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N-Methyl Transfer Induced Copper-Mediated Oxidative Diamination of Alkynes

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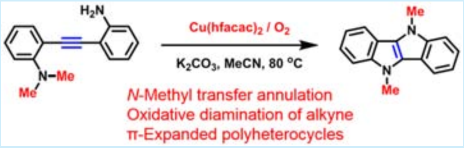
Supporting Information

ABSTRACT: A novel intramolecular oxidative diamination of bis(2-aminophenyl)acetylene for the synthesis of the structurally intriguing π-conjugated polyheterocyclic scaffold, 5,10-dihydroindolo[3,2-*b*]indole (DHII), has been developed under Cu(hfacac)$_2$/O$_2$ oxidation systems. The structure design of bis(2-aminophenyl)acetylene bearing both *N*,*N*-dimethylamine and primary amine groups is crucial for constructing the corresponding DHII scaffold. Notably, an intermolecular *N*-methyl transfer from the nitrogen atom of *N*,*N*-dimethylamine to the primary amine takes place, which is a critical step for the successful implementation of the present annulation process.



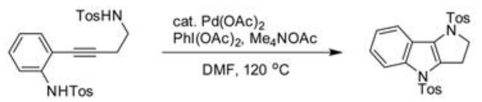
N-Methyl transfer annulation
Oxidative diamination of alkyne
π-Expanded polyheterocycles

The diamination of C−C multiple bonds provides one of the most effective and straightforward approaches for construction of vicinal diamine components which are important functional frameworks in numerous biologically active compounds and chemically significant molecules.[1,2] However, compared with those well-established direct diamination reactions of alkenes,[1] the diamination of alkynes has been far less developed.[3] The successful diamination of alkynes is anticipated to provide efficient synthetic methodologies for facile construction of various functionally important nitrogen-containing polyheterocycles from readily available chemical building blocks, which still remains challenging. Nonetheless, a few examples toward direct diamination of alkynes has been reported.[3] For example, a sole example of intramolecular alkyne diamination was first reported by Muñiz in his pioneering study of alkene diamination,[3a] in which *N*-tosylated 2-(4-aminobut-1-yn-1-yl)aniline was found to proceed in the oxidative diamination in the presence of a Pd-catalyst and hypervalent iodine oxidant to form a 1,2,3,4-tetrahydropyrrolo[3,2-*b*]indole structure (Scheme 1a). As of late, Zhu and co-workers have demonstrated that 2-(*N*,*N*-dimethylamino)-phenylethynyl benzamides underwent the demethylation-accompanied intramolecular alkyne diamination under the Pd-cayalyzed aerobic conditions to give the tetracyclic indoloisoquinolinone scaffold (Scheme 1b).[3c,d]

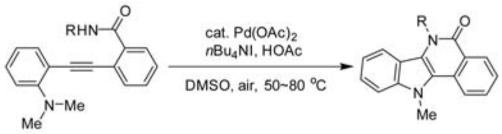
In light of the logical progression on the direct alkyne diamination toward heterocycle synthesis,[3] we envisaged that if bis(2-aminophenyl)acetylene having an appropriate *N*-protecting group is used as a substrate under aerobic conditions, the π-conjugated tetracyclic 5,10-dihydroindolo[3,2-*b*]indole (DHII) scaffold would be formed through a direct intramolecular diamination of an alkyne (Scheme 1c), while the related transformations have rarely been reported.[3a,c] Owing to the electron-rich and facile oxidizing natures of the DHII scaffold, the DHII-containing materials have been widely applied in organic electronics[4] including prototypical polaronic ferromagnetic materials,[4a,b] organic photovoltaics,[4c−e] and organic light-emitting diodes.[4f] DHIIs are also expected to exhibit potential biological activities due to the existence of the indole moiety.[4g] In general, the DHII scaffold could be synthesized by the reduction of 2,2′-dinitrobenzil with a Zn or Sn reductant under acidic conditions, or from the eight-membered dibenzo[*b*,*f*]-[1,5]diazocine-6,12(5*H*,11*H*)-dione through a multistep process under harsh conditions.[4,5] Taking into consideration the aforementioned scenarios and our recent research project on developing new synthetic methodologies of π-conjugated polycycles,[6] we report herein a novel synthetic method of DHII scaffold through a Cu-mediated intramolecular oxidative diamination of 2-((2-aminophenyl)ethynyl)-*N*,*N*-dimethylaniline under aerobic conditions using molecular oxygen as

Scheme 1. Intramolecular Diamination of Alkynes for Heterocycle Synthesis

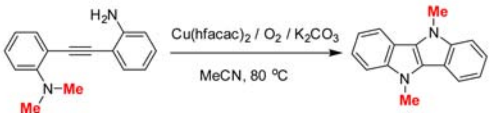
(a) Diamination of alkyne with tosylamides: a sole example by Muñiz



(b) Diamination of alkyne with *N*,*N*-dimethylamine and benzamide: Zhu *et al*



(c) Diamination of alkyne with *N*,*N*-dimethylamine and primary amine: **this study**



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an oxidant (Scheme 1c). Notably, an *N*-methyl transfer takes place from the *N*,*N*-dimethylamine to the primary amine during the annulation, which is an essential step for implementation of the present alkyne diamination.

In preliminary experiments, we found that the reaction of 2-((2-aminophenyl)ethynyl)-*N*,*N*-dimethylaniline (**1a**) under Muñiz's conditions (Scheme 1a)[3a] resulted in a complete decomposition of the starting substrate **1a** without formation of any products, while Zhu's conditions (Scheme 1b)[3c] only produced the indole product **4c** (Scheme 2) in 70% yield. After optimization of a variety of oxidative diamination conditions using various metal complexes by employing **1a** as a starting substrate, copper salts were found to be the most effective for implementation of the present transformation and the results are summarized in Table 1. Various catalytic amounts of copper salts were examined in the presence of molecular oxygen and K_2CO_3 base in CH_3CN solvent at 80 °C for the reaction of **1a**. The use of catalytic amounts of CuCl, $CuCl_2$, $Cu(OAc)_2$, $Cu(OTf)_2$, $Cu(acac)_2$ (acac: acetylacetonate), and $Cu(hfacac)_2$ (hfacac: hexafluoroacetylacetonate) proved to be inferior to the formation of the expected product **2a** (entries 1−6), in which $Cu(hfacac)_2$ afforded **2a** with the highest yield of 31% with recovery of **1a**. It was mentioned that, in the absence of K_2CO_3, the catalytic $Cu(hfacac)_2$ did afford **2a** in 30% yield, but the remaining **1a** was completely decomposed (entry 7). However, further efforts to render catalytic transformations using $Cu(hfacac)_2$ as a catalyst gave unsatisfactory results (Supporting Information (SI), Table S1). The structure of **2a** was determined unambiguously by single crystal X-ray crystallography (SI, Figure S1). Interestingly, in the crystal structure of **2a**, two methyl groups are substituted at the two nitrogen atoms of the DHII core, respectively, indicating the involvement of an *N*-methyl transfer process in the present transformation. To our delight, a significantly improved yield (80%) of **2a** was obtained using a stoichiometric amount of $Cu(hfacac)_2$ (1 equiv) in conjunction with K_2CO_3 (3 equiv) under oxygen (entry 8). It was noted that $Cu(hfacac)_2$ was highly superior to the other copper salts in this stoichiometric reaction (SI, Table S2). The reaction under an air atmosphere led to a very poor yield of **2a** with a serious decomposition of **1a** (entry 9), indicating the critical role of molecular oxygen. The use of other oxidants instead of O_2, such as *tert*-butyl hydroperoxide (TBHP), di-*tert*-butylperoxide (DTBP), $PhI(OAc)_2$, and *o*-chloranil, resulted in a serious decomposition of **1a** (entries 10−13). K_2CO_3 proved to be the most effective base (SI, Table S2), and without bases the reaction led to complete decomposition (entry 14).

Scheme 2. Optimization of *o*-Alkynylaniline Substrates

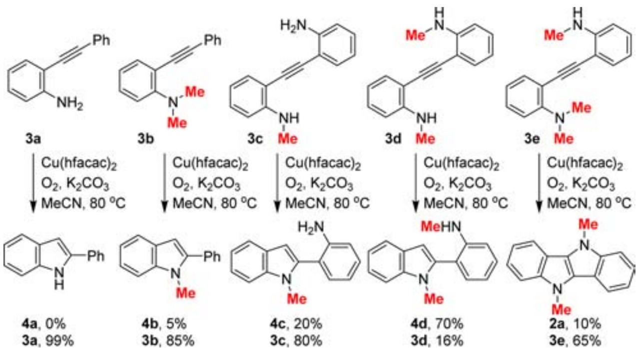
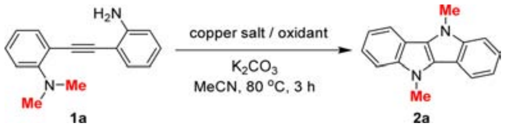


Table 1. Optimization of Reaction Conditions for Diamination of 1a[a]



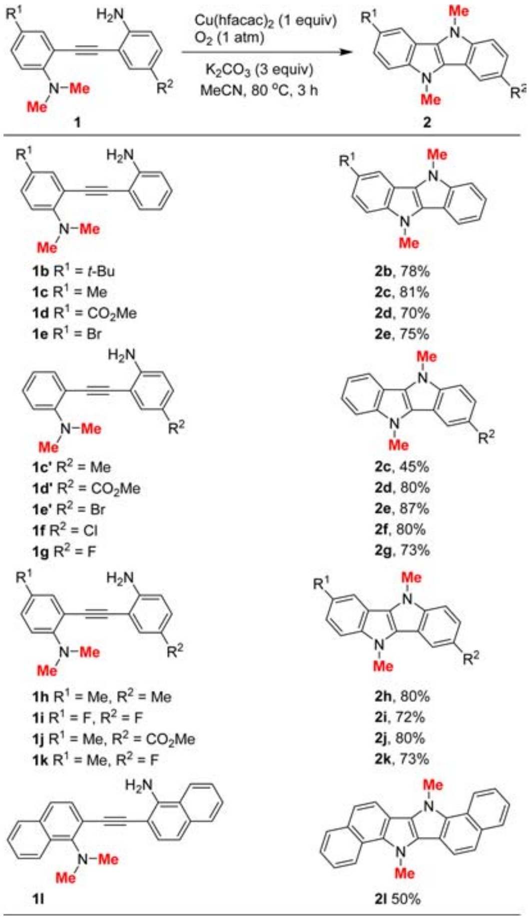
entry	Cu salt (equiv)	oxidant (2 equiv)	**2a** (%)[b]	**1a** (%)[b]
1	CuCl (0.2)	O_2 (1 atm)	11	5
2	$CuCl_2$ (0.2)	O_2 (1 atm)	10	3
3	$Cu(OAc)_2$ (0.2)	O_2 (1 atm)	4	0
4	$Cu(OTf)_2$ (0.2)	O_2 (1 atm)	17	19
5	$Cu(acac)_2$ (0.2)	O_2 (1 atm)	0	99
6	$Cu(hfacac)_2$ (0.2)	O_2 (1 atm)	31	57
7[c]	$Cu(hfacac)_2$ (0.2)	O_2 (1 atm)	30	0
8	$Cu(hfacac)_2$ (1.0)	O_2 (1 atm)	85 (80)	0
9	$Cu(hfacac)_2$ (1.0)	air (1 atm)	3	37
10	$Cu(hfacac)_2$ (1.0)	TBHP	12	0
11	$Cu(hfacac)_2$ (1.0)	DTBP	50	0
12	$Cu(hfacac)_2$ (1.0)	$PhI(OAc)_2$	13	0
13	$Cu(hfacac)_2$ (1.0)	*o*-chloranil	0	0
14[c]	$Cu(hfacac)_2$ (1.0)	O_2 (1 atm)	0	0

[a] Reaction conditions: **1a** (0.2 mmol), copper salt (0.2−1.0 equiv), oxidant (1 atm or 2 equiv), K_2CO_3 (entries 1−7:0.6 equiv, 12 h; entries 8−14:3 equiv, 3 h) in MeCN (0.2 M) at 80 °C unless otherwise noted. [b] The ^1H NMR yield determined using CH_2Br_2 as an internal standard. Isolated yield is shown in parentheses. [c] In the absence of K_2CO_3.

Under the optimal conditions obtained from entry 8 in Table 1, several structurally similar *o*-alkynylanilines **3a−d** were examined as shown in Scheme 2. No reaction occurred with 2-(phenylethynyl)aniline (**3a**), but *N*,*N*-dimethyl-2-(phenylethynyl)aniline (**3b**) afforded the desired indole product **4b** in 5% yield. The reactions of 2-((2-aminophenyl)ethynyl)-*N*-methylaniline (**3c**) and 2,2′-(ethyne-1,2-diyl)bis(*N*-methylaniline) (**3d**) afforded the *N*-methyl-protected indole products **4c** and **4d** in 20% and 70% yields, respectively, without forming the corresponding DHII products. Although the diaryl alkyne **3e** bearing both *N*,*N*-dimethylamine and secondary *N*-methylamine groups at the *ortho*-position of two phenyl rings, respectively, underwent the mechanistically related reaction to produce the corresponding product **2a** via a demethylation, the yield was as low as 10%. The significant reactivity difference between the reactions of **1a** and **3a−f** revealed the indispensable role of the molecular structure of **1a** for the efficient construction of the DHII scaffold.

The electronic effect of substituents on the starting aniline moieties has been studied under the standard conditions as shown in Scheme 3. It was noted that all the reactions were completed within 3 h without formation of other byproducts including the corresponding indoles. 2-((2-Aminophenyl)-ethynyl)-*N*,*N*-dimethylanilines with electron-rich substituents, such as *t*-Bu (**1b**) and Me (**1c**), at the *para*-position (R^1) of *N*,*N*-dimethylamine afforded slightly higher yields of the corresponding DHIIs **2b** and **2c** as compared to the substrates with electron-poor substituents, such as CO_2Me (**1d**) and Br (**1e**) at R^1. The introduction of an electron-rich substituent of methyl (**1c′**) at the *para*-position (R^2) of the primary amine lowered the yield of **2c** (45%). In contrast, the substrates with electron-poor substituents, such as CO_2Me (**1d′**), Br (**1e′**), Cl (**1f**), and F (**1g**), at R^2 afforded high yields of the corresponding DHIIs. Comparatively, the presence of both

Scheme 3. Electronic Effect of Substituents[a]

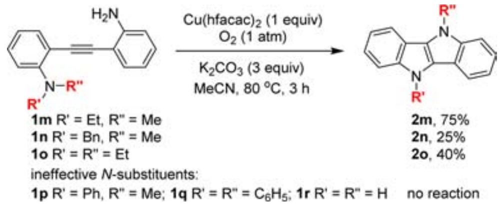


[a] Reaction conditions: **1** (0.2 mmol), Cu(hfacac)$_2$·xH$_2$O (1 equiv), O$_2$ balloon (1 atm), K$_2$CO$_3$ (3 equiv), CH$_3$CN (0.2 M), at 80 °C for 3 h. The isolated yields are shown.

electron-rich (**1h**) and -poor (**1i**) substituents at R^1 and R^2, respectively, did not affect the efficiency in achieving high yields of **2h** and **2i**. As expected, the substrates **1j** and **1k** having both electron-rich and -poor substituents at R^1 and R^2, respectively, showed high compatibility and efficiency to furnish the corresponding DHIIs **2j** and **2k** in high yields. Interestingly, **1l** composed of bis(naphthalen-1-amine) also underwent the present diamination smoothly to give the highly π-extended DHII derivative **2l** in 50% yield. It is noted that presumably the relatively low mass balance of the present reactions is in correlation with the low stability of the proposed radical species **B** and **C** as shown in Scheme 6.

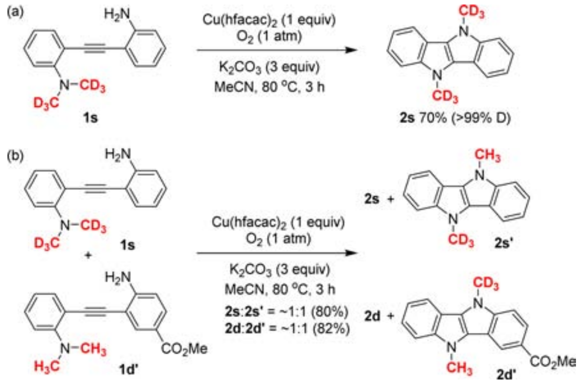
We also examined other bis(2-aminophenyl)acetylenes (**1m**−**r**) by replacement of *N*,*N*-dimethylamine with other *N*,*N*-difunctional amines without changing the primary amine group under the standard conditions (Scheme 4). Substrate **1m** having an *N*-ethyl-*N*-methyl group showed a comparable reactivity for constructing the corresponding DHII **2m**. The reactions with **1n** and **1o** bearing *N*-benzyl-*N*-methylamine and *N*,*N*-diethylamine, respectively, did afford the corresponding products **2n** and **2o**, but the yields were relatively low. In contrast, other *N*-substituents such as *N*-methyl-*N*-phenylamine (**1p**), *N*,*N*-diphenylamine (**1q**), and −NH$_2$ (**1r**) did not yield any products, demonstrating the importance of the *N*,*N*-dialkylamine group for constructing the DHII scaffold.

Scheme 4. Investigation of Other *N*-Substituents



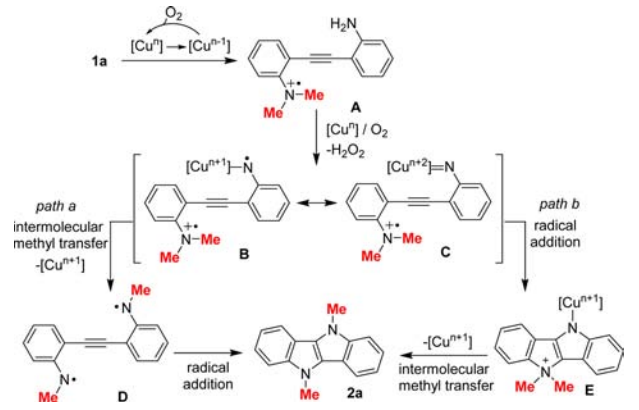
The deuterium labeling experiments were performed to gain some mechanistic insights. Under the standard conditions, the substrate **1s** having an *N*,*N*-bis(methyl-d_3)amine group yielded the corresponding product **2s** with two methyl-d_3 substituents at the two nitrogen atoms of the DHII core, respectively, without observation of a D−H exchange (Scheme 5a). This result clearly demonstrated that the methyl-d_3 group on the DHII core is originated from the *N*,*N*-bis(methyl-d_3)amine group. Moreover, a crossover reaction between the deuterated **1s** and the protonated **1d′** (1:1 ratio) was performed (Scheme 5b). Other than the corresponding products **2s** and **2d**, the crossover products **2s′** and **2d′** having both CH$_3$ and CD$_3$ at the DHII core were obtained with nearly a 1:1 ratio for **2s** vs **2s′** and **2d** vs **2d′** (also see SI, Scheme S1). The formation of the crossover products in an ∼1:1 ratio implied that the *N*-methyl transfer should mainly proceed through an intermolecular pathway. In addition, the presence of 1 equiv of the radical scavengers, such as 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) or (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), completely or partially inhibited the reaction of **1a** under the standard conditions (SI, Scheme S2), indicating the involvement of the radical species in the mechanism.

Scheme 5. Deuterium Labeling Experiments



While the exact mechanism remains to be confirmed, a tentative reaction pathway is outlined in Scheme 6 in terms of the experimental information, such as the crucial roles of the Cu salt and oxygen, electronic effect of substituents, unique structural design of the starting substrate, deuterium labeling experiments, and radical inhibiting reactions. Initially, a one-electron oxidation of the electron-rich *N*,*N*-dimethylamine by a copper salt takes place to form a radical cation **A**.[7] The combination of copper with oxygen oxidizes the primary amine to afford an aniline-copper radical **B** along with the exclusion of H$_2$O$_2$. The radical species **B** should be stabilized by its resonance form of the Cu-nitrenoid complex **C**.[8] The role of K$_2$CO$_3$ is thought to decompose H$_2$O$_2$ generated in situ, which may be unfavorable for the stabilization of the less stable radical species **B** and/or **C**. Subsequently, an intermolecular *N*-methyl

Scheme 6. Plausible Reaction Mechanism



transfer[9] takes place from the *N*,*N*-dimethylamine radical cation to the N−Cu radical in **B** or **C** to give the *N*-methylamine radical species **D** which undergoes an intramolecular radical addition to alkyne to form the corresponding product **2a** (path a). Alternately, an intramolecular radical addition to the alkyne moiety in **B** or **C** occurs prior to the *N*-methyl transfer to form a Cu-DHII indolium **E** which subsequently undergoes an intermolecular *N*-methyl transfer to afford **2a** (path b).

In summary, we have developed a novel copper-mediated intramolecular oxidative diamination of alkyne through an *N*-methyl transfer process. The present diamination of the designed bis(2-aminophenyl)acetylenes bearing both *N*,*N*-dimethylamine and primary amine moieties enables structurally intriguing π-conjugated polyheterocyclic DHIIs to be constructed in good to high yields with broad functional group compatibility. The combination of Cu(hfacac)$_2$ with molecular oxygen in the presence of K_2CO_3 is unique for achieving a high conversion efficiency. Notably, the *N*-methyl transfer is a critical process for the successful implementation of the present double annulation. Further mechanistic studies and application of the present methodology for synthesis of highly π-expanded heteropolyaromatic functional materials are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01067.

Experimental procedures and characterization data (PDF)

X-ray data for **2a** (CIF)

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Notes

The authors declare no competing financial interest.

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