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Straightforward Access to Novel Indolo[2,3-b]indoles via Aerobic Copper-Catalyzed [3 + 2] Annulation of Diarylamines and Indoles

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Herein, we reported an unprecedented aerobic copper-catalyzed [3 + 2] annulation reaction of diarylamines with indoles, which allows direct access to novel 2-diarylaminoindolo[2,3-*b*]indoles, a class of potential photoelectric device molecules. The developed transformation proceeds with broad substrate scope, good functional group tolerance, high chemo-selectivity, and no need for pre-preparation of specific agents, which offers a practical way for diverse and atom-economic synthesis of the desired products that are difficult to prepare with the conventional approaches.

Indole-fused heterocyclic motifs are extensively distributed in functional products such as natural alkaloids, pharmaceuticals, agrochemicals, and functional materials.^{1,2} Over the past decades, although significant advances have been made on the functionalization of indolyl C2, C3 and other positions under transition metal catalysis,³ there are only limited examples focusing on simultaneous functionalization two indolyl sites. For instance, the Yang and Davies groups have successively reported the [3 + 2] cycloaddition reactions of substituted indoles with 2-aryl-N-tosylaziridines (Scheme 1, eq. 1)⁴ or Nsulfonyl-1,2,3-triazoles (eq. 2).⁵ Recently, an electrooxidative [3+2] annulation between phenol and indole derivatives was demonstrated by Lei et al (eq. 3).⁶ These representative examples have offered useful platforms to access polycyclic indoles.

Here, it is important to note that, as class of structurally unique ring-fused indoles, indolo[2,3-*b*]indoles have been found to exhibit a broad spectrum of applications, including electroluminescent devices,⁷ organic semiconductor⁸ and electronic devices.⁹ In general, the synthesis of indolo[2,3*b*]indoles mainly relies on a the Suzuki cross-coupling of 3intramolecular reductive cyclization (Scheme 1, eq. 4).⁷ In recent years, several strategies have also been nicely developed, which offer alternative ways to access the related compounds.¹⁰ Despite the significant utility of these protocols, many of them suffer from one or more limitations, such as the need for pre-preparation of specific coupling agents, poor total product yields, the use of noble metal catalysts and wastegenerating reductants. In this context, the development of shortcuts for the synthesis of indolo[2,3-*b*]indoles, especially for those of structurally novel ones from readily available feedstocks with naturally abundant catalyst system, would be of important significance in scientific community, as it would offer the potential for the discovery of new functional products with original chemical and physical properties.

halogenated indoles with 2-nitroarylboronic acids followed by



Scheme 1 Previous [3 + 2] annulation of indoles and the new work.

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As our sustained efforts toward the construction of Nheterocycles,¹¹ we have recently reported an aerobic coppercatalyzed synthesis of benzimidazoles from diaryl and alkylamines via tandem triple C-H aminations.^{11a} This work motivated us to trap the aryl radical cation arising from single electron oxidation (SEO) of diphenylamine 1a by 1methylindole 2a. However, we observed that, instead of the anticipated 3-arylated indole 3aa', a 2-diphenylamino indolo[2,3-b]indoles 3aa was observed in 10% yield (Scheme 1, eq. 5). Based on this finding, we wished herein to report, for the first time, an aerobic copper catalyzed [3+2] annulation of diarylamines with 1-methylindoles, which offers а straightforward approach for efficient synthesis of novel indolo[2,3-b]indoles.

Table 1 Optimization of the reaction conditions.^a



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	Entry	Catalyst	Solvent	Additive	Yield% of 3aa ^b
	1	CuCl	CH ₃ CN	-	trace
	2	$CuCl_2$	CH ₃ CN	-	18
	3	Cu(OTf) ₂	CH ₃ CN	-	0
	4	$CuBr_2$	CH ₃ CN	-	0
	5	CuF_2	CH ₃ CN	-	trace
	6	$CuCl_2$	toluene	-	16
	7	$CuCl_2$	<i>p</i> -xylene	-	24
	8	$CuCl_2$	chlorobenzene	-	23
	9	$CuCl_2$	1,4-dioxane	-	(32, 40, 28) ^c
	10	$CuCl_2$	1,4-dioxane	-	47 ^d
	11	$CuCl_2$	1,4-dioxane	Na ₂ CO ₃ (1 eq.)	trace d
	12	$CuCl_2$	1,4-dioxane	Zn(OTf) ₂ (1 eq.)	0 <i>d</i>
	13	$CuCl_2$	1,4-dioxane	3 Å MS (20 mg)	60 ^d
	14	$CuCl_2$	1,4-dioxane	3 Å MS (10 mg)	66 ^d
	15	$CuCl_2$	1,4-dioxane	3 Å MS (5 mg)	45 ^d

^a Reaction conditions: unless otherwise stated, all the reactions charged with an O₂ balloon were performed with 1a (0.50 mmol), **2a** (0.25 mmol), catalyst (20 mol %), additive (indicated amount), solvent (1.5 mL) at 80 °C for 16 h; ^b isolated yield; ^c yields are with respect to the catalyst loading of 20 mol %, 30 mol %, 40 mol %, respectively; ^d 2a (0.375 mmol), CuCl₂ (30 mol %).

To formulate a more efficient reaction system, the synthesis of 2-diarylaminoindolo[2,3-b]indole 3aa from diphenylamine 1a and 1methylindole 2a was chosen as a model system to screen different reaction parameters (Table 1, and Table S1-S7 in Electronic Supporting Information (ESI)). Initially, we evaluated several copper catalysts and solvents (Table 1, entries 1-9), the results showed that all of them were inferior to CuCl₂ and 1,4-dioxane, and 30 mol % of catalyst was sufficient for the reaction (entry 9). Slight increase of indole amount (2a) was able to improve the isolated yield to 47% (entry 10). Thus, CuCl₂ and 1,4-dioxane were chosen as the preferred combination to further test the influence of additives (entries 11 and 12). The results showed that the introduction of both base and Lewis acid had detrimental influence on the product formation (entries 11 and 12). Gratifying Prite 1880 1806 00138 Å molecular sieve (MS) in the reaction further improved the yield to 60% (entry 13), and 10 mg was sufficient to obtain a satisfactory isolated yield (entry 14). Thus, the optimal conditions are as shown in entry 14 of Table 1 when 10 mg of MS was introduced.

With the availability of the optimal reaction conditions, we then evaluated the generality of the synthetic protocol. First, a wide array of diarylamines 1 in combination with 1-methylindole 2a were tested. As shown in Scheme 2, all the reactions proceeded smoothly and furnished the desired 2-diarylaminoindolo[2,3-b]indoles 3 in moderate to good yield upon isolation (3aa-3ka). Various functional groups (i.e. -Me, -Ph, -F, -Cl, -Br, -CO₂Et) on diarylamines 1 were well tolerated, and the electronic property of these substituents influenced the product yield to some extent. Especially, diarylamines 1 containing a strong electron-withdrawing group afforded the products 3ha in relatively low yield, presumably because the electron-deficient diarylamine disfavors the formation of requisite intermediates via single electron oxidation. Noteworthy, all the reactions utilizing unsymmetrical diarylamines (1b-1j) occurred selective C-H amination and cyclization on the nonsubstituted aryl ring. In addition to the para C-H amination via homo-coupling of diarylamines 1, the reaction of two different diarylamine 1k and 1a also smoothly coupled with indole 2a, affording the cross-coupling product 3ka, exclusively.



Scheme 2 Variation of diarylamines. ^a 1a/1k = 1:1.

Subsequently, we tested the variation of indoles coupling partners. Thus, the reactions of various indoles 2 and diphenylamine **1a** was performed under the standard conditions. As illustrated in Scheme 3, all the reactions underwent smooth dehydrogenative C-H amination and annulation, affording the 2-

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diarylaminoindolo[2,3-b]indoles 3 in moderate to good isolated yield. First, different N-alkyl indoles, including the one containing easily oxidative allylic group (2d), are well compatible with the transformation (3ab-3ae). Then, the halogen-substituted indoles also smoothly coupled with diphenylamine 1a to give the desired products in reasonable yields (3af-3ah). In comparison, the estersubstituted indole (3i) gave much lower yield (3ai), this phenomenon is assigned to the ester functionality reducing the electron-density of indole skeleton, thus disfavouring the coupling and cyclization processes. As expected, indoles with electrondonating substituents efficiently reacted with 1a and delivered the desired products (3aj-3am). Noteworthy, N-non-substituted indoles are not compatible with the transformation, as such substrates can easily undergo oxidative decomposition under the present catalyst system. The reaction utilizing lilolidine **3m** generated the polycyclic product 3am in 40% yield, which has demonstrated the potential of the developed chemistry in further construction of complex indolefused N-heterocycles.



Scheme 3 Variation of indoles.

In effort to gain mechanistic insights into the reaction, we conducted several control experiments. As illustrated in Scheme 4, interruption of the model reaction after 1 h led to observe a small amount of homo-coupling product **1aa**, arising from the aryl *para* C–H amination of **1a** with another molecule of **1a**. Thus, we treated compound **1aa** and indole **2a** under the standard conditions. The reaction resulted in product **3aa** in high yield (eq. 1), which indicates that **1aa** is a key reaction intermediate. Then, the addition of excess TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) to the model reaction significantly decreased the product yield (eq. 2), suggesting that the reaction involves radical intermediates.

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However, the *para*-site-blocked diarylamine **1k** was whethen the couple with indole **2a** to yield product **3ka**- \mathfrak{P} (Eq. 3)) suggesting that the first aryl C–H amination *para* to the N-atom of **1a** plays a decisive role on the formation of the product, which occurs prior to the annulation process.





Further, electron paramagnetic resonance (EPR) experiments were designed to reveal more details of the radical information (see ESI for details). As shown in Figure 1, the treatment of CuCl₂ and 3 Å molecular sieve under the standard conditions for 30 min exhibited an EPR signal of the copper complex (g = 2.09899) (Figure 1, black line), arising from the coupling of the unpaired electron of Cu^{II} with its nuclear spin (d⁹, S = 1/2, I = 3/2).¹² The addition of diphenylamine **1a** to $CuCl_2$ caused a new weak radical signal (g = 1.99645), this change is attributed to the single electron transfer from 1a to Cu^{II}, which results in an EPR active radical intermediate (red line). Then, the addition of N-methylindole 2a to CuCl₂ did not exhibit a significant change in the signal, suggesting that the reaction initiating with an indolyl radical is less likely. As expected, the introduction of both reactants 1a and 2a to CuCl₂ caused a quick quench of the signal of active radical intermediate (green line), showing that the radical arising from **1a** takes part in the reaction.



Figure 1 Electron paramagnetic resonance (EPR) spectra.

Based on the above findings, a plausible reaction pathway is depicted in Scheme 5. The single electron oxidation (SEO)¹³ of diphenylamine **1a** under aerobic copper catalysis initially forms aryl radical cation, which is trapped by the amino group of another molecular of diphenylamine. Then, the SEO of the coupling adduct

followed by deprotonations forms the *para* C–H amination product **1aa**.^{11a} Similarly, the SEO of **1aa** results in an aryl radical cation **1aa'**, which reacts with indole nucleophile **(2a)** *in situ* and affords the coupling adduct **3aa-1**. The subsequent intramolecular nucleophilic addition of the amino group to the iminium motif of **3aa-1** forms radical **3aa-2** via deprotonation. Finally, the desired product **3aa** is generated via aerobic copper-catalyzed SEO and deprotonation of **3aa-2** followed by dehyroaromatization of **3aa-3**.



Scheme 5 Plausible reaction pathways.

In summary, through a new aerobic copper-catalyzed [3 + 2] annulation reaction of diarylamines and indoles, we have straightforward synthesis of novel developed а 2diarylaminoindolo[2,3-b]indoles with structural diversity. The developed chemistry proceeds with the striking features broad substrates, good functional tolerance, high chemo-selectivity, excellent step and atom-efficiency, and no need for pre-installation of specific coupling agents, the use of naturally abundant Cu/O₂ catalyst system, which offers a practical platform for diverse synthesis of the desired products that are difficult to prepare with the conventional approaches. The developed chemistry is expected to spur others to consctruct valuable N-heterocycles via single electron oxidation induced C-H functionalization, and discover new functioanl products including optoelectronic materials.

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Conflicts of interest

There are no conflicts to declare.

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