₂ or peroxides in the presence of copper(II) triflate species (entries 1 and 2). In a sharp contrast, the use of PhI(OAc)₂ as an oxidant significantly improved the

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Scheme 1. Oxidative Carbazole Synthesis via C–H/N–H Couplings

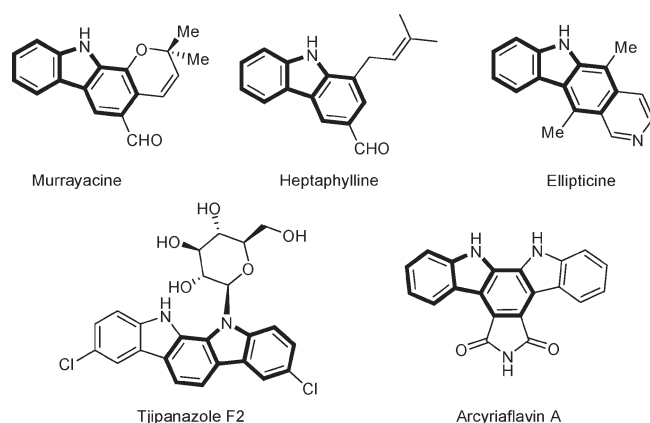
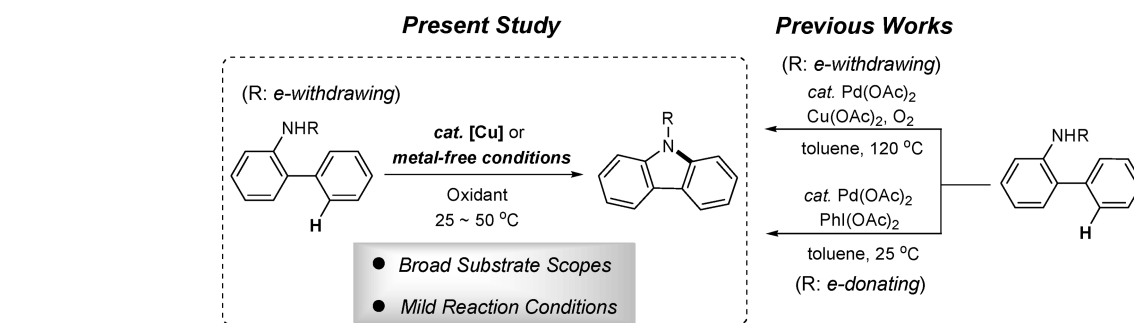


Figure 1. Biologically active alkaloids bearing a carbazole motif.

reaction efficiency to provide *N*-acetylcarbazole in 63% yield within 10 min at 50 °C (entry 3).

Changing the *N*-substituent from an acetyl to a sulfonyl group (**1b**) further increased the product yield (entry 4). In particular, the addition of an acid additive such as acetic acid also enhanced the reaction efficiency (entry 5). When trifluoroacetic acid was employed as an additive, 9-benzenesulfonyl carbazole was isolated in excellent yield within 10 min at 50 °C (entry 6). Importantly, the reaction proceeded smoothly even at room temperature, albeit with a slight decrease of the product yield (entry 7). Cu(OTf)₂ was proved to be the choice of catalyst since other copper sources showed lower efficiency (entry 8). On the other hand, introducing an electron-donating *N*-substituent in the substrate (e.g., **1c**) deteriorated the reaction progress (entry 9).

Further investigation of the reaction conditions revealed that the C–N bond formation took place even in the absence of copper catalysts to some extent (entry 10). Moreover, when *N*-sulfonylamidobiphenyl (**1b**) was used as a substrate, the reaction efficiency was greatly increased up to 75% NMR yield in the presence of an acid additive when PhI(OTFA)₂ was employed instead of PhI(OAc)₂ (entry 11).^{17,18} This observation that a significant amount of background reaction is operative under metal-free conditions is highly noteworthy, considering the previous reports that the oxidative cyclization of *N*-substituted amidobiphenyls required a palladium catalyst in combination with certain external oxidants such as Cu(II)/O₂ or PhI(OAc)₂, revealed by Buchwald^{14b} and Gaunt,⁵ respectively (Scheme 1).

In order to elucidate how the copper species is involved in our cyclization procedures, we first carried out a comparison experiment

Table 1. Optimization of Oxidant and Additives^a

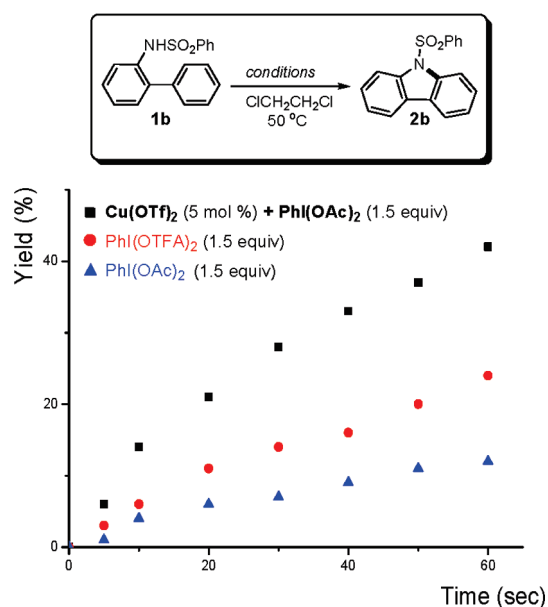
| entry | R ¹ | catalyst | oxidant | additive | yield (%) ^b |
|-----------------|----------------------------------|----------------------|------------------------|----------------------|------------------------|
| 1 ^c | Ac (1a) | Cu(OTf) ₂ | O ₂ (1 atm) | — | <1 |
| 2 ^c | 1a | Cu(OTf) ₂ | <i>t</i> -BuOOBz | — | <1 |
| 3 | 1a | Cu(OTf) ₂ | PhI(OAc) ₂ | — | 63 |
| 4 | SO ₂ Ph (1b) | Cu(OTf) ₂ | PhI(OAc) ₂ | — | 74 |
| 5 | 1b | Cu(OTf) ₂ | PhI(OAc) ₂ | CH ₃ COOH | 84 |
| 6 | 1b | Cu(OTf) ₂ | PhI(OAc) ₂ | CF ₃ COOH | 93 (90) ^d |
| 7 ^e | 1b | Cu(OTf) ₂ | PhI(OAc) ₂ | CF ₃ COOH | 75 |
| 8 | 1b | Cu(OAc) ₂ | PhI(OAc) ₂ | CF ₃ COOH | 20 |
| 9 | Me (1c) | Cu(OTf) ₂ | PhI(OAc) ₂ | CF ₃ COOH | <1 |
| 10 ^f | 1b | — | PhI(OAc) ₂ | CF ₃ COOH | 40 |
| 11 ^f | 1b | — | PhI(OTFA) ₂ | CF ₃ COOH | 75 (75) ^d |
| 12 ^f | 1a | — | PhI(OTFA) ₂ | — | 9 |
| 13 ^f | 1a | — | PhI(OTFA) ₂ | CF ₃ COOH | 38 |

^a Reaction conditions: substrate (**1**, 0.2 mmol), Cu catalyst (5 mol %), oxidant (1.5 equiv), and additive (3.0 equiv) in 1,2-dichloroethane for 10 min at 50 °C. ^b NMR yield of **2** (internal standard: 1,1,2,2-tetrachloroethane). ^c Carried out for 12 h. ^d Isolated yield in parentheses. ^e Carried out at 25 °C for 30 min. ^f Conditions: substrate (**1**, 0.2 mmol), oxidant (1.5 equiv), and additive (3.0 equiv) in 1,2-dichloroethane for 10 min at 50 °C.

to see the initial rate difference (*within 1 min*) between the Cu-catalyzed and metal-free conditions (Scheme 2). It was observed that copper species (5 mol %) significantly accelerated the reaction rate compared to the metal-free conditions using PhI(OAc)₂ oxidant alone. On the other hand, the use of PhI(OTFA)₂ instead of PhI(OAc)₂ improved the reaction efficiency, but it was still significantly lower than under the Cu-catalyzed conditions. Therefore, it is evident that the copper species plays a pivotal role in facilitating the C–N bond formation under the employed catalytic conditions.

The above result that significant conversion took place even under metal-free conditions left us with an important question about the exact role of copper catalyst in combination with the hyperiodine(III) oxidant, especially with regard to our initial postulation of the Cu(I)/Cu(III) catalytic cycle.¹⁹ In order to gain mechanistic insights to answer this question, we undertook

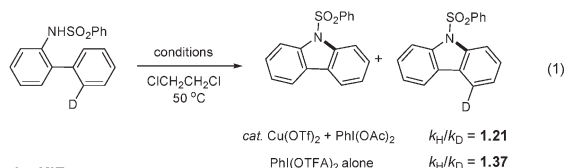
Scheme 2. Initial Rates in the Cu-Catalyzed and Metal-Free Reaction Conditions



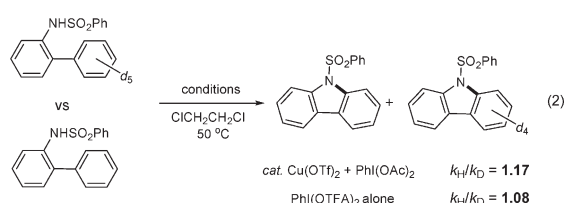
detailed studies of (i) kinetic isotope effects, (ii) kinetic profile of each reactant under either Cu-catalyzed or metal-free conditions, and (iii) effects of radical scavengers.

Intra- and intermolecular kinetic isotope effects (KIE, k_H/k_D) were readily obtained using deuterium-labeled substrates (eqs 1 and 2). No significant intramolecular isotopic effect was observed, and k_H/k_D values were similar under either Cu-catalyzed (1.21) or metal-free conditions (1.37). Likewise, negligible KIE values were determined in the case of intermolecular experiments (1.17 and 1.08, respectively). These negligible KIE values indicate that C–H bond cleavage of a phenyl moiety for the C–N bond formation may not be involved in the rate-determining step during the course of carbazole synthesis. Interestingly, our observation is distinct from the recently developed Cu-catalyzed intramolecular C–H amination of *N*-aryl-2-aminopyridines in the synthesis of pyrido[1,2-*a*]benzimidazoles, in which the intramolecular KIE was measured to be 2.4.^{10f}

Intramolecular KIE



Intermolecular KIE



We next carried out kinetic profile studies to determine the order of reaction components in the present carbazole synthesis. Initial rates were monitored upon changing the concentration of each reactant using 2-acetamidobiphenyl (**1a**) and hypervalent

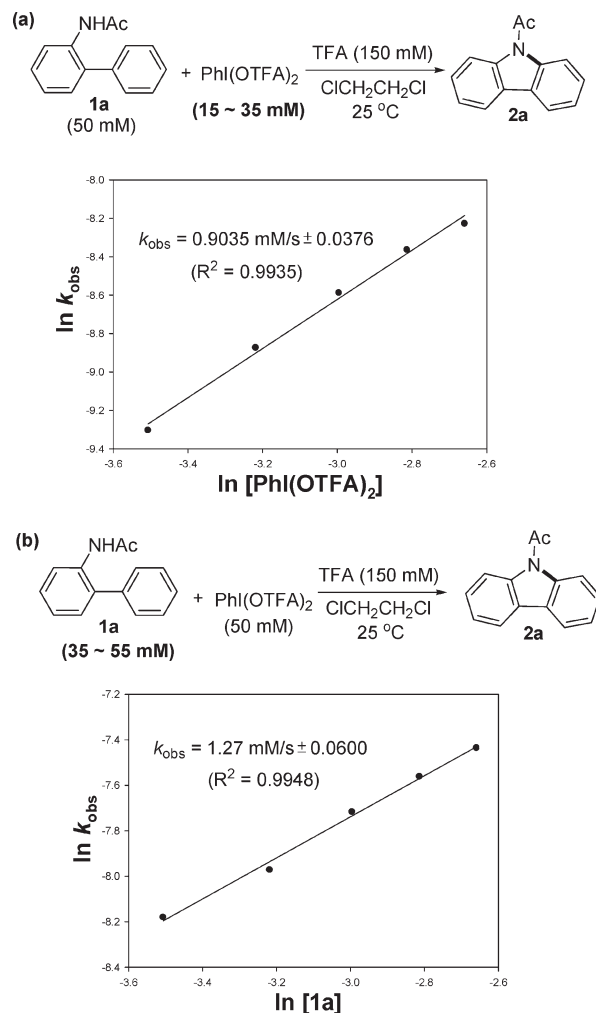


Figure 2. Plot of initial rates versus concentration of (a) oxidant $\text{PhI}(\text{OTFA})_2$ and (b) substrate **1a** under metal-free conditions.

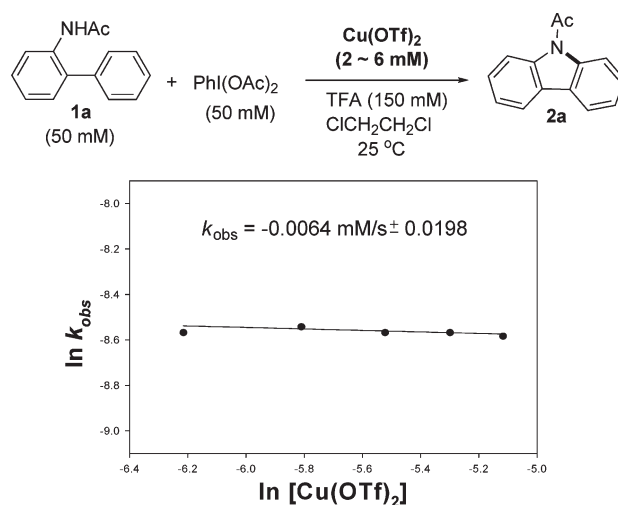


Figure 3. Plot of initial rates of copper species.

iodine(III) as substrate and oxidant, respectively (see Supporting Information for experimental details). NMR analysis was carried out by taking aliquots from the reaction mixture at regular

intervals. As shown in Figure 2, the reaction exhibited approximately first-order dependence on both $\text{PhI}(\text{OTFA})_2$ and substrate **1a** under metal-free conditions.

Kinetic profiles of the copper species were also obtained to show that the cyclization proceeded almost independently with regard to the concentration of $\text{Cu}(\text{OTf})_2$ in the range of 2–6 mol % at room temperature, suggesting that the copper species are not involved in the rate-limiting step (Figure 3).

It was initially envisaged that the cyclization could be promoted by generating plausible $\text{Cu}(\text{III})$ intermediates under oxidative conditions since those higher oxidation states of copper species were known to be highly electrophilic,^{11a–d,19} facilitating the subsequent aromatic attack on the metal center. However, the observed kinetic insensitivity to the copper species led us to challenge our initial postulation. Instead, we now propose that *the copper species works as a Lewis acid to activate hypervalent iodine(III) oxidants.*²⁰ In fact, very recently, Gaunt et al. reported that a *meta*-selective arylation of α -aryl carbonyl compounds proceeds even in the absence of copper catalysts, albeit at higher temperatures compared to Cu-catalyzed conditions.²¹ This result is especially noteworthy in that the reaction was originally proposed to be catalyzed at ambient temperature by a copper(III) species.^{11e}

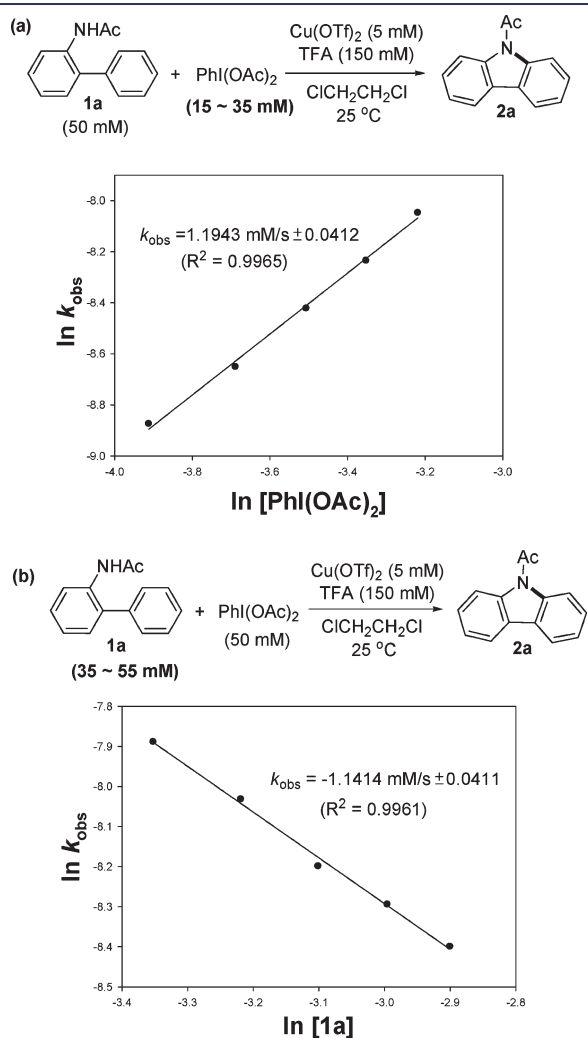


Figure 4. Plot of initial rates versus concentration of (a) oxidant and (b) substrate **1a** under Cu-catalyzed conditions.

Table 2. Effects of Radical Inhibitor on the Reaction Efficiency^a

| Entry | Radical Scavenger | cat. $\text{Cu}(\text{OTf})_2$ + $\text{PhI}(\text{OAc})_2$ | $\text{PhI}(\text{OTFA})_2$ only |
|-------------------------------------|-------------------|---|----------------------------------|
| Yield of 2b (%) ^b | | | |
| 1 | — | 93 | 75 |
| 2 ^c | | 5 | 3 |
| 3 ^c | BHT | 11 | 9 |

^a Reaction conditions: **1b** (0.2 mmol), $\text{Cu}(\text{OTf})_2$ (5 mol %, if necessary), oxidant (1.5 equiv), CF_3COOH (3 equiv), and radical scavenger (1.0 equiv) in 1,2-dichloroethane for 10 min at 50 °C. ^b NMR yield of **2b** (internal standard: 1,1,2,2-tetrachloroethane). ^c Carried out for 24 h.

The kinetic order of oxidant $\text{PhI}(\text{OAc})_2$ was next measured to be first-order under the Cu-catalyzed conditions (Figure 4a), indicating that the oxidant participates most likely in the rate-limiting step, as already seen in the metal-free conditions (Figure 2a). On the other hand, it was highly intriguing to observe that the initial reaction was inhibited upon increasing the substrate concentration (Figure 4b). This inverse order dependence of substrate implies that a complex, presumably in a resting stage, may form by the interaction of copper species with substrate, and its formation suppresses the Lewis acidic behavior of the copper employed. A similar inverse order on a substrate was previously found in the metal-catalyzed hydroamination of alkenes and alkynes, in which a slimmer type of resting state of substrate-bound complex was assumed to form, thus slowing down the reaction progress.²²

A radical inhibition test was next carried out in order to get insight into whether the reaction proceeds via radical intermediates. When 1,1-diphenylethylene or 2,6-di-*tert*-butyl-4-methylphenol (BHT), which are both known to be effective radical scavengers, was added to the reaction mixture, the reaction progress was significantly decreased under either the Cu-catalyzed or metal-free conditions, and only poor product yields were obtained, even after longer reaction times, suggesting that our present oxidative C–N bond-forming reaction involves radical intermediates (Table 2).

Based on the above experimental mechanistic data, a plausible pathway for the oxidative carbazole synthesis is proposed in Scheme 3, although more comprehensive experiments are required in order to describe exact mechanistic details. Initially, 2 equiv of the biphenylamido substrate is presumed to bind reversibly to a metal center to form a tetradentate copper species (**3**), and the subsequent step is proposed to form an *N*-iodoamido species (**4**) upon release of acetic acid and $\text{Cu}(\text{OTf})_2$ which is ready to participate in the next cycles.^{17b,c,f} In fact, it was previously reported that certain Lewis acids facilitate the conversion of hypervalent iodine(III) reagents in a number of reactions.¹⁸ In accordance with the above radical inhibition experiments, the following electrophilic aromatic attack of the *ortho*-phenyl group onto an amido moiety of **4** is presumed to occur via a radical

Scheme 3. Proposed Mechanistic Pathway

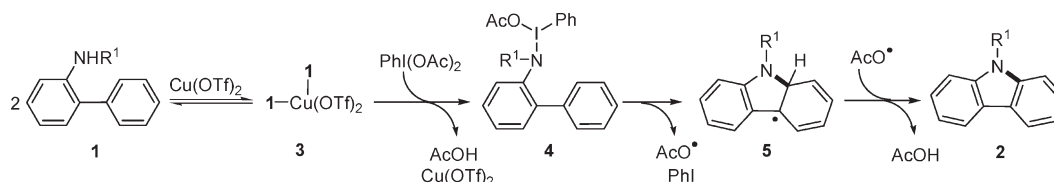


Table 3. Screening of Various Additives

| entry | additive (equiv) | yield (%) ^b |
|-------|--|------------------------|
| 1 | — | 40 |
| 2 | Cu(OTf) ₂ (0.05) | 93 |
| 3 | BF ₃ ·Et ₂ O (1.0) | 47 |
| 4 | TMSOTf (1.0) | 25 |
| 5 | Zn(OAc) ₂ (0.05) | 15 |
| 6 | Zn(OTf) ₂ (0.05) | 55 |
| 7 | Fe(OTf) ₂ (0.05) | 59 |
| 8 | Sc(OTf) ₃ (0.05) | 68 |
| 9 | CF ₃ SO ₃ H (0.1) | 44 |
| 10 | CF ₃ SO ₃ H (1.0) | 30 |

^a Reaction conditions: **1b** (0.2 mmol), additive (indicated equiv), PhI(OAc)₂ (1.5 equiv) and trifluoroacetic acid (3.0 equiv) in 1,2-dichloroethane for 10 min at 50 °C. ^b NMR yield of **2b** (internal standard: 1,1,2,2-tetrachloroethane).

pathway to generate a radical species (**5**). The final step of the carbazole synthesis would most likely be H-abstraction from **5** by an *in situ*-generated acetoxyl radical.^{17c}

Since the oxidative cyclization exhibits a first-order rate dependence on the employed oxidant irrespective of the presence of copper species, it is reasonable to assume that the formation of a key intermediate (**4**) is involved in the rate-determining step. On the other hand, under the metal-free conditions, the *N*-iodo intermediate **4** is expected to form in one step directly from a bimolecular reaction between substrate **1** and iodine(III) species, and the rate of its formation in the absence of copper species is lower compared to that of the Cu-mediated reaction, as shown in Scheme 2.

The above mechanistic consideration, especially with respect to the role of copper species working as a Lewis acid to activate hypervalent iodine(III) oxidants, is further examined by performing additional experiment on the effects of other Lewis acids under otherwise the same reaction conditions (Table 3). It was observed

that, while the most frequently used Lewis acid BF₃·Et₂O displayed little effects (entry 3), some Lewis acids retarded the conversion (entries 4 and 5). Interestingly, certain metal Lewis acids containing trifluoromethanesulfonate as a ligand increased the reaction efficiency (entries 6–8), albeit to a lower extent compared to the presently employed copper triflate (entry 2). Although we cannot rule out the possibility of ligand exchange between Cu(OTf)₂ and PhI(OAc)₂ to generate an active iodine species,²³ a moderate product yield (entries 9 and 10) was obtained when trifluoromethanesulfonic acid was employed as an additive. This result indicates that Cu(OTf)₂ itself plays a role to activate the PhI(OAc)₂ oxidant for the facile oxidative transformation.

However, other mechanistic possibilities can also be conceived (e.g., Scheme 4), in which an aromatic cation radical (**7**) is generated by a single electron transfer, presumably through a charge-transfer π -complex (**6**), as proposed by Kita et al.¹⁸ In fact, it was demonstrated that aromatic cation radicals can be induced when hypervalent iodine(III) reagents react with electron-rich arenes such as *para*-substituted phenol ethers,^{18a} thiophenes,^{18c} or naphthalene derivatives.^{18f} In those cases, it was shown that subsequent trapping of the aromatic cation radicals by certain nucleophiles such as TMSN₃ or mesitylene provided the corresponding coupled adducts with high efficiency.

Substrate Scope and Reactivity Pattern. In the present oxidative C–N bond formation, the combined use of Cu(OTf)₂ catalyst and PhI(OAc)₂ oxidant showed much improved reaction efficiency compared to the corresponding metal-free conditions, in which employment of PhI(OTFA)₂ gave higher product yields than PhI(OAc)₂. Therefore, we set up two experimental procedures to apply for a wide range of substrates: (i) the use of PhI(OAc)₂ oxidant in the presence of Cu(OTf)₂ catalyst for 10 min at 50 °C, and (ii) employment of PhI(OTFA)₂ alone in the absence of copper species for 10 min at the same temperature.

In general, the catalytic carbazole synthesis proceeded smoothly with substrates bearing electron-donating substituents (R²) at the “right” side nucleophilic phenyl part (Table 4, entries 2–5 and 7). In those cases, the cyclization was quite facile, even at room temperature (entries 2–5). It is especially noteworthy that *not only N-sulfonyl but also N-acetyl groups can be readily utilized in the reaction, both giving reasonable product yield at ambient temperature* (entry 3), thus

Scheme 4. Alternative Mechanistic Route

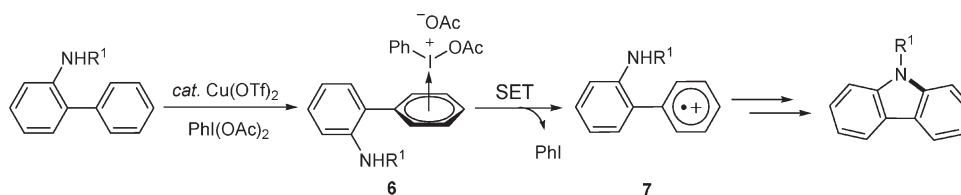


Table 4. Scope of the “Right” Side (R^2) Aromatic Ring

$\text{1} \xrightarrow[\text{25} \sim \text{50 } ^\circ\text{C, 10 min}]{\text{ClCH}_2\text{CH}_2\text{Cl, conditions}} \text{2}$

| Entry | Substrate | Product | Cu-Catalyzed ^a | Metal-Free ^{b,c} |
|----------------|-----------|---------|---------------------------|---------------------------|
| | | | Yield (%) ^d | |
| 1 ^e | (1b) | (2b) | 90 | 75 (40) |
| 2 | (1c) | (2c) | 91 ^f | 75 (20) |
| 3 | (1d) | (2d) | 66 ^f | 20 (20) |
| 4 | (1e) | (2e) | 89 ^f | 68 (31) |
| 5 | (1f) | (2f) | 80 ^f | 64 (25) |
| 6 ^e | (1g) | (2g) | 63 | 61 (17) |
| 7 | (1h) | (2h) | 65 | 15 (8) |
| 8 ^e | (1i) | (2i) | 53 | 9 (8) |

^a Conditions: **1** (0.2 mmol), Cu(OTf)₂ (5 mol %), and PhI(OAc)₂ (1.5 equiv) in 1,2-dichloroethane for 10 min at 50 °C. ^b Conditions: **1** (0.2 mmol) and PhI(OTFA)₂ (1.5 equiv) in 1,2-dichloroethane for 10 min at 50 °C. ^c Yields in parentheses were determined using PhI(OAc)₂ (1.5 equiv) as oxidant. ^d Isolated yield. ^e 3 equiv of CF₃COOH was used. ^f Carried out at 25 °C.

demonstrating that the reaction is highly flexible with respect to the substrate type. In contrast, electron-withdrawing substituents at the same “right” side exhibited lower reactivity, giving satisfactory product yields only in the presence of trifluoroacetic acid additive (e.g., entries 6 and 8). Interestingly, *single regioisomers were exclusively generated from substrates having substituents at the 5-position, and this selectivity was maintained regardless of electronic properties of those substituents* (entries 7 and 8).

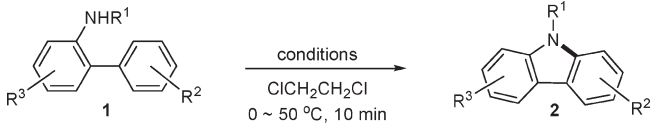
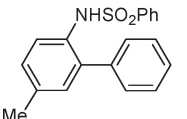
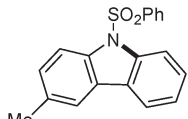
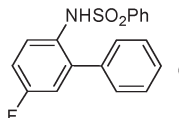
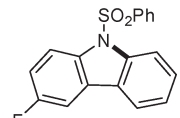
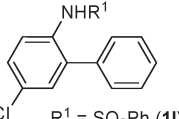
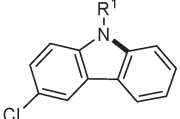
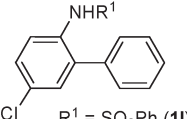
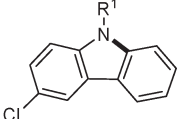
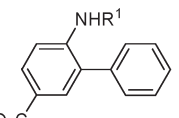
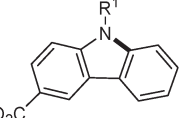
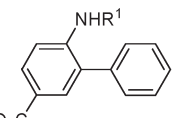
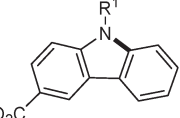
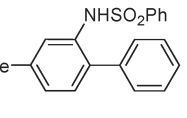
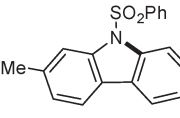
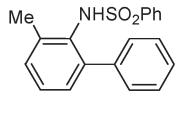
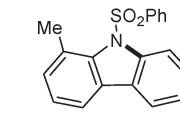
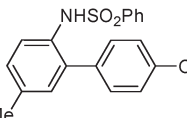
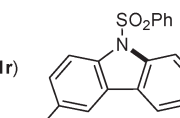
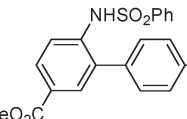
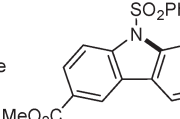
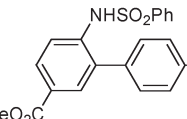
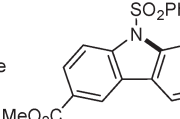
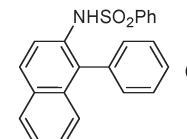
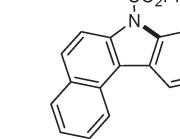
In comparison, product yields are generally lower under the employed metal-free conditions. The difference is more significant in the reaction of 2-acetamido-4'-methoxybiphenyl (**1d**, entry 3) or substrates bearing substituents at the 5-position (entries 7 and 8). It should also be pointed out that the PhI(OTFA)₂ oxidant gave significantly higher product yields than PhI(OAc)₂ in many cases,

but still lower than that those obtained under Cu-catalyzed conditions in all cases investigated.

It was observed that the reactivity pattern of the “left” amido-containing aryl part was opposite to that of the “right” phenyl side, and electron-withdrawing substituents on that portion facilitate the cyclization (Table 5, entries 1–6). The metal-free conditions using PhI(OTFA)₂ alone offered product yields comparable to those obtained under Cu-catalyzed conditions, especially in the cyclization of substrates bearing electron-withdrawing substituents on the “left” side (entries 2, 3, 5, and 6).

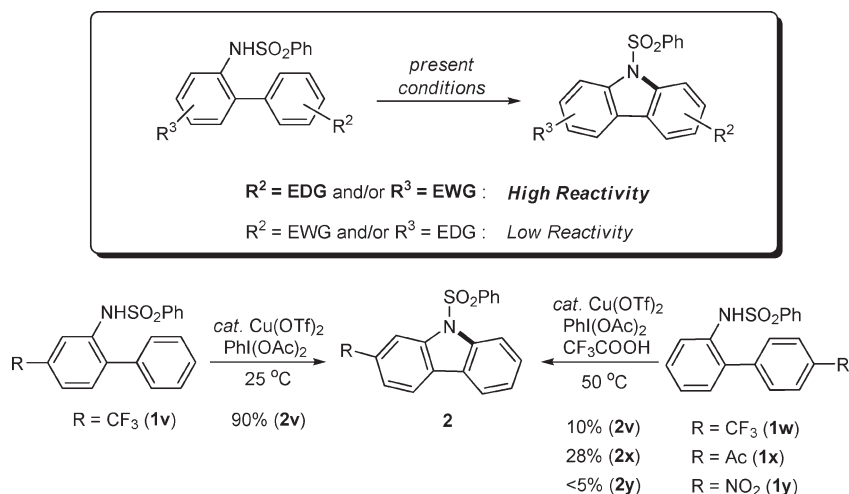
However, reaction of *N*-acetylamido substrates was rather sluggish under metal-free conditions (entry 4). Disubstituted carbazoles could be readily obtained in good yields (entries

Table 5. Scope of the “Left” Side (R^3) Amidoaryl Ring

|  | | | | |
|--|--|--|---------------------------|------------------------------------|
| Entry | Substrate | Product | Cu-Catalyzed ^a | Metal-Free ^{b,c} |
| | | | Yield (%) ^d | |
| 1 ^e |  (1j) |  (2j) | 59 | 34 (20) |
| 2 ^e |  (1k) |  (2k) | 66 | 95 (20) |
| 3 ^e |  (1l) |  (2i) | 87 | 87 (59) |
| 4 ^e |  (1m) |  (2m) | 72 | 44 (19) |
| 5 |  (1n) |  (2n) | 98 ^f | 98 (78) |
| 6 |  (1o) |  (2o) | 93 ^f | 86 (74) |
| 7 ^e |  (1p) |  (2p) | 60 | 29 (27) |
| 8 ^e |  (1q) |  (2q) | 47 | 15 (20) |
| 9 ^e |  (1r) |  (2r) | 87 | 55 (43) |
| 10 |  (1s) |  (2s) | 98 ^f | 64 (90) |
| 11 |  (1t) |  (2t) | 71 ^g | 35 ^f (64 ^f) |
| 12 ^e |  (1u) |  (2u) | 53 | 36 (34) |

^a Conditions: **1** (0.2 mmol), Cu(OTf)₂ (5 mol %), PhI(OAc)₂ (1.5 equiv) in 1,2-dichloroethane for 10 min at 50 °C. ^b Conditions: **1** (0.2 mmol), PhI(OTFA)₂ (1.5 equiv) in 1,2-dichloroethane for 10 min at 50 °C. ^c Yield in parentheses was determined using PhI(OAc)₂ (1.5 equiv) as an oxidant. ^d Isolated yield. ^e 3 Equiv of CF₃COOH was used. ^f Carried out at 25 °C. ^g Carried out at 0 °C.

Scheme 5. Generalized Reactivity Pattern

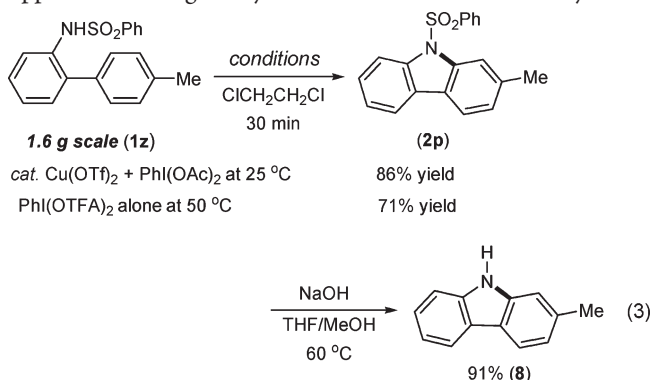


9–11). A benzocarbazole derivative was obtained in moderate yield upon the reaction of 1-phenyl-2-naphthalenyl-sulfonamide (entry 12). It is noteworthy that the reaction proceeded smoothly at room temperature (entries 5, 6, and 10) or even at 0 °C (entry 11) for certain substrates under Cu-catalyzed conditions, while lower conversion was observed under metal-free conditions at the same temperatures.

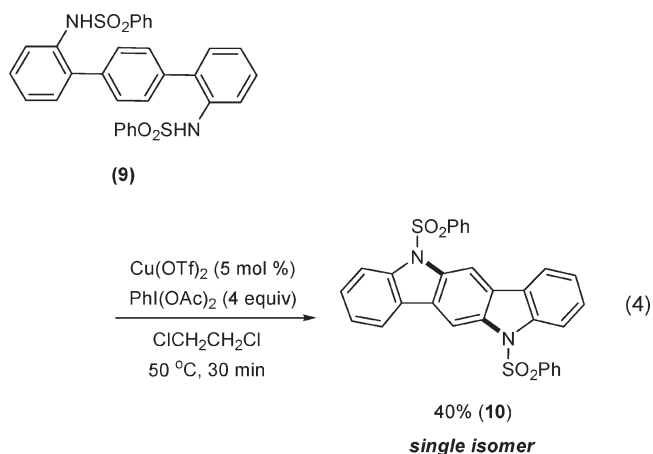
On the basis of the above observations, a reactivity pattern of amidobiphenyl substrates can be depicted as shown in Scheme 5. It can be generalized that the electronic influences of substituents on the “right” and “left” aryl sides are complementary to each other under both Cu-catalyzed and metal-free conditions. High product yield is attained with substrates bearing electron-donating groups (R^2) at the “right” phenyl part and/or electron-withdrawing substituents (R^3) at the amido-containing “left” aryl side. In contrast, poor reactivity was found with substrates having electron-withdrawing groups (R^2) at the “right” phenyl side and/or electron-donating substituents (R^3) at the “left” amidoaryl position. Importantly, this electronic propensity can be reflected in a flexible synthesis of substituted carbazoles. For instance, 3-trifluoromethyl *N*-sulfonylcarbazole can be envisioned to be prepared via two routes, depending on the position of the CF_3 substituent. Whereas the reaction of 2-benzensulfonylamido-4'-(trifluoromethyl)biphenyl (**1w**) resulted in poor conversion as predicted by the above reactivity pattern, the use of 2-benzensulfonylamido-4-(trifluoromethyl)biphenyl (**1v**) dramatically improved the cyclization efficiency in accordance with the general reactivity pattern, thus providing the desired product **2v** in high yield under either Cu-catalyzed or metal-free conditions.

The present oxidative cyclization procedure for the preparation of carbazoles could readily be scaled up to gram quantity without difficulty (eq 3). When 2-benzensulfonylamido-4-methylbiphenyl (**1z**) was employed as a test substrate, the cyclization took place smoothly under either Cu-catalyzed (at room temperature) or metal-free conditions (at 50 °C) to provide the desired carbazole in good yields. *N*-Desulfonylation of the obtained carbazole **2p** was successfully achieved under the conventional basic conditions, leading to 2-methylcarbazole (**8**) in high yield. This easy removal of *N*-protecting groups such as sulfonyl as well as acetyl moieties gives further

merit to the present methodology, allowing a broad range of applications in organic synthesis and medicinal chemistry.¹⁵



In addition, the present protocol could be applied to the one-step synthesis of *N*-protected indolo[3,2-*b*]carbazole, which is known to be an active component in a number of electronic devices such as light emitting diodes (LEDs),^{24a} field effect transistors (FETs),^{24b} and organic thin-film transistors (OTFTs).^{24c} When 2,2'-bis(sulfonamide)-*p*-terphenyl (**9**) was subjected to the developed Cu-catalyzed conditions using 4 equiv of PhI(OAc)_2 , the anticipated double cyclization took place to afford 5,11-dibenzensulfonyl-5,11-dihydroindolo[3,2-*b*]carbazole (**10**) as a single isomer in moderate yield (eq 4).



CONCLUSION

In summary, we have developed an intramolecular oxidative C–N bond-forming reaction of *N*-substituted 2-amidobiphenyls for the synthesis of carbazoles under mild conditions. Surprisingly, it was observed that the cyclization took place readily under both Cu-catalyzed and metal-free conditions, although product yields were generally lower in the latter case. While bis-(trifluoroacetoxy)iodobenzene alone can be used as an oxidant for the corresponding carbazole synthesis, a combined use of copper(II) triflate and phenyliodonium diacetate offered a more diverse range of products with higher efficiency. A series of mechanistic studies including kinetic isotope effects, reaction rate profile, and radical inhibition experiments led us to propose that the employed copper species catalyzes the activation of hypervalent iodine(III) oxidants, leading to more facile C–N bond formation. Considering its excellent reaction efficiency, wide substrate scope, and very mild reaction conditions, the present intramolecular oxidative C–N bond formation will be an attractive route to the practical synthesis of carbazoles and other related nitrogen-containing heterocycles. Detailed mechanistic studies as well as extension of the present protocol to an intermolecular version are now underway.

EXPERIMENTAL SECTION

Representative Procedure for the Copper-Catalyzed Carbazole Synthesis (Table 4, Entry 1, Compound 2b). To an oven-dried 10 mL round-bottom flask, equipped with a magnetic stir bar, were added 2-benzenesulfonamidobiphenyl (61.9 mg, 0.2 mmol), Cu(OTf)₂ (3.6 mg, 5 mol %), and CF₃COOH (46 μ L, 0.6 mmol, 3.0 equiv) in 1,2-dichloroethane (1.0 mL). A solution of PhI(OAc)₂ (96.6 mg, 0.3 mmol) in 1,2-dichloroethane (1.0 mL) was slowly added over 5 min. After the reaction mixture was stirred for 10 min at 50 °C, the crude mixture was filtered through a plug of Celite and then washed with EtOAc (20 mL). The crude residue was purified by flash column chromatography on silica gel to afford 9-benzenesulfonylcarbazole in 90% yield (55.3 mg): mp 121–123 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.80 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 8.1 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 138.3, 137.9, 133.7, 129.0, 127.4, 126.42, 126.39, 123.9, 120.0, 115.1; IR (film) 3060, 1600, 1443, 1370, 1175, 978, 752 cm⁻¹; HRMS (EI⁺) *m/z* calcd for C₁₈H₁₃NO₂S [M]⁺ 307.0667, found 307.0667.

Representative Procedure for the Metal-Free Carbazole Synthesis (Table 5, Entry 3, Compound 2i). To an oven-dried 10 mL round-bottom flask, equipped with a magnetic stir bar, were added 2-benzenesulfonylamido-5-chlorobiphenyl (68.5 mg, 0.2 mmol) and CF₃COOH (46 μ L, 0.6 mmol, 3.0 equiv) in 1,2-dichloroethane (1.0 mL). A solution of PhI(OTFA)₂ (129 mg, 0.3 mmol) in 1,2-dichloroethane (1.0 mL) was slowly added over 5 min. After the reaction mixture was stirred for 10 min at 50 °C, the crude mixture was filtered through a plug of Celite and then washed with EtOAc (20 mL). The crude residue was purified by flash column chromatography on silica gel to afford the 9-benzenesulfonyl-3-chlorocarbazole in 87% yield (59.5 mg): mp 146–148 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.31 (d, *J* = 8.5 Hz, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 7.85–7.83 (m, 2H), 7.80–7.77 (m, 2H), 7.54–7.42 (m, 3H), 7.38–7.30 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 138.8, 137.5, 136.6, 134.0, 129.8, 129.1, 128.1, 127.8, 127.4, 126.4, 125.3, 124.2, 120.2, 119.9, 116.2, 115.2; IR (film) 2919, 1599, 1443, 1410, 1372, 1177, 1091, 925, 730 cm⁻¹; HRMS (EI⁺) *m/z* calcd for C₁₈H₁₂ClNO₂S [M]⁺ 341.0277, found 341.0277.

ASSOCIATED CONTENT

S Supporting Information. Detailed experimental procedures and characterization of new compounds, including ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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