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Selective Aerobic C–H Amination of Phenols with Primary Amines over Copper toward Benzoxazoles

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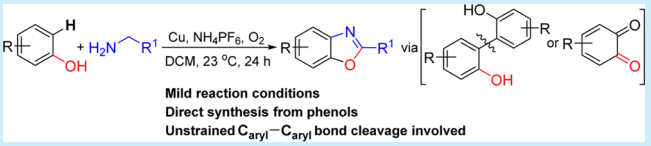
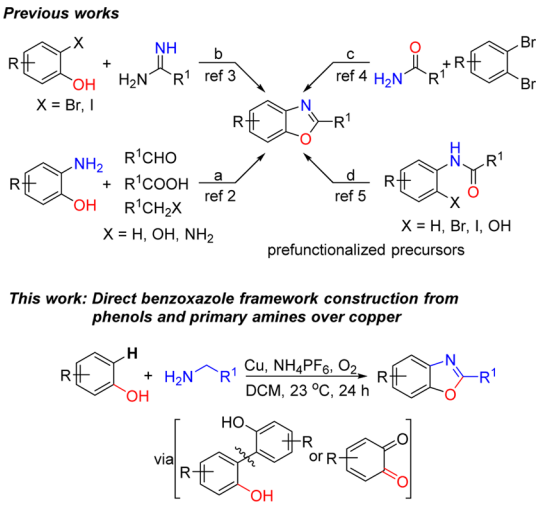
Supporting Information

ABSTRACT: Using O_2 as the oxidant, the benzoxazole frameworks can be directly constructed from the readily available phenols and primary amines in the presence of NH_4PF_6 over copper under mild conditions. Mechanistic studies showed that a novel mechanism involving biphenyldiols and *o*-quinones very possibly takes effect in the reaction, because both can selectively give the benzoxazoles under the reaction conditions. An unprecedented unstrained C_{aryl}–C_{aryl} bond cleavage takes place in the reaction.



Since benzoxazole skeletons are ubiquitous structures occurring in numerous natural products, biologically active compounds, and function-oriented materials,[1] considerable efforts have been paid to exploring new and efficient methods to construct these motifs.[2−6] Condensation of 2-aminophenols with aldehydes, carboxylic acids, or benzylic compounds are typical strategies (Scheme 1, a).[2] Intermolecular coupling reactions of halogenated phenols with amidines, 1,2-dihalogenated aromatics with amides, as well as intramolecular reactions of *ortho*-substituted acyl anilides are also developed as alternative effective ways for benzoxazole construction (Scheme 1, b–d).[3−5] Despite these notable advances, one common limitation is that they all require the use of prefunctionalized substrates, which are not easily available, usually more expensive and consequently the reaction procedures always suffer from low atom- and step-economy. In comparison with above methods, using the abundant and easily available phenols and primary amines instead of the functionalized substrates should be a more straightforward approach for benzoxazole framework construction. Yet, this ideal strategy has not been realized so far.

Scheme 1. Strategies toward Benzoxazoles



Aerobic oxidation of phenols is a fascinating topic since it is relevant to biosynthesis.[7] Because of the facile oxidation of phenols to structurally diverse compounds such as *ortho*-oxidation products, coupling products, polymers and etc., their selective transformation is thus very challenging and has fueled much research.[7,8] In recent years, great advancements have been made in this field.[8−10] For example, selective oxygenations of phenols to *para*- or *ortho*-quinones have been well developed,[9a−e] and the cross-couplings of phenols with secondary amines have also been achieved.[10]

Herein, we report an aerobic C–H amination and annulation of phenols with primary amines over copper for the construction of the benzoxazole skeletons. This selective transformation is conducted under mild conditions, in which the diverse oxidation products of phenols are converted into benzoxazoles. Interestingly, the biphenyldiols could be transformed into benzoxazoles via an unstrained C_{aryl}–C_{aryl} bond cleavage, which is not recognized.[11]

We commenced our study by the reaction of 2,4-di-*tert*-butylphenol (**1a**) and butan-1-amine (**2a**, 2.0 equiv) by the use of $CuPF_6$ (30 mol %) as catalyst in DCM at 30 °C under O_2 for 24 h;[9a−d] the desired product 5,7-di-*tert*-butyl-2-propylbenzo[*d*]-oxazole (**3a**) was obtained in 30% GC yield (Table 1, entry 1).

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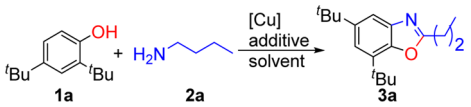
Table 1. Optimization of the Reaction Conditions[a]



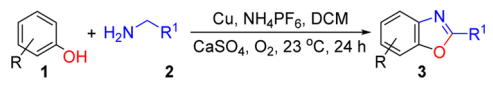
entry	[Cu]	additive	solvent	yield (%)[b]
1	$CuPF_6$	none	DCM	30
2	Cu	NH_4PF_6	DCM	26
3	CuCl	NH_4PF_6	DCM	11
4	CuI	NH_4PF_6	DCM	24
5	Cu_2O	NH_4PF_6	DCM	22
6	$CuCl_2$	NH_4PF_6	DCM	trace
7	$Cu(OAc)_2$	NH_4PF_6	DCM	trace
8	CuO	NH_4PF_6	DCM	trace
9	none	NH_4PF_6	DCM	nd
10	Cu	none	DCM	trace
11	Cu	KPF_6	DCM	trace
12	Cu	$NaPF_6$	DCM	trace
13	Cu	NH_4I	DCM	trace
14	Cu	NH_4PF_6	DCE	11
15	Cu	NH_4PF_6	$CHCl_3$	9
16	Cu	NH_4PF_6	CH_3CN	trace
17	Cu	NH_4PF_6	toluene	trace
18	Cu	NH_4PF_6	DMSO	trace
19[c]	Cu	NH_4PF_6	DCM	37
20[d]	Cu	NH_4PF_6	DCM	10
21[c,e]	Cu	NH_4PF_6	DCM	45
22[c,e,f]	Cu	NH_4PF_6	DCM	69
23[c,e,f,g]	Cu	NH_4PF_6	DCM	53

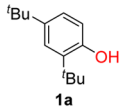
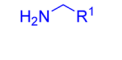
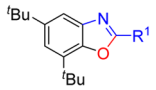
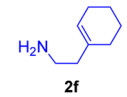
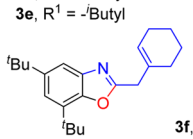
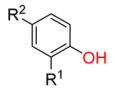
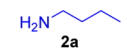
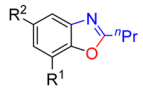
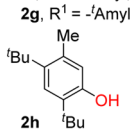
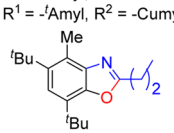
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (2.0 equiv), [Cu] (30 mol %), and additive (30 mol %) in the solvent (2 mL) at 30 °C under O_2 for 24 h. [b]GC yield using dodecane as an internal standard. [c]Anhydrous $CaSO_4$ (200 mg). [d]4 Å molecular sieves (200 mg). [e]23 °C. [f]Cu 60 mol %, NH_4PF_6 45 mol %. [g]Under air.

Due to the concern for the high cost of $CuPF_6$, we envisioned utilizing much cheaper copper sources, and the hexafluorophosphate anion (PF_6^-) could generate $CuPF_6$ in situ, which might promote this transformation. Based on this hypothesis, a series of copper sources with NH_4PF_6 were screened. Copper powder is superior to the Cu(I) and Cu(II) complexes, including CuCl, CuI, Cu_2O, $CuCl_2$, $Cu(OAc)_2$, and CuO, and **3a** was obtained in 26% yield (Table 1, entries 2−8). No desired product was observed in the absence of a copper salt (Table 1, entry 9). NH_4PF_6 was essential for the reaction, and only a trace of **3a** was detected in the absence of it (Table 1, entry 10). However, the reaction was restrained by replacement of NH_4PF_6 with KPF_6 or $NaPF_6$, probably due to their poor solubility in the solvent (Table 1, entries 11 and 12). The addition of NH_4I resulted in a trace of **3a**, illustrating that the NH_4^+ cation did not contribute to this transformation (Table 1, entry 13). For solvents, DCM was identified as being optimal (Table 1, entries 14−18). Notably, when anhydrous $CaSO_4$ (200 mg) was added to remove the water that was generated during the reaction, the yield of **3a** was improved to 37% (Table 1, entry 19). Whereas, when 4 Å molecular sieves (200 mg) were used, **3a** was only obtained in 10% yield (Table 1, entry 20). The reaction was sensitive to the temperature, as a decrease in the reaction temperature to 23 °C gave a higher yield of **3a** (45% Table 1, entry 21). A significant improvement was achieved by tuning the loading of the copper powder and NH_4PF_6, and a good yield (69%) of **3a** was gained in the presence of 60 mol % of copper powder and 45 mol % of NH_4PF_6 (Table 1, entry 22; for details, see Supporting Information (SI), Table S1). The reaction could also proceed under air, affording a 53% yield of **3a** (Table 1, entry 23).

With the optimized conditions in hand, the scope and generality of this reaction were investigated next. The reaction of 2,4-di-*tert*-butylphenol **1a** and 2.0 equiv of butan-1-amine **2a** gave **3a** in 65% isolated yield (Table 2, entry 1). Long-chain

Table 2. Substrate Scope[a,b]



entry	phenol **1**	amine **2**	product **3**	yield (%)
				
1	**1a**	**2a**, R^1 = -^{n}Propyl	**3a**, R^1 = -^{n}Propyl	65
2		**2b**, R^1 = -^{n}Amyl	**3b**, R^1 = -^{n}Amyl	64
3		**2c**, R^1 = -^{n}Undecyl	**3c**, R^1 = -^{n}Undecyl	58
4		**2d**, R^1 = -Ethyl	**3d**, R^1 = -Ethly	45
5		**2e**, R^1 = -^{t}Butyl	**3e**, R^1 = -^{t}Butyl	40
				
6		**2f**	**3f**, 30	
7		**2g**, R^1 = -Ph	**3g**, R^1 = -Ph	0
8		**2h**, R^1 = -CH_2Ph	**3h**, R^1 = -CH_2Ph	25
9		**2i**, R^1 = -C_2H_4Ph	**3i**, R^1 = -C_2H_4Ph	51
10		**2j**, R^1 = -C_3H_6Ph	**3j**, R^1 = -C_3H_6Ph	61
11		**2k**, R^1 = -CF_3	**3k**,R^1 = -CF_3	0
				
12	**2b**, R^1 = -^{t}Bu, R^2 = -Cumyl	**2l**, R^1 =-^{t}Bu, R^2 = -Cumyl		68
13	**2c**, R^1 = -^{t}Bu, R^2 = -^{t}Amyl	**3m**, R^1 =-^{t}Bu, R^2 = -^{t}Amyl		67
14	**2d**, R^1 = -^{t}Bu, R^2 = -^{i}Pr	**3n**, R^1 =-^{t}Bu, R^2 = -^{i}Pr		43
15	**2e**, R^1 = -^{t}Amyl, R^2 = -^{t}Amyl	**3o**, R^1 = -^{t}Amyl, R^2 = -^{t}Amyl		61
16	**2f**, R^1 = -^{t}Amyl, R^2 = -^{t}Bu	**3p**, R^1 = -^{t}Amyl, R^2 = -^{t}Bu		60
17	**2g**, R^1 = -^{t}Amyl, R^2 = -Cumyl	**3q**, R^1 = -^{t}Amyl, R^2 = -Cumyl		61
				
18	**2h**		**3r**, 0	

[a]Reaction conditions:**1** (0.2 mmol), amine compounds **2** (2.0 equiv), Cu (60 mol %), NH_4PF_6 (45 mol %), anhydrous $CaSO_4$ (200 mg) in DCM (2 mL) at 23 °C under O_2 for 24 h. [b]Isolated yields.

amines such as hexan-1-amine and dodecan-1-amine were suitable for the reaction, giving the corresponding products in 64% and 58% yields, respectively (Table 2, entries 2 and 3). Propan-1-amine gave a relatively lower yield (45%, Table 2, entry 4), probably because of its strong volatility. When 3-methylbutan-1-amine was employed as the substrate, the desired product was obtained in a much lower yield (40%), probably due to the steric effect (Table 2, entry 5). 2-(Cyclohex-1-en-1-yl)ethan-1-amine was tolerated in this transformation, forming the corresponding products in 30% yield (Table 2, entry 6). For phenyl substituted amines, benzylamine could not be transformed into the corresponding benzoaxzole (Table 2, entry 7). Whereas, by extension of the carbon chain, a good yield (61%) could be obtained (Table 2, entries 8−10). Our effort toward an electron-poor amine exemplified by 2,2,2-trifluoro ethan-1-amine failed (Table 2, entry 11). Next, a range of substituted phenols were examined by the reactions with butan-1-amine. It was found that strong electron-donating substituents on phenols were beneficial for the reaction. For example, cumenyl and *tert*-amyl groups on the *para*-position gave the corresponding

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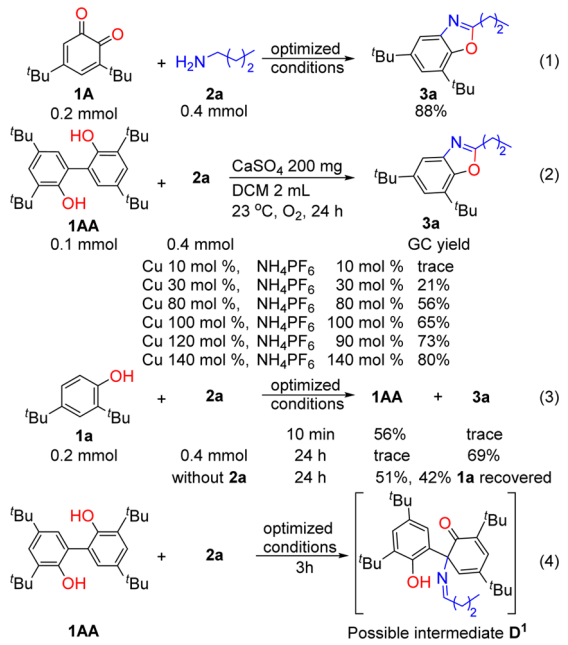
products in 68% and 67% yields, respectively (Table 2, entries 12 and 13). While 2-(*tert*-butyl)-4-isopropylphenol was used, the yield decreased to 43% (Table 2, entry 14). Other electron-rich phenols were also determined to be suitable for this transformation with satisfactory yields (60−61%, Table 2, entries 15−17). However, by the reaction of 2,4-di-*tert*-butyl-5-methylphenol, having greater electron density, no desired product was observed, which is probably attributed to its strong steric hindrance (Table 2, entry 18).

Given that phenols could be easily oxidized to *ortho*-quinones and homocoupling products under aerobic oxidative conditions over cooper,[7−9] control experiments involving these side products were performed to gain mechanistic details of this reaction. First, 3,5-di-*tert*-*o*-quinone **1A** was reacted with **2a** under the optimized conditions, affording **3a** in 88% isolated yield (Scheme 2, eq 1). When the homocoupling product

Scheme 2. Control Experiments

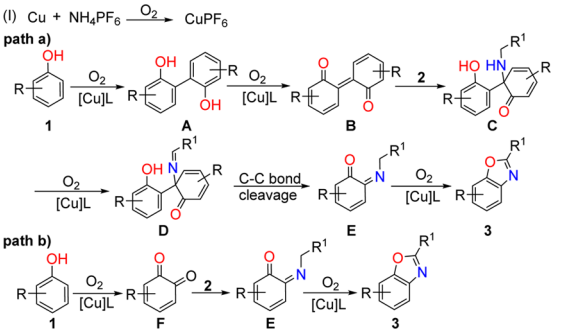


biphenyldiol **1AA** was employed as the substrate under similar conditions, **3a** could also be afforded in 73% GC yield (based on 0.1 mmol, Scheme 2, eq 2). Noting that a catalytic amount of Cu resulted in only a trace of product, the loading of Cu was increased to 1.4 equiv, affording **3a** in 80% GC yield. These results illustrated that both *ortho*-quinone and biphenyldiol probably served as the intermediates in this annulation reaction, and stoichiometric Cu was required for the transformation of biphenyldiol to benzoxazoles. Indeed, the homocoupling product **1AA** could be observed in 56% yield in 10 min under the optimized reaction conditions. After the reaction was completed, a trace of **1AA** remained, in which **1AA** was converted into **3a**. Only a 51% yield of **1AA** was observed in the absence of **2a**, showing that the amines could also act as a ligand and accelerate the oxidative transformation of phenols (Scheme 2, eq 3). Notably, the path via **1AA** that discarded half of **1a** lowered the total yield of the product **3a**, which also suggested that another reaction pathway should be involved for the reaction.

It was particularly noted that the formation of benzoxazoles from biphenyldiols proceeded via an intriguing C_{aryl}−C_{aryl} bond cleavage. Other than aromatic ring-opening reactions,[9a,12,13] until now, this type of unstrained C_{aryl}−C_{aryl} bond cleavage has not been reported. In addition, an adduct ($\mathbf{D^1}$) of **1AA** with an amine that was the probable intermediate was trapped by GC-MS (Scheme 2, eq 4; see SI for details). Unfortunately, the attempt failed to isolate pure $\mathbf{D^1}$, which was easily transformed into **3a**, with concomitant release of unknown side products.

Although the specific mechanism remains unclear, tentative pathways were proposed based on the above results and literature reports.[6f,9a,12,14,15] First, $CuPF_6$ is formed in situ from the Cu powder and NH_4PF_6 under O_2 (Scheme 3. eq I). Phenol **1**

Scheme 3. Possible Reaction Mechanism



is oxidized to biphenyldiol **A** in the present of O_2, copper, and amine.[9a] Biphenyldiol **A** is oxidized by O_2 over copper salt to generate diphenoquinone **B**.[12] Diphenoquinone **B**[16] undergoes an addition reaction with amine **2** leading to an amino-substituted intermediate **C**, and **C** is subsequently oxidized to imine intermediate **D**.[14] An oxidative C−C bond cleavage takes place to give intermediate **E**. Finally, the desired product **3** is produced via tautomerism of **E** and subsequent intramolecular cyclization (Scheme 3, path a).[6f] On the other hand, phenol **1** is oxidized to *ortho*-quinone **F**, and **F** is easily converted into **3** by a nucleophilic addition of an amine and intramolecular cyclization (Scheme 3, path b).[15]

In summary, we have developed a novel and direct synthesis toward benzoxazole frameworks from readily available phenols and primary amines over cooper under mild aerobic conditions. Oxidation products of phenols such as biphenyldiols and *ortho*-quinones could be selectively converted into the annulation products, which might be the reaction intermediates. A unique C_{aryl}−C_{aryl} bond cleavage is involved in the procedure, which provides a new dimension of inert C−C bond activation. Further investigation on the mechanism and the scope of the reaction is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01061.

Experimental procedures, full spectroscopic data, copies of ^{1}H and ^{13}C NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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