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Copper(II)-Catalyzed C–N Coupling of Aryl Halides and N-Nucleophiles Promoted by Quebrachitol or Diethylene Glycol

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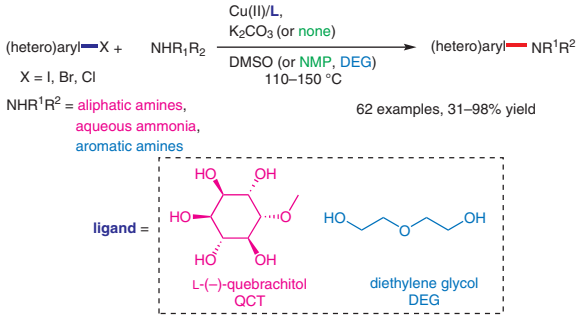

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Abstract Herein, we report the natural ligand quebrachitol (QCT) as a promoter for a Cu(II) catalyst, which is highly effective for N-arylation of various amines and related aryl halides. A series of diarylamine derivatives were obtained in high yields by using diethylene glycol (DEG) as both ligand and solvent. The C–N coupling reactions proceed under mild conditions and exhibit good functional group tolerance.

Key words N-arylation, quebrachitol, diethylene glycol, $Cu(OAc)_2$, Ullman coupling

Arylamine scaffolds are ubiquitous structural motifs in numerous natural products and synthetic molecules with various important functions,[1] such as anti-Alzheimer's disease drug tacrine,[2a] retinoid X receptor antagonist HX531,[2b] antifungal drug itraconazole,[2c] anti-inflammatory agent diclofenac acid,[2d] and anti-cancer agent imatinib.[2e] The traditional synthetic methods for these challenging molecules depend on using highly activated aryl halides,[3a] the Ullmann-type coupling reaction,[3b] or Buchwald–Hartwig reaction.[3c] The classical Cu-mediated Ullmann-type coupling reaction generally suffers from harsh reaction conditions (severe temperatures, high-boiling solvent, and strong bases), the use of large excess amounts of copper reagents, narrow substrate scope, and erratic yield.[4] Subsequently, combinations of palladium salts with phosphine ligands[5a] and several bidentate ligand-promoted copper-catalyzed Ullmann-type reactions[5b,c] were used that overcame these typical drawbacks.

In the area of auxiliary-ligand-promoted copper-catalyzed C–N coupling reactions, many bidentate ligands have been reported to display an accelerating effect on these reactions. In the presence of ligands, the reaction temperatures and catalyst loadings can be significantly decreased while the reaction yields are increased. Recently, Ma and co-workers discovered some extremely effective ligands (*N*,*N*′-disubstituted oxalamides) for promoting copper-catalyzed coupling reactions under relatively mild conditions.[6]

Quebrachitol (2-O-methyl-L-inositol) (QCT, Figure 1) is a naturally occurring chiral inositol with superior water solubility that originates mainly from waste water of natural rubber industry.[7–9] It has attracted considerable attention because of its usefulness in various reactions. QCT provided an alternative optical structure for the preparation of compounds.[10] Although the use of saccharides as ligands for organic transformations was already reported,[11] in order to search for effective natural ligands for general Cu-catalyzed couplings, it was found that QCT facilitated the coupling reaction of amines with aryl halides. The C–N bond-formation reactions involving aryl halides with amines or aqueous ammonia have been particularly applied in the preparation of pharmaceuticals or intermediates.[12–14]

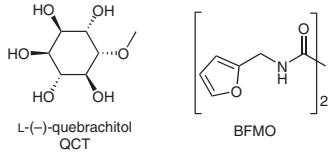

Figure 1 Chemical structure of quebrachitol and BFMO

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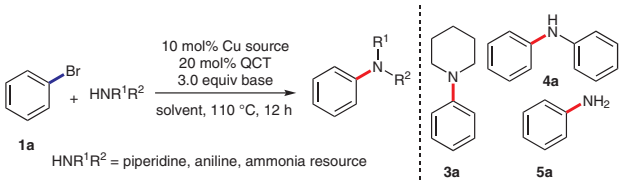
The Ma group discovered that the Cu/oxalic diamide (BFMO) catalyst system was effective for promoting Cu-catalyzed N-arylation of anilines and cyclic secondary amines (Figure 1).[15] In 2019, our group developed an efficient catalytic system for the assembly of N-arylazoles with aryl halides and related N-heterocycles, in which the inexpensive copper powder and the 'green' ligand QCT were employed.[16] Compared with other synthesized ligands, QCT is earth-abundant, efficient, and well soluble in water, which is promising for industrial applications. In contrast to bidentate ligands, polyols may couple with copper as tridentate ligands to complete the catalytic cycle. Meanwhile, they contain multiple chiral centers, which may open a new scope for the chiral synthesis of various optically active compounds in a cheap way.

Here is further demonstrated its use in the couplings of aryl halides with amines. Simultaneously, the scopes of aryl halides and amine sources are evaluated. Obviously, developing uses for QCT could help to solve the waste water problem in the natural rubber industry. Additionally, a catalyst system of $Cu(OAc)_2{\cdot}H_2O$/diethylene glycol (DEG) could obviously promote the C–N coupling of aryl halides with arylamines, providing an alternative methodology for the preparation of diarylamines.

We began by examining the reaction of bromobenzene and piperidine in DMSO (Table 1). Under basic conditions in the presence of CuI, no desired product **3a** was observed (entry 1). The subsequent research displayed that the catalytic activity of CuI could be inhibited by QCT. With the use of Cu_2O and $CuSO_4$, similar results were noticed (entries 2, 3). A control experiment confirmed that QCT was required to form **3a** in high yield (entry 5). Use of $K_3PO_4{\cdot}3H_2O$ or Cs_2CO_3 led to a lower yield of **3a** (entries 6, 7). Attempts to optimize the reaction conditions through modification of the solvent proved unsuccessful, but further studies revealed a significant effect of aprotic polar solvents, with DMSO proving to be optimal in terms of yield and safety (entries 4, 8, 9). Under these optimized conditions, the amination reaction was conducted on a 32 mmol scale, delivering 4.8 g of **3a** in 92% yield (entry 10). Considering the special biological activity of diarylamines, we were drawn to the potential use of this protocol to couple aryl halides with aromatic amines (Table 1 and Table S1). Regrettably, under standard conditions, the target product **4a** was obtained in only 35% yield (entry 11). With the use of *t*-BuOK, a complicated result was obtained (entry 12); and the main product isolated was biphenyl. However, another polar solvent, DMF, was not a suitable solvent for the C–N coupling (entry 13). The primary byproducts were *N*-phenylformamide and *N*-formyl-*N*-phenylformamide, which resulted from DMF acting as both reactant and solvent (Scheme 1). Notably, these two compounds possess similar polarity and solubility, leading to difficulties in separation and purification.

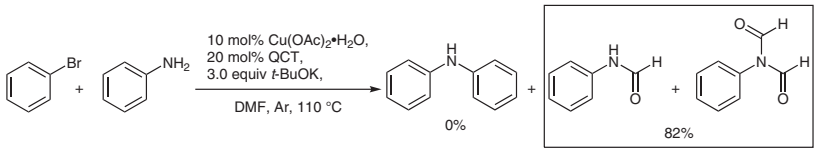
Table 1 Identification of the Reaction Conditions[a]



Entry	HNR^1R^2, Cu source, base, solvent	Yield (%)[b]
1	piperidine, CuI, K_2CO_3, DMSO	0
2	piperidine, Cu_2O, K_2CO_3, DMSO	0
3	piperidine, $CuSO_4$, K_2CO_3, DMSO	trace
4	**piperidine, $Cu(OAc)_2{\cdot}H_2O$, K_2CO_3, DMSO**	**93**
5[c]	piperidine, $Cu(OAc)_2{\cdot}H_2O$, K_2CO_3, DMSO	46
6	piperidine, $Cu(OAc)_2{\cdot}H_2O$, $K_3PO_4{\cdot}3H_2O$, DMSO	32
7	piperidine, $Cu(OAc)_2{\cdot}H_2O$, Cs_2CO_3, DMSO	35
8	piperidine, $Cu(OAc)_2{\cdot}H_2O$, K_2CO_3, DMF	trace
9	piperidine, $Cu(OAc)_2{\cdot}H_2O$, K_2CO_3, NMP	trace
10[d]	piperidine, $Cu(OAc)_2{\cdot}H_2O$, K_2CO_3, DMSO	92
11	aniline, $Cu(OAc)_2{\cdot}H_2O$, K_2CO_3, DMSO	35
12	aniline, $Cu(OAc)_2{\cdot}H_2O$, *t*-BuOK, DMSO	trace
13	aniline, $Cu(OAc)_2{\cdot}H_2O$, *t*-BuOK, DMF	0
14	aniline, $Cu(OAc)_2{\cdot}H_2O$, *t*-BuOK, ethylene glycol	54/18[f]
15	aniline, $Cu(OAc)_2{\cdot}H_2O$, *t*-BuOK, DEG	64/14[f]
16	aniline, $Cu(OAc)_2{\cdot}H_2O$, *t*-BuOK, DEG	63/15[f]
17	**aniline, $Cu(OAc)_2{\cdot}H_2O$, K_2CO_3, DEG**	**72/10[f]**
18[e]	NH_3 (aq), $Cu(OAc)_2{\cdot}H_2O$, K_2CO_3, DMSO	45
19	NH_3 (aq), $Cu(OAc)_2{\cdot}H_2O$, DMSO	48
20[e]	**NH_3 (aq), $Cu(OAc)_2{\cdot}H_2O$, NMP**	**90**
21[e]	NH_4Cl, $Cu(OAc)_2{\cdot}H_2O$, NMP	64
22[e]	$(NH_4)_2CO_3$, $Cu(OAc)_2{\cdot}H_2O$, NMP	48
23[d,e]	NH_3 (aq), $Cu(OAc)_2{\cdot}H_2O$, NMP	90

[a] Standard conditions: **1a** (1.28 mmol), **2** (1.53 mmol), QCT (0.26 mmol), base (3.85 mmol), solvent (3 mL), argon atmosphere, 110 °C, 12 h.
[b] Isolated yield.
[c] Control experiment: no QCT.
[d] The loading of **1a** was 5 g.
[e] The reaction was performed with an ammonia source (12.8 mmol) in a sealed reaction vessel.
[f] The isolated yield of ether compound.

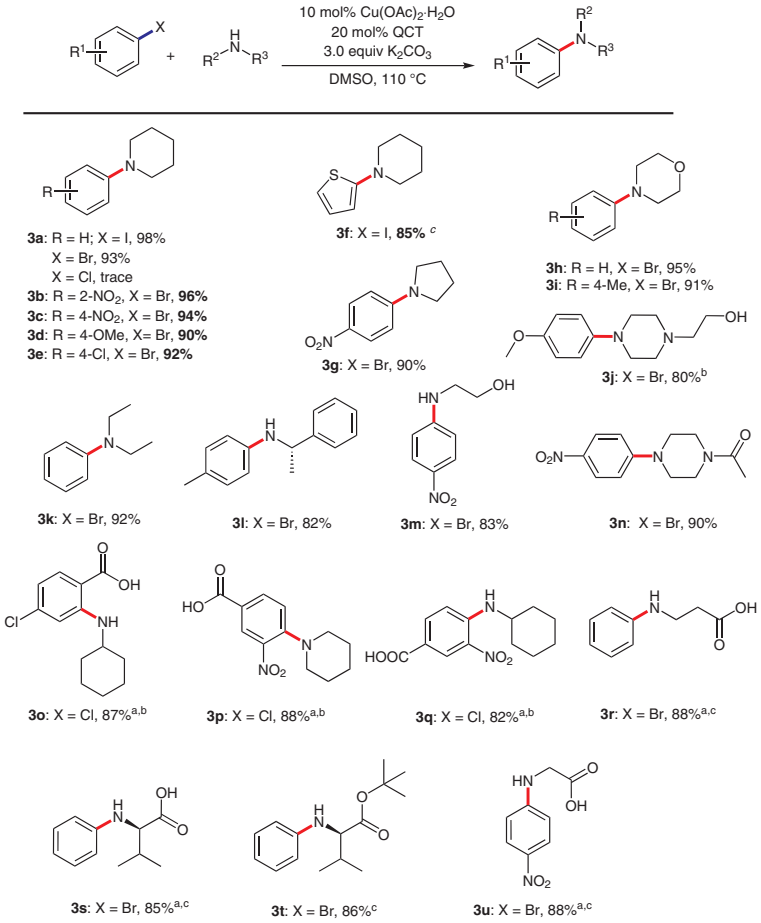
Therefore, considering the nature of the protic solvent, the intricate reaction would be avoided by the use of ethylene glycol. A number of glycols with different linkers were systematically examined. Fortunately, it was discovered that DEG could serve as a ligand for the Cu-catalyzed coupling and, similar to ethylene glycol, render the amination of aryl bromides to proceed smoothly. Notably, the ether byproduct was effectively reduced by using DEG as a solvent compared with ethylene glycol. Surprisingly, with ethylene glycol, 54% yield of **4a** was obtained under the initial screening conditions; however, the ether byproduct was



Scheme 1 The $Cu(OAc)_2·H_2O$/QCT system catalyzes the arylation of aniline in the presence of *t*-BuOK in DMF.

inevitably produced (entry 14). Replacing ethylene glycol with DEG offered an opportunity to implement a synthesis of diphenylamine **4a** directly from bromobenzene and aniline (entry 15), and the ether byproduct was isolated in 14% yield. Furthermore, the disadvantages resulting from the formation of byproduct could be alleviated by replacing *t*-BuOK with K_2CO_3, and the ether product was just obtained in 10% yield (entry 17). A control experiment confirmed that $Cu(OAc)_2·H_2O$ played a crucial role in the transformation, but QCT did not display the potential accelerating effect (entry 16). We reasoned that DEG acted as both ligand and solvent.

Next, we tried to associate the unique chelating properties of QCT with the potential benefit of using aqueous ammonia as an environmentally friendly direct nitrogen source to achieve numerous amination reactions (Table 1, entries 18–23). Our investigations commenced with the amination between bromobenzene and aqueaous ammonia using $Cu(OAc)_2·H_2O$ and QCT. A screening of reaction parameters revealed that when the reaction was conducted in DMSO, aniline **5a** was formed in low yield (45%, entry 18). Moreover, the base was not necessary for the formation of **5a** (entry 18 versus 19). By changing the polar aprotic solvent to *N*-methyl-2-pyrrolidone (NMP), aniline was pre-

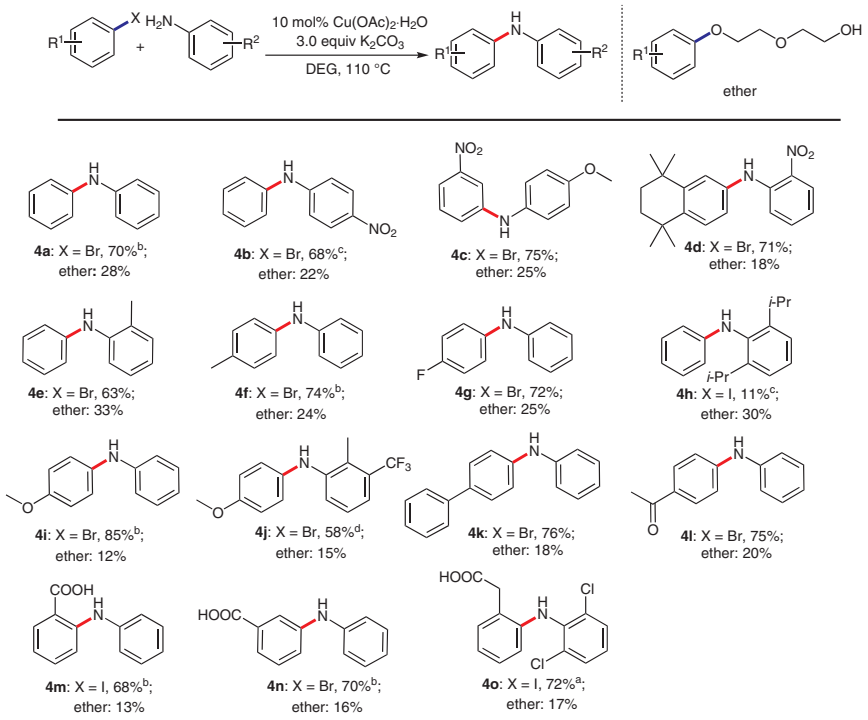


Scheme 2 $Cu(OAc)_2·H_2O$/QCT-catalyzed coupling reaction of aryl halides with aliphatic amines. *Standard conditions*: aryl halide (1.28 mmol), aliphatic amine (1.53 mmol), $Cu(OAc)_2·H_2O$ (0.13 mmol), QCT (0.26 mmol), K_2CO_3 (3.85 mmol), DMSO (3 mL), argon atmosphere, 110 °C, 12 h; isolated yield. [a] K_2CO_3 (5.13 mmol); [b] 20 h; [d] 24 h.

pared in 90% yield (entry 20). By using NH_4Cl as ammonia source, the amination was slightly favored (64%, entry 21), whereas performing the reaction with $(NH_4)_2CO_3$ led to a decreased yield (48%, entry 22). Under these optimized conditions, the desired aniline **5a** was isolated in 90% yield on a 5 g scale (entry 23).

Having the optimized conditions in hand, we investigated the scope of the aryl halides and aliphatic amines (Scheme 2). A wide range of functional groups on the aryl halides and amines was tolerated, including nitro (**3c**, **3g**, **3m**, **3n**, **3q**, **3u**), methoxy (**3d**, **3j**), methyl (**3i**), carboxyl (**3o–s**), carbonyl (**3n**), and hydroxyl (**3j**, **3m**). Substrates bearing either electron-withdrawing or electron-donating groups on the benzene ring cross-coupled with high yield (**3b–3d**). Unfortunately, less reactive aryl chloride could not give the coupling product (**3a**); however, an *ortho* carboxylic acid or nitro group could increase the reactive of aryl chlorides, leading to the product in good yield (**3o** and **3p**). The presence of a carboxyl group on the benzene ring could accelerate the coupling reaction and increase the yield (**3o** and **3p**). Primary amines (**3l**, **3o**, and **3q**), noncyclic secondary amine (**3k**), cyclic secondary amines (**3a**, **3g**, **3j**, and **3n**) could equally participate in this transformation. Excellent selectivity was observed, with only desired amination products obtained, avoiding the etherification byproducts (**3j** and **3m**), which simplified the workup procedure. The application of this reaction was expanded when amino acids (**3r**, **3s**, and **3u**) and amino acid ester (**3t**) could also provide the targets. The protocol could be applied in the preparations of some drugs and pharmaceutical intermediates. For example, the key intermediate of itraconazole, **3n**, was readily obtained in 90% yield by using 1-bromo-4-nitrobenzene and 1-(piperazin-1-yl)ethan-1-one as the starting materials. The previous method for preparing **3n** relied on S_NAr reaction and Ullman-type C–N coupling,[17] in which more expensive 4-fluoronitrobenzene, Pd catalyst, and phosphine reagents were used and resulted in the formation of a large amount of waste materials.

Subsequently, a wide range of aromatic amines were arylated under the optimized conditions to explore the scope of the $Cu(OAc)_2{\cdot}H_2O$/DEG catalyst system. As shown in Scheme 3, the direct amination of aryl bromides readily provided the desired products in moderate yields, and most of the amines functioned well, even though a small amount of ether byproduct inevitably formed. The sterically bulky 2,6-diisopropylaniline (**4h**), afforded the desired product in low yield (11%), probably because of the steric hindrance. Our coupling method was suitable for the synthesis of **4d**, a key intermediate for preparing the retinoid X receptor (RXR) antagonist HX-531, which could be used for the treatment of diabetes.[18] Diclofenac acid (**4o**), a potent and nonselective anti-inflammatory agent, could be readily obtained in 72% isolated yield by coupling with the corresponding aryl iodide.



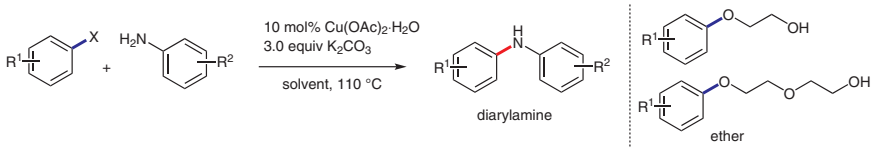
Scheme 3 $Cu(OAc)_2{\cdot}H_2O$/DEG-catalyzed coupling reaction of aryl halides with aromatic amines.*Standard conditions*: aryl halide (1.28 mmol), aromatic amine (1.53 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.13 mmol), K_2CO_3 (3.84 mmol), DEG (3 mL), argon atmosphere, 110 °C, 12 h; isolated yield. [a] QCT (0.26 mmol), K_2CO_3 (5.13 mmol), DMSO (3 mL); [b] 8 h; [c] 20 h; [d] 30 h.

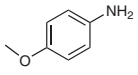
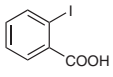
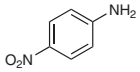
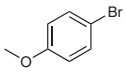
Considering the effect of etherification, parallel experiments were conducted with use of ethylene glycol or DEG as the solvent (Table 2). The data showed that DEG could effectively reduce the formation of the ether byproduct and provide diarylamine products in moderate yields; however, the electron-deficient 4-nitroaniline and sterically hindered *o*-toluidine gave the target compounds in 57 and 63% conversion, respectively, and the etherification was not effectively inhibited. As evidenced by the examples presented in Table 2, DEG indeed facilitated the amination and somewhat inhibited the side reaction, proving the efficiency of DEG relative to that of ethylene glycol.

Primary aromatic amines are ubiquitous reagents in organic synthesis with applications in pharmaceuticals. Therefore, the scope of aryl halides was also investigated, as shown in Scheme 4. The reaction tolerated a diverse array of functional groups on the aryl halides, including alkyl (**5b**, **5c**), methoxy (**5d**), hydroxy (**5e**, **5f**), mercapto (**5g**), nitro (**5h**), cyano (**5i**), carbonyl (**5q**), and carboxyl (**5v**). Substrates bearing either electron-withdrawing or electron-donating groups on the bromobenzene furnished the products with moderate to high yields, but a lower yield was observed when the substituent was hydroxyl (**5e**, **5f**).

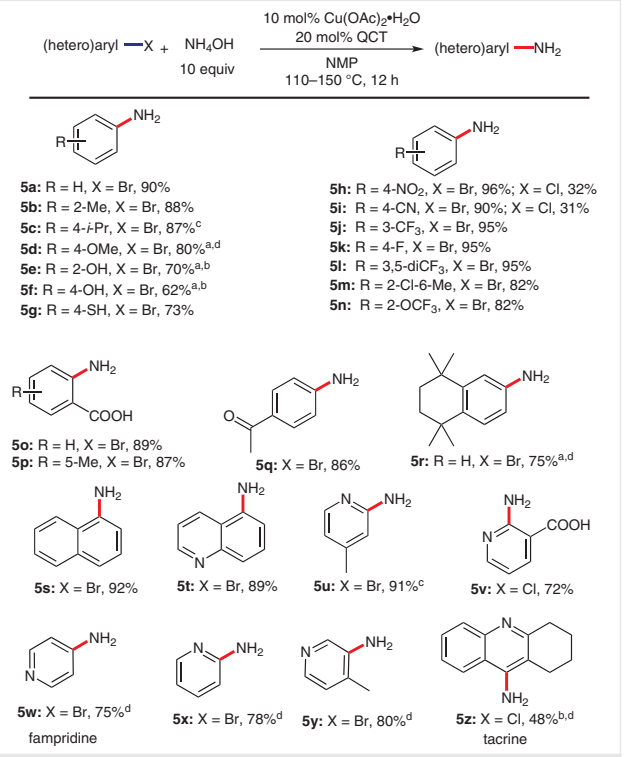
The presence of an *ortho* carboxyl group on the aromatic ring also increased the yield of **5v**. Amination occurred smoothly with bromide as the leaving group compared with the chlorine substituent (**5m**). Tamibarotene, a retinoic acid receptor alpha (RARα) agonist, was approved in Japan for the treatment of acute promyelocytic leukemia.[19] Chen et al. disclosed an effective process for the preparation of tamibarotene,[20] in which the key intermediate **5r** could also be prepared with use of the $Cu(OAc)_2{\cdot}H_2O$ and QCT catalytic system, leading to 75% yield. Comparably, this key intermediate was previously prepared through nitrification and reduction, which led to serious pollution with strong acids such as concd H_2SO_4 and HNO_3.[21] Moreover, **5r** could also act as a key intermediate for the synthesis of HX-531.[18] Substituted anilines were not only the primary focus of this study, but also the substituted heterocyclic aromatic amines were evaluated. Fampridine **5w**, a selective neuronal potassium channel blocker, was approved by the FDA for the treatment of walking ability defects in patients with

Table 2 Arylation of Aryl Halides in Ethylene Glycol and DEG[a]



Entry	Aryl halides	Aromatic amine	Conversion (%) Ethylene glycol Ether/Diarylamine	DEG Ether/Diarylamine
1			44/52	28/67
2			33/66	29/71
3			33/64	28/70
4			48/49	40/57
5			35/62	33/63
6			22/74	12/85

[a] *Standard conditions*: aryl halides (1.28 mmol), aromatic amine (1.53 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.13 mmol), K_2CO_3 (3.84 mmol), solvent (3 mL), argon atmosphere, 110 °C, 20 h.

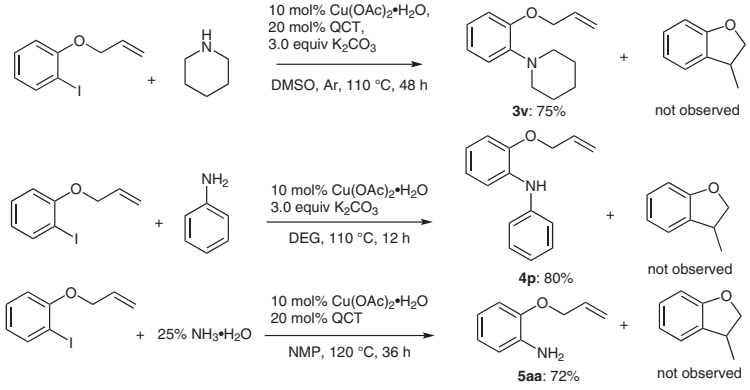


Scheme 4 $Cu(OAc)_2 \cdot H_2O$/QCT-catalyzed amination reaction of (hetero)aryl halides with aqueous ammonia. *Standard conditions*: aryl halides (1.28 mmol), 25% NH_3 (aq) (1.8 mL, 12.8 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.13 mmol), QCT (0.26 mmol), NMP (1.8 mL), sealed reaction vessel, 110 °C, 12 h; isolated yield. [a] 120 °C; [b] 150 °C, KI (0.13 mmol); [c] 20 h; [d] 30 h.

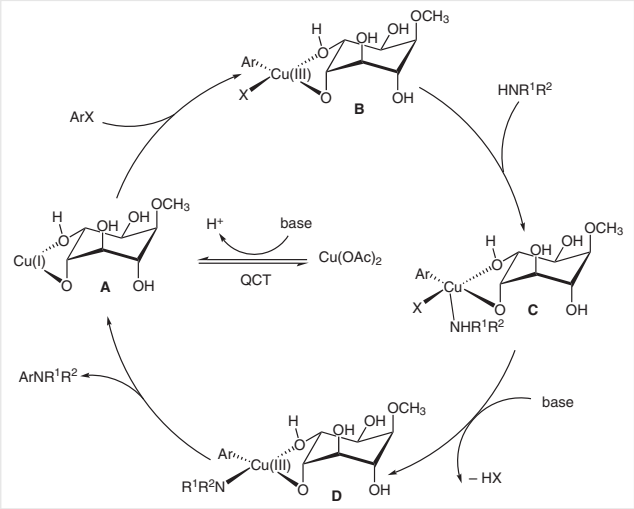
multiple sclerosis. This compound was prepared through reduction of azides or a nitro group in the literature.[22] In our hands, direct coupling with aqueous ammonia gave **5w** in 75% yield. Tacrine, an inhibitor of both acetyl (AChE) and butyryl-cholinestrase (BChE), was approved by the FDA for the treatment of Alzheimer's disease.[23] In previous pioneering work **5z** was prepared by amination in 30% yield.[24] We were pleased to find that **5z** was obtained in 48% yield through coupling with aqueous ammonia, and the incomplete conversion of the starting material led to the lower yield. 2-Chloronicotinic acid underwent amination to afford **5v** in 72% yield. Additionally, the $Cu(OAc)_2 \cdot H_2O$/DEG catalytic system was promising in the preparation of diarylamine derivatives, but could not promote the coupling reaction of aryl halides with aliphatic amines and aqueous ammonia (data not shown).

To gain insight into the plausible coupling mechanism, the respective coupling reaction of piperidine, aniline, and aqueous ammonia with 1-(allyloxy)-2-iodobenzene, a frequently used radical probe, was implemented (Scheme 5).[25] Because of the exclusive formation of C–N coupling products, it demonstrated that this C–N bond formation might proceed through an ionic and not a free radical mechanism. Therefore, we postulate that these reactions proceeded through a prototypical Cu(I)/Cu(III) catalytic cycle (Scheme 6). Initially, the Cu(II) precursor would transform into Cu(I) deanol complex **A** in situ; then, oxidative addition of an organic halide to the Cu(I) species would form deanol-coordinated Cu(III) species **B**; subsequently, ligand exchange between **A** and the amine would form intermediate **C**; last, reductive elimination would form the C–N bond and regenerate Cu(I).[26,27]

In summary, we have developed two catalytic systems for the amination of aryl halides that utilize readily available aromatic amines, aliphatic amines, aqueous ammonia, and related aryl halides under mild reaction conditions.[28] This reaction allows the conversion of simple starting materials to complex aromatic amines, which are important synthetic intermediates in the preparation of bioactive molecules such as fampridine and tacrine. The key to this discovery was the identification of a natural ligand QCT that can be extracted from industrial waste water of natural rubber. The formation of the C–N bond is significantly promoted by $Cu(OAc)_2 \cdot H_2O$/QCT; in contrast, QCT could inhibit the catalytic activity of CuI in the process of C–N coupling. The mechanism of this process might be explored in the future. $Cu(OAc)_2 \cdot H_2O$, having the advantages of cheapness, easy re-



Scheme 5 Radical clock experiment of 1-(allyloxy)-2-iodobenzene with piperidine, aniline, or aqueous ammonia



Scheme 6 Plausible mechanism for $Cu(OAc)_2$/QCT-catalyzed *N*-arylation

moval, and simple workup in the C–N coupling reaction, demonstrated application value in pharmaceutical processes; for example, the amination method provides access to some pharmaceutical intermediates, and could be easily used to prepare a variety of other interesting scaffolds as well. With regard to the poor reactivity of aryl halides towards aromatic amines, DEG could reduce the yield of the ether byproduct, and act as an alternative solvent to ethylene glycol. These two catalytic systems provided an alternative strategy for the C–N coupling and served to prepare universal amination products. Efforts to apply our Cu-based system to the pharmaceutical process in scale-up and to explore the detailed mechanism are currently underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690707.

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(28) **General Information**

All starting materials, reagents, and solvents were commercially available and used without further purification. Melting points were determined with a X-4 apparatus and are uncorrected. The nuclear magnetic resonance (NMR) spectra were recorded with a Bruker 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6 by using tetramethylsilane (TMS) as an internal standard. Electrospray ionization mass spectrometry (ESI-MS) analyses were recorded with an Agilent 1100 Series MSD Trap SL (Santa Clara, CA, USA). The reactions were monitored by thin-layer chromatography (TLC: HG/T2354-92, GF254), and compounds were visualized on TLC with UV light.

Synthesis of 3a–v; General Procedure A

To a solution of aliphatic amine (1.53 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.13 mmol), QCT (0.26 mmol), K_2CO_3 (3.85 mmol) in DMSO (3 mL) were added aryl halides (1.28 mmol). The flask was evacuated and backfilled with argon (3×), and the resulting mixture was heated in an oil bath with appropriate temperature under rapid stirring for the indicated time. After the complete consumption of aryl halide as monitored by TLC, the flask was cooled to r.t. The flask was opened to air, and the reaction mixture (if the product was acidic, the mixture was acidified) was extracted with EtOAc (3×10 mL), and the organic layer was washed with water (2×10 mL) and once with brine (10 mL), dried with magnesium sulfate and concentrated in vacuo. The product was purified by column chromatography on silica gel.

Synthesis of 4a–p; General Procedure B

To a solution of aromatic amine (1.53 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.13 mmol), K_2CO_3 (3.84 mmol) in DEG (3 mL) were added aryl halides (1.28 mmol). The flask was evacuated and backfilled with argon (3×), and the resulting mixture was heated in an oil bath with appropriate temperature under rapid stirring for the indicated time. After the complete consumption of aryl halide as monitored by TLC, the flask was cooled to r.t. The flask was opened to air, and the reaction mixture (if the product was acidic, the mixture was acidified) was extracted with EtOAc (3×10 mL), and the organic layer was washed with water (2×10 mL) and once with brine (10 mL), dried with magnesium sulfate and concentrated in vacuo. The product was purified by column chromatography on silica gel.

Synthesis of 5a–z, 5aa; General Procedure C

A sealed reaction vessel was charged with ammonia (aq, 25%) (1.8 mL, 12.8 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.13 mmol), QCT (0.26 mmol) in NMP (1.8 mL) and aryl halides (1.28 mmol). The resulting mixture was heated in an oil bath with appropriate temperature under rapid stirring for the indicated time. After complete consumption of the aryl halide as monitored by TLC, the reaction vessel was cooled to rt. It was opened to air, and the reaction mixture was extracted with EtOAc (3×10 mL), and the organic layer was washed with water (2×10 mL) and once with brine (10 mL), dried with magnesium sulfate and concentrated in vacuo. The product was purified by column chromatography on silica gel.

4-Chloro-2-(cyclohexylamino)benzoic acid (3o): According to the general procedure A, **3o** was obtained as a white solid (0.28 g, 87%). Mp 173–176 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.04 (br, 1 H), 7.77 (d, *J* = 8.5 Hz, 1 H), 6.77 (d, *J* = 1.6 Hz, 1 H), 6.54–6.51 (dd, *J* = 8.5, 1.8 Hz, 1 H), 3.46 (br, 1 H), 1.91–1.88 (m, 2 H), 1.68–1.64 (m, 2 H), 1.58–1.55 (m, 1 H), 1.46–1.35 (m, 2 H), 1.30–1.18 (m, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.0, 151.2, 139.8, 134.1, 114.2, 111.2, 109.1, 49.8, 32.6, 31.1, 25.7, 24.4. For IR and MS data see: Martin, A.; Mesa, M.; Docampo, M.; Gomez, V.; Pellon, R. *Synthetic Commun.* **2006**, *36*, 271.

1-[2-(Allyloxy)phenyl]piperidine (3v): According to the general procedure A, **3v** was obtained as a colorless oil (0.21 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): 6.95–6.88 (m, 3 H), 6.86–6.82 (m, 1 H), 6.14–6.04 (m, 1 H), 5.49–5.43 (m, 1 H), 5.28–5.24 (m, 1 H), 4.57–4.55 (m, 2 H), 3.03–2.99 (q, *J* = 9.9, 5.5 Hz, 4 H), 1.78–1.72 (m, 4 H), 1.60–1.53 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.4, 143.2, 133.7, 122.3, 121.4, 118.6, 116.6, 113.3, 68.9, 52.3, 26.5, 24.6. For IR and MS data see: Sung, S.; Sale, D.; Braddock, D. C.; Armstrong, A.; Brennan, C.; Davies, R. P. *ACS Catalysis* **2016**, *6*, 3965.

5,5,8,8-Tetramethyl-*N*-(2-nitrophenyl)-5,6,7,8-tetrahydronaphthalen-2-amine (4d): According to the general procedure B, **4d** was obtained as yellow solid (0.29 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.48 (br, 1 H), 8.21–8.19 (dd, *J* = 8.6, 1.5 Hz, 1 H), 7.36–7.32 (m, 2 H), 7.21–7.19 (dd, *J* = 8.7, 1.1 Hz, 1 H), 7.18 (d, *J* = 2.3 Hz, 1 H), 7.06–7.03 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.75–6.71 (m, 1 H), 1.71 (s, 4 H), 1.30 (s, 6 H), 1.28 (s, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.7, 143.7, 142.7, 135.8, 135.6, 132.8, 127.8, 126.7, 122.6, 122.0, 117.0, 116.1, 35.0, 34.9, 34.5, 34.1, 31.9, 31.8. For IR and MS data see: Yan, C.; Yang, L.; Fan, W.; Qian, S.; Wu, Y. Sichuan Daxue Xuebao, *Ziran Kexueban*. **2010**, *47*, 847.

***N*-(4-Methoxyphenyl)-2-methyl-3-(trifluoromethyl)aniline (4j)**: According to the general procedure B, **4j** was obtained as white solid (0.21 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.09 (m, 3 H), 7.00 (br, 2 H), 6.89–6.87 (m, 2 H), 3.81 (s, 3 H), 2.33 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.8, 145.1, 135.5, 130.9, 129.9 (*J* = 29.1 Hz), 128.9, 126.2, 124.7 (*J* = 274.9 Hz), 123.2, 118.4, 117.2 (*J* = 6.0 Hz), 114.9, 55.6, 13.2 (*J* = 2.3 Hz). HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_{13}F_3NO$: 280.0955; found: 280.0962. See high-resolution mass spectra in SI.

2-(Allyloxy)-*N*-phenylaniline (4p): According to the general procedure B, **4p** was obtained as a brown oil (0.23 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 3 H), 7.16–7.14 (m, 2 H), 6.96–6.78 (m, 4 H), 6.18 (br, 1 H), 6.14–6.04 (m, 1 H), 5.44–5.38 (dq, *J* = 17.2, 3.1, 1.6 Hz, 1 H), 5.32–5.28 (dq, *J* = 10.5, 2.7, 1.3 Hz, 1 H), 4.61–4.59 (dt, *J* = 8.9, 1.4 Hz, 2 H). For IR and MS see: Ding, X.; Huang, M.; Yi, Z.; Du, D.; Zhu, X.; Wan, Y. *J. Org. Chem.* **2017**, *82*, 5416.

2-(Allyloxy)aniline (5aa): According to the general procedure C, **5aa** was obtained as brown oil (0.14 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81–6.77 (m, 2 H), 6.73–6.67 (m, 2 H), 6.12–6.03 (m, 1 H), 5.42 (dq, *J* = 17.2, 3.2, 1.6 Hz, 1 H), 5.26 (dq, *J* = 10.5, 2.8, 1.4 Hz, 1 H), 4.55 (dt, *J* = 5.3, 1.5 Hz, 2 H), 3.64 (br, 2 H). GC-MS: 149 [M]. For IR and MS see: Carmona, R. C.; Koester, O. D.; Correia, C. R. D. *Angew. Chem. Int. Ed.* **2018**, *5737*, 12067.

Characterization data for all known compounds are provided in the Supporting Information.