JOC The Journal of Organic Chemistry
Article
pubs.acs.org/joc

Designing a Cu(II)−ArCu(II)−ArCu(III)−Cu(I) Catalytic Cycle: Cu(II)-Catalyzed Oxidative Arene C−H Bond Azidation with Air as an Oxidant under Ambient Conditions

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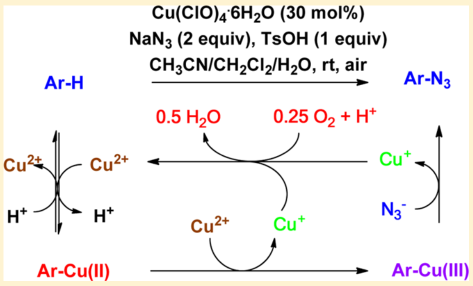
Supporting Information

ABSTRACT: On the basis of our recent discovery of high valent organocopper compounds, we have designed and achieved efficient copper(II)-catalyzed oxidative arene C−H bond azidation under very mild aerobic conditions by using NaN_3 as an azide source. In the presence of a Cu(II) catalyst, a number of azacalix[1]arene[3]pyridines underwent direct arene C−H bond cupration through an electrophilic aromatic metalation pathway to form an arylcopper(II) intermediate. Oxidized by a free copper(II) ion, the arylcopper(II) intermediate was transformed into an arylcopper(III) species that subsequently cross-coupled with azide to furnish the formation of aryl azide products with the release of a copper(I) ion. Under ambient catalytic reaction conditions, the copper(I) species generated was oxidized by air into copper(II), which entered into the next catalytic cycle. Application of the method was demonstrated by the synthesis of functional azacalix[1]arene[3]pyridines by means of simple and practical functional group transformations of azide. The showcase of the Cu(II)−ArCu(II)−ArCu(III)−Cu(I) catalytic cycle would provide a new strategy for the design of copper(II)-catalyzed aerobic oxidative arene C−H bond activation and transformations.



INTRODUCTION

Recent years have witnessed the renaissance and up-surge of copper-catalyzed and copper-mediated organic reactions. In addition to the notable advantages such as the natural abundance, cost effectiveness, and eco-friendliness of copper in comparison to noble metals, copper salts have also been shown to exhibit unexpected versatility in effecting diverse carbon−carbon and carbon−heteroatom bond forming reactions.[1−3] More importantly, recent discoveries of well-defined high valent organocopper compounds and their reactivity have unveiled the mechanistic mysteries of reactions, providing, therefore, great opportunities in the rational design of novel organocopper reactions in organic synthesis.[4−6]

In a seminal study in 2006, Yu and co-workers[7] reported $Cu(OAc)_2$-catalyzed regioselective C−H bond functionalization of arenes that contain a pyridin-2-yl directing group using oxygen as an terminal oxidant at 130 °C. Ever since, a large number of copper-promoted arene C−H bond transformations have been developed.[2−4,8] On the other hand, by means of direct interaction of an arene-embedded azacrown with $Cu(ClO_4)_2$ under anaerobic conditions, Ribas et al.[9a] obtained an organometallic ArCu(III) compound.[9b] The formation of ArCu(III) species was initially believed to proceed through a disproportionation reaction between a free copper(II) ion and $[Cu^{II}·(Ar\text{-}H)](ClO_4)_2$, a putative complex of arene substrate and copper(II) ion. Recently, Ribas et al.[9c] have proposed a mechanism that involves a concerted rate-limiting proton-coupled electron transfer step of $[Cu^{II}·(Ar\text{-}H)](ClO_4)_2$. Using the same arene-embedded azacrowns as reactants, Ribas, Stahl, and coworkers[9b] realized Cu(II)-catalyzed arene C−H bond methoxylation and amidation, respectively, by methanol and pyridine-2(1*H*)-one. In their study, a high valent organometallic species ArCu(II) was never obtained.[9a−c] In 2009, we[10] reported our serendipitous discovery that interaction of azacalix[1]arene[3]pyridine macrocycles with $Cu(ClO_4)_2$ under mild aerobic conditions afforded efficiently the corresponding (substituted) phenylcopper(III) compounds. It has been demonstrated that arylcopper(III) compounds, which are very stable under atmospheric conditions, undergo highly efficient coupling reactions with a variety of carbon and heteroatom nucleophiles to afford diverse functionalized arene derivatives along with the formation of copper(I) species.[9b,10−12]

Very recently, we[6] have synthesized arylcopper(II) compounds and substantiated that arylcopper(II) compounds are precursors to arylcopper(III) compounds. On the basis of experimental evidence, including reaction kinetics, linear free

Received: September 14, 2014
Published: October 28, 2014

energy relationships (LFER) and kinetic isotope effect (KIE), and theoretical calculations, for instance, reaction of azacalix[1]arene[3]pyridines with $Cu(ClO_4)_2$ proceeded through an electrophilic aromatic metalation pathway to afford arylcopper(II) compounds. The stable and structurally well characterized arylcopper(II) molecule was then oxidized by a copper(II) ion to produce an arylcopper(III) compound while a copper(II) ion was reduced into a copper(I) ion (Figure 1).

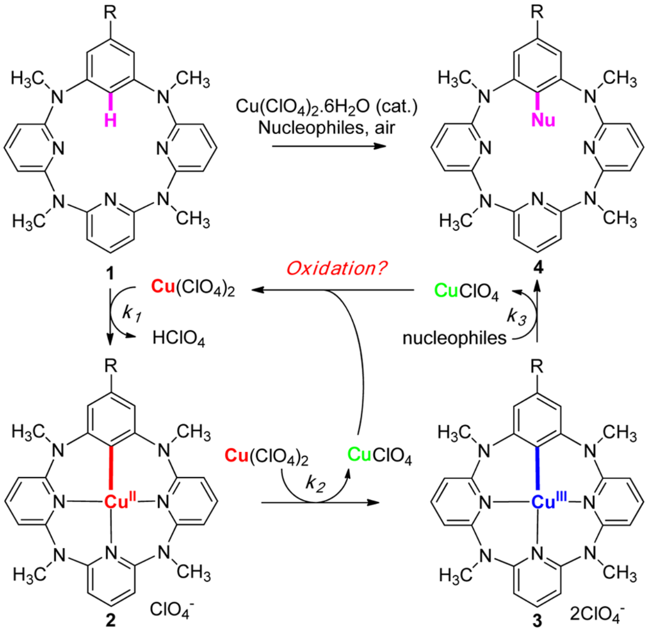
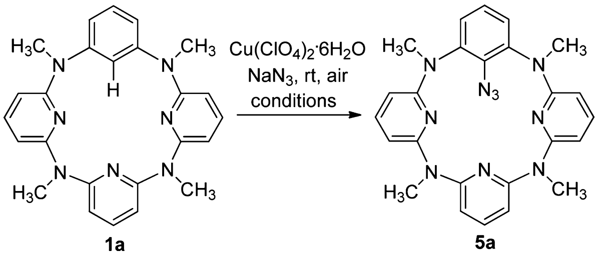


Figure 1. Designed copper(II)-catalyzed arene C−H bond functionalization involving a Cu(II)−ArCu(II)−ArCu(III)−Cu(I) catalytic cycle.

We thus envisioned that, if all copper(I) ions generated both from the reduction of Cu(II) ions and the reductive elimination of arylcopper(III) species with nucleophiles can be oxidized into copper(II) ions by an oxidant, copper(II)-catalyzed oxidative arene C−H bond functionalization reactions involving a Cu(II)−ArCu(II)−ArCu(III)−Cu(I) catalytic cycle would be devised (Figure 1). The challenges in achieving the designed Cu(II)−ArCu(II)−ArCu(III)−Cu(I) catalytic cycle include (i) the regulation of reaction rates in the order of k_2 (oxidation of arylcopper(II) intermediate by free Cu(II) ions) > k_1 (formation of arylcopper(II) intermediate) and (ii) the regeneration of free Cu(II) ions from oxidation of Cu(I) by an efficient oxidation system that are compatible with the overall reaction, as either the entire conversion of all free copper(II) into arylcopper(II) or the failure of regeneration of copper(II) from copper(I) would terminate the catalytic cycle.

Aryl azides are very useful intermediates in synthetic organic chemistry, bioorganic chemistry, and material science.[13] The major synthetic methods[14] for aryl azides include aromatic nucleophilic substitution reactions (S_NAr reactions),[15] the reaction of arenediazonium salts with sodium azide,[16] and the reactions from hydrazines.[17] Aryl azides can also be synthesized from the reaction of aryl Grignard[18] and lithium reagents[19] with tosyl azide. The copper-catalyzed reaction of aromatic amines with triflyl azide constitutes another useful approach to aryl azides.[20] However, these methods require prefunctionalized starting materials, and in many cases, the reactions proceed at an elevated temperature. Recently, $Pd(OAc)_2$[21]- and $(RhCp^*Cl_2)_2$[22]-catalyzed C−H bond azidations of 2-arylpyridines have been realized in the presence of inorganic and organic oxidants, respectively. It is noteworthy that Tang and Jiao[23] and Fan et al.[24] reported successful CuBr- and $Cu(OAc)_2$-catalyzed azidation of anilines, respectively, although

Table 1. Reaction of Azacalix[1]arene[3]pyridine 1a with NaN_3



entry	**1a**:NaN_3	Cu(II) (mol %)	CH_3CN:DCM[a]	additive (equiv)[b]	time (h)	yield of **5a** (%)
1	1:1	100	3.0:0		6	74
2	1:1	100	2.0:1.0		6	88
3	1:1	100	1.5:1.5		6	88
4	1:1	50	1.5:1.5		24	72
5	1:1	50	1.5:1.5	$HClO_4$ (1)	24	21
6	1:2	50	1.5:1.5	$HClO_4$ (1)	24	97
7	1:2	50	1.5:1.5		24	76
8	1:2	50	2.0:1.0	$HClO_4$ (1)	2	92
9	1:2	50	3.0:0	$HClO_4$ (1)	2	65
10	1:2	30	2.0:1.0	$HClO_4$ (1)	16	94
11	1:2	10	2.0:1.0	$HClO_4$ (1)	36	92
12	1:2	30	2.0:1.0	TsOH (1)[c]	24	97
13	1:2	30	2.0:1.0	TsOH (1)[d]	24	98
14	1:2	0	2.0:1.0	TsOH (1)[d]	24	0[e]

[a] Total volume of solvent was 2 mL. [b] Aqueous perchloric acid (1M) was used. [c] Water (0.1 mL) was added. [d] Water (0.2 mL) was added. [e] Starting material **1a** was recovered in 95% yield.

azidotrimethylsilane ($TMSN_3$) and *tert*-butyl hydroperoxide (TBHP) (2 equiv) are required in the former case, while azidobenziodoxolone is used as an azidating agent in the later one. The development of efficient, cost-effective, safe, and environmentally benign methods for the selective synthesis of aryl azides is highly desirable.

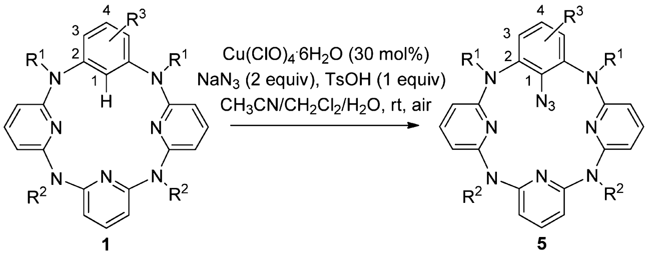
To test our working hypothesis of designed copper(II)-catalyzed arene C−H bond functionalization involving a Cu(II)−ArCu(II)−ArCu(III)−Cu(I) catalytic cycle, we undertook the study of azidation reaction of azacalix[1]arene[3]-pyridines. We report herein a highly efficient $Cu(ClO_4)_2$-catalyzed oxidative adization of arenes using the cheapest sodium azide as an azidating agent and air (oxygen) as a terminal oxidant at ambient temperature (Figure 1, Nu = N_3).

■ RESULTS AND DISCUSSION

We[6] have shown in our previous investigation that interaction of azacalix[1]arene[3]pyridines with $Cu(ClO_4)_2{\cdot}6H_2O$ in the presence of an excess amount of a base such as collidine led to the exclusive formation of arylcopper(II) compounds. In the absence of the base, on the contrary, the reaction afforded arylcopper(III) compounds almost quantitatively, although 150 mol % copper(II) source was needed. We initiated our study by examining the one-pot reaction of tetramethylazacalix[1]-arene[3]pyridine **1a** with sodium azide in the presence of a stoichiometric amount of copper(II) perchlorate hexahydrate. Air (oxygen) was used as an oxidizing agent. As indicated by the results summarized in Table 1, the reaction was found to take place smoothly in acetonitrile under aerobic conditions at ambient temperature, and azidation product **5a** was isolated as the sole product in 74% (entry 1, Table 1). The use of a mixture of acetonitrile and dichloromethane (DCM) (2:1 to 1:1 in volume) as a reaction media led to an improved chemical yield (88%) of **5a** (entries 2 and 3, Table 1).

Encouraged by these results, copper(II) catalyzed reactions were tested. Unfortunately, the reaction became slower when the copper(II) salt was halved (entry 4, Table 1). This was probably due to the fact that the presence of excessive azacalix[1]arene[3]pyridine **1a** drives the transformation of copper(II) ions into arylcopper(II) intermediate **2**,[6] which decreases the oxidation of **2** into arylcopper(III) intermediate **3** because of the drastically lowered concentration of free copper(II) ions. To down-regulate the reaction velocity of the step for the formation of the arylcopper(II) intermediate, a strong Brønsted acid was employed to protonate reactant **1a**. Surprisingly, the addition of 1 equiv of perchloric acid led to a further decrease of the chemical yield (entry 5, Table 1). Having considered the formation of HN_3 from the interaction of sodium azide and perchloric acid, which might alleviate the nucleophilicity of azide, another equivalent of sodium azide was added. To our delight, the reaction proceeded efficiently in 24 h to produce product **5a** in an almost quantitative yield (entry 6, Table 1). It was noteworthy that both perchloric acid and solvent were very critical to the reaction. In the absence of acid, the reaction gave a diminished yield of product **5a** (entry 7, Table 1). The mixture of acetonitrile and dichloromethane in a 2:1 ratio was found optimal to effect the azidation reaction, with an excellent yield of **5a** being achieved in a short reaction period (entries 6, 8, and 9, Table 1). Under these optimized conditions, copper(II) salt in 30 mol % and even in 10 mol % was able to catalyze direct arene C−H bond azidation reaction effectively. Aryl azide **5a** was isolated in 94% and 92% yield after 16 and 36 h, respectively (entries 10 and 11). Instead of perchloric acid, other Brønsted acids also acted as an additive to facilitate the reaction. The Cu(II)-catalytic direct arene azidation reaction in the presence of *p*-toluenesulfonic acid (TsOH), for example, proceeded efficiently to produce a quantitative yield of product **5a** (entries 12 and 13, Table 1). It should be noted that the addition of water was beneficial to the reaction, as water prevented precipitation of copper salts from the reaction mixture. In the absence of copper(II) salt, no azidation reaction was observed (entry 14, Table 1).

Table 2. Copper(II)-Catalyzed Direct Azidation of Azacalix[1]arene[3]pyridines 1 with Sodium Azide[a]



entry	1	substituents	*t* (h)	yield of **5** (%)
1[a]	**1a**	$R^1 = R^2 = CH_3$, $R^3 = H$	16	**5a** (94)
2	**1a**	$R^1 = R^2 = CH_3$, $R^3 = H$	24	**5a** (98)
3	**1b**	$R^1 = R^2 = CH_3$, R^3 = 4-Me	24	**5b** (99)
4	**1c**	$R^1 = R^2 = CH_3$, R^3 = 3-Me	24	**5c** (94)
5	**1d**	$R^1 = R^2 = CH_3$, R^3 = 4-Cl	24	**5d** (90)
6	**1e**	$R^1 = R^2 = CH_3$, R^3 = 3-Cl	48	**5e** (93)
7[b]	**1f**	$R^1 = CH_3$, $R^2 = CH_2Ph$, $R^3 = H$	20	**5f** (87)
8	**1f**	$R^1 = CH_3$, $R^2 = CH_2Ph$, $R^3 = H$	20	**5f** (83)
9	**1g**	$R^1 = CH_2Ph$, $R^2 = CH_3$, $R^3 = H$	24	**5g** (96)
10	**1h**	$R^1 = H$, R^2 = Boc, $R^3 = H$	20	**5h** (80)
11	**1i**	$R^1 = H$, R^2 = Boc, R^3 = 3-Br	20	**5i** (88)

[a] Aqueous perchloric acid (1 M, 0.1 mL) was used as an additive. [b] Aqueous perchloric acid (1 M, 0.1 mL) and 0.1 mL water were used.

Under the optimized conditions, such as using $Cu(ClO_4)_2{\cdot}6H_2O$ (30 mol %) as a catalyst, TsOH as an additive (1 equiv), air as an oxidant, and a mixture of acetonitrile (2.0 mL), DCM (1.0 mL), and water (0.2 mL) as reaction media, the reaction scope was then investigated. The Cu(II)-catalyzed arene C−H bond azidation was found to be applicable to all azacalix[1]-arene[3]pyridine substrates[6,25] that were prepared readily by means of a fragment coupling approach[26] (see the Supporting Information). In all cases, the azidation reaction took place efficiently and regiospecifically on the lower rim position of the benzene ring to afford aryl azide products **5** in good to excellent yields (Table 2). For example, the arene units bearing an electron-donation methyl group at either *para* or *meta* position were functionalized to give azide products **3b** or **3c** in 94% to 99% yields (entries 3 and 4, Table 2). The aromatic C−Cl and C−Br bonds were tolerated by the catalytic system, with the products **5d**, **5e**, and **5i** being obtained in 88% to 93% yields (entries 5, 6, and 11, Table 2). While the reaction of the substrate **1d** containing a *para*-chloro substituent proceeded equally efficiently (entry 5, Table 2), the move of the chloro substituent from the *para* (**1d**) to the *meta* position (**1e**), however, led to the decrease of reaction rate (entry 6, Table 2). Variations of the substituents on the bridging nitrogen atoms were also accepted, and consequently products **5f** and **5g** were prepared in good to excellent yields (entries 7−9, Table 2). Noticeably, the Cu(II)-catalytic reaction was also tolerant to the free amino group and Boc group despite the use of 1 equiv of a strong Brønsted acid. This has been exemplified nicely by the conversion of $(NH)_2(NBoc)_2$-bridged calix[1]arene[3]-pyridines **1h** and **1i** into the corresponding azido functionalized products **5h** and **5i** in 80% and 88% yield, respectively (entries 10 and 11, Table 2).

To shed light on the active catalytic species, we performed the reactions of sodium azide with isolated arylcopper(II) and arylcopper(III) compounds, respectively. As shown in Figure 2, in the absence of *p*-toluenesulfonic acid, arylcopper(III) compound **3a** reacted very efficiently with NaN_3 to give aryl azide product **5a** in an almost quantitative yield within 0.5 h. The same reaction between arylcopper(II) compound **2a** and NaN_3, however, proceeded sluggishly, with aryl azide **5a** being isolated in only 22% yield in 1 h. It should be pointed out that elongating the reaction time from 1 to 30 h led to conversion of arylcopper(II) into product **5a** in 91% yield. In the absence of water, however, no reaction was observed between arylcopper(II) and NaN_3. Since arylcopper(II) compounds were able to undergo protonolysis upon the treatment with Brønsted acids, slow reaction of arylcopper(II) compounds with NaN_3 in the presence of water was most probably attributed to the formation of HN_3, which decomposes arylcopper(II) compound **2a** to generate azacalix[1]arene[3]pyridine **1a** and copper(II) ion. The resulting copper(II) ion was then able to oxidize arylcopper(II) **2a** to produce arylcopper(III) **3a**, which cross-coupled readily with NaN_3 to form final product **5a**. The involvement of acid in the reaction of arylcopper(II) with NaN_3 was also evidenced by the observation of acceleration and complete transformation of arylcopper(II) species **2a** into product **5a** when equimolar TsOH was employed. The outcomes indicated clearly that it is the arylcopper(III) that acts as an active species to react with azide to form aryl azide.

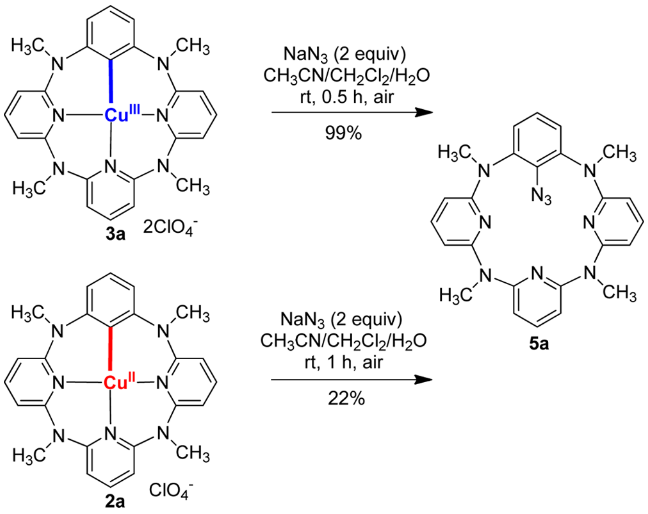


Figure 2. Reactions of sodium azide with arylcopper(II) compound **2a** and with arylcopper(III) compound **3a**.

On the basis of the aforementioned results, a most plausible mechanism was proposed for the copper(II)-catalyzed oxidative C−H bond azidation of arene compounds **1**. As depicted in Figure 3, the reaction involved an unprecedented Cu(II)−ArCu(II)−ArCu(III)−Cu(I) catalytic cycle. Electrophilic aromatic metalation of reactants **1** by copper(II) ion affords arylcopper(II) intermediates **2**. Under acidic conditions, intermediates **2** exist in an equilibrium with the starting materials **1** as arylcopper(II) species **2** are susceptible to protolysis, since the reaction of isolated arylcopper(II) **2a** with $HClO_4$ gave back to arene **1a**. Oxidation of arylcopper(II) intermediates **2** by free copper(II) ions results in the formation of arylcopper(III) compounds **3** that undergo cross-coupling reaction with nucleophilic azide to produce aryl azide products **5**. Copper(I) ions generated from both the oxidation reaction between arylcopper(II) and free copper(II) ions and from the reaction of arylcopper(III) and azide are auto-oxidized by air into copper(II) ions that enter into the next catalytic cycle.

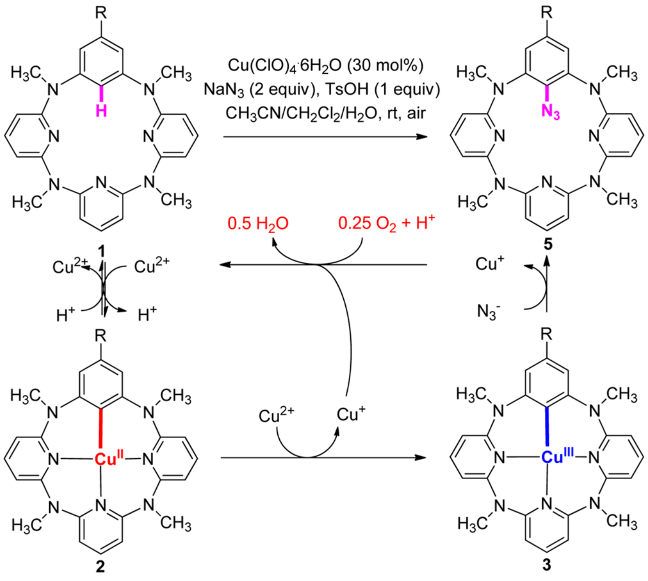


Figure 3. Proposed mechanism of copper(II)-catalyzed oxidative arene C−H bond azidation under aerobic conditions.

It may be worth emphasizing that the function of a Brønsted acid in catalysis is 3-fold. First of all, it may partially protonate the azacalix[1]arene[3]pyridine reactant to prevent the complete transformation of catalytic copper(II) ions into the arylcopper(II) intermediate, allowing, therefore, unreacted free copper(II) species to oxidize arylcopper(II) intermediate **2** into arylcopper(III) compound **3**. In addition, a proton or acidic condition was beneficial to the oxidation of copper(I) by oxygen, facilitating the regeneration of copper(II) to enter into the next catalytic cycle. Finally, an acidic media helped substantially to dissolve sodium azide to form a meaningful concentration of azide anion, which cross-coupled with arylcopper(III) species.

Heteroatom-bridged calix(het)arenes, or heteracalixaromatics, are powerful and versatile macrocyclic molecules in supramolecular chemistry.[26] The resulting regiospecifically azido-substituted azacalix[1]arene[3]pyridines provide conceivably a platform for the construction of functional macrocyclic host molecules based on the versatility of functional group transformations of aryl azide. As a demonstration, facile catalytic hydrogenation of **5a** in methanol at ambient temperature led to the formation of amino-bearing azacalix[1]-arene[3]pyridine **6** in a nearly quantitative yield (Figure 4). The installation of an amino group into the lower rim position generated a dual host **6** for both hydrogen bond donor and acceptor from a solely hydrogen bond acceptor **1**. Another example shown in Figure 4 is the synthesis of a functional macrocycle of an extended cavity. Simple and straightforward reaction of **5a** with dimethyl acetylenedicarboxylate (DMAD)

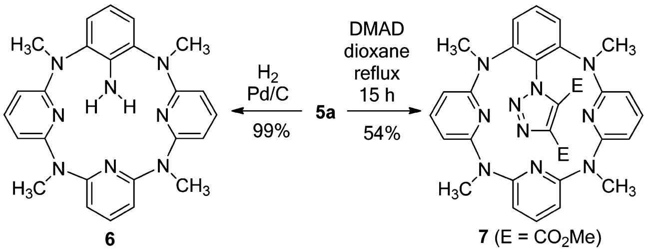


Figure 4. Synthesis of functional azacalix[1]arene[3]pyridines.

in refluxing 1,4-dioxane furnished the production of **7** in 54% yield (Figure 4).

■ CONCLUSION

In summary, we have reported a designed copper(II)-catalyzed oxidative arene C−H bond azidation under very mild aerobic conditions using sodium azide as an azide source. The catalytic reaction proceeded through direct C−H bond cupration to form an arylcopper(II) intermediate, which underwent oxidation by a free copper(II) ion to produce arylcopper(III) species along with the formation of a copper(I) ion. Reaction between the resulting arylcopper(III) and azide furnished the formation of an aryl azide product with the release of copper(I) ion. Under acidic reaction conditions, copper(I) species formed were auto-oxidized by air into arylcopper(II), which entered into the next catalytic cycle. Application of the method was demonstrated by the construction of functional azacalix[1]-arene[3]pyridines based on simple and practical functional group transformations of the azide moiety. The strategy of employing a Cu(II)−ArCu(II)−ArCu(III)−Cu(I) catalytic cycle under very mild aerobic conditions would open a new avenue to copper-catalyzed oxidative arene C−H bond activation and transformations.

■ EXPERIMENTAL SECTION

General Procedure for the $Cu(ClO_4)_2$-Catalyzed Azidation of Azacalix[1]arene[3]pyridines 1 with Sodium Azide. *Precautions should be taken when mixing sodium azide with acid!* Azacalix[1]-arene[3]pyridine **1a**−**1i** (0.1 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (37.1 mg, 0.03 mmol), TsOH (17.2 mg, 0.1 mmol), and sodium azide (13.0 mg, 0.2 mmol) were stirred together in a mixture of acetonitrile (2 mL)/dichloromethane (1 mL)/water (0.2 mL) at room temperature under aerobic conditions. After about 20−48 h, aqueous ammonia was added and the mixture was extracted with dichloromethane. The extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was chromatographed on a silica gel column with a mixture of petroleum ether and ethyl acetate (v:v = 3:1) as the eluent to give pure product **5a**−**5i**.

5a. (24 h, white solid, 45.5 mg, 98% yield): mp 170−171 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (t, *J* = 8.0 Hz, 2H), 7.15 (t, *J* = 7.7 Hz, 1H), 6.89 (dd, J_1 = 6.4 Hz, J_2 = 8.9 Hz, 1H), 6.82−6.79 (m, 2H), 6.56 (d, *J* = 7.7 Hz, 2H), 6.10 (d, *J* = 8.0 Hz, 2H), 6.03 (d, *J* = 8.0 Hz, 2H), 3.26 (s, 6H), 3.11 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 158.9, 158.8, 157.3, 140.7, 139.0, 138.6, 137.3, 128.3, 124.4, 120.1, 96.1, 94.7, 38.2, 36.2 ppm; IR (KBr) 2088(s), 1576(s), 1473(s), 1420(s), 1369(s), 1275(s), 1155(s), 1118(s); ESI-MS (*m/z*) 465.4 $[M + H]^+$, 487.4 $[M + Na]^+$, 437.3 $[M + H - N_2]^+$. Anal. Calcd for $C_{25}H_{24}N_{10}$: C, 64.64; H, 5.21; N, 30.15. Found: C, 64.76; H, 5.19; N, 30.31.

5b. (24 h, white solid, 47.4 mg, 99% yield): mp 136−137 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (t, *J* = 8.1 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.63 (s, 2H), 6.58 (d, *J* = 7.8 Hz, 2H), 6.09 (d, *J* = 8.1 Hz, 2H), 6.01 (d, *J* = 8.1 Hz, 2H), 3.26 (s, 6H), 3.09 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 158.89, 158.85, 157.3, 140.2, 139.0, 136.3, 134.1, 133.8, 129.0, 120.1, 96.0, 94.6, 38.2, 36.3, 20.7 ppm; IR (KBr) 2907(w), 2124(s), 1576(s), 1473(s), 1420(s), 1135(m); ESI-MS (*m/z*) 479.3 $[M + H]^+$, 451.3 $[M + H - N_2]^+$. Anal. Calcd for $C_{26}H_{26}N_{10}$: C, 65.25; H, 5.48; N, 29.27. Found: C, 65.21; H, 5.52; N, 29.14.

5c. (24 h, white solid, 45.0 mg, 94% yield): mp 163−164 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.423 (t, *J* = 8.1 Hz, 1H), 7.417 (t, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.78−6.70 (m, 2H), 6.56 (d, *J* = 7.2 Hz, 2H), 6.54 (d, *J* = 7.5 Hz, 1H), 6.07 (d, *J* = 8.1 Hz, 2H), 6.01 (d, *J* = 8.1 Hz, 1H), 5.97 (d, *J* = 8.1 Hz, 1H), 3.25 (s, 3H), 3.248 (s,3H), 3.10 (s, 3H), 3.04 (s, 3H), 1.98 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.3, 158.83, 158.76, 158.6, 157.4, 156.4, 139.1, 139.0, 138.6, 138.0, 137.3, 137.2, 136.8, 128.2, 125.7, 120.5, 119.8, 95.9, 95.5, 94.6, 93.9, 38.3, 37.0, 36.1, 17.6 ppm; IR (KBr) 3436(w), 2904(w), 2107(s), 1577(s), 1472(s), 1421(s), 1154(m), 1115(m); ESI-MS (*m/z*) 479.2 $[M + H]^+$, 451.2 $[M + H - N_2]^+$. Anal. Calcd for $C_{26}H_{26}N_{10}$: C, 65.25; H, 5.48; N, 29.27. Found: C, 65.08; H, 5.38; N, 29.59.

5d. (24 h, white solid, 44.9 mg, 90% yield): mp 149−150 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (t, *J* = 8.1 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 6.81 (s, 2H), 6.63 (d, *J* = 7.8 Hz, 2H), 6.10 (d, *J* = 8.1 Hz, 2H), 6.01 (d, *J* = 8.1 Hz, 2H), 3.26 (s, 6H), 3.08 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 158.82, 158.76, 157.1, 141.2, 139.2, 137.0, 136.3, 129.0, 128.5, 120.4, 96.4, 94.6, 38.0, 36.2 ppm; IR (KBr) 3433(w), 2907(w), 2121(m), 1577(s), 1561(s), 1474(s), 1426(s), 1156(m); ESI-MS (*m/z*) 499.2 $[M + H]^+$, 471.2 $[M + H - N_2]^+$. Anal. Calcd for $C_{25}H_{23}ClN_{10}$: C, 60.18; H, 4.65; N, 28.07. Found: C, 60.05; H, 4.66; N, 28.25.

5e. (48 h, white solid, 46.4 mg, 93% yield): mp 165−166 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (t, *J* = 8.1 Hz, 1H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 7.5 Hz, 1H), 6.12 (d, *J* = 8.4 Hz, 1H), 6.09 (d, *J* = 8.7 Hz, 1H), 6.01 (d, *J* = 8.1 Hz, 1H), 6.00 (d, *J* = 7.8 Hz, 1H), 3.26 (s, 6H), 3.08 (s, 3H), 3.07 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 158.9, 158.8, 158.7, 158.6, 157.1, 156.3, 139.4, 139.3, 139.2, 138.6, 137.6, 137.4, 133.6, 129.4, 124.8, 120.34, 120.31, 96.5, 96.0, 94.5, 94.1, 38.0, 36.9, 36.2, 36.1 ppm; IR (KBr) 3421(w), 2099(s), 1584(s), 1562(s), 1473(s), 1420(s), 1154(w); ESI-MS (*m/z*) 499.2 $[M + H]^+$, 471.2 $[M + H - N_2]^+$. Anal. Calcd for $C_{25}H_{23}ClN_{10}$: C, 60.18; H, 4.65; N, 28.07. Found: C, 60.20; H, 4.64; N, 28.22.

5f. (20 h, white solid, 51.1 mg, 83% yield): mp 184−185 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.07 (m, 13H), 6.95−6.90 (m, 1H), 6.85−6.82 (m, 2H), 6.64 (d, *J* = 7.7 Hz, 2H), 6.06−6.00 (m, 4H), 5.20 (d, J_{AB} = 17.0, 2H), 4.72 (d, J_{AB} = 17.0, 2H), 3.12 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 158.8, 157.7, 157.2, 140.6, 139.7, 137.4, 137.3, 128.6, 128.3, 126.8, 126.6, 124.5, 121.1, 96.6, 95.1, 53.2, 38.4 ppm; IR (KBr) 2086(m), 1576(s), 1473(s); ESI-MS (*m/z*) 617.5 $[M + H]^+$. Anal. Calcd for $C_{37}H_{32}N_{10}$: C, 72.06; H, 5.23; N, 22.71. Found: C, 72.30; H, 5.39; N, 22.73.

5g. (24 h, white solid, 59.2 mg, 96% yield): mp 180−181 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.13 (m, 13H), 6.85−6.74 (m, 3H), 6.60 (d, *J* = 7.7, 2H), 6.10 (d, *J* = 8.0, 2H), 6.01 (d, *J* = 8.0, 2H), 4.79 (d, J_{AB} = 16.6, 2H), 4.44 (d, J_{AB} = 16.7, 2H), 3.27 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 158.8, 157.7, 157.2, 140.6, 139.7, 137.4, 137.3, 128.6, 128.3, 126.8, 126.6, 124.5, 121.1, 96.6, 95.1, 53.2, 38.4 ppm; IR (KBr) 2086(m); 1574(s), 1473(s), 1425(s); ESI-MS (*m/z*) 617.5 $[M + H]^+$, 589.5 $[M + H - N_2]^+$, 639.4 $[M + Na]^+$; Anal. Calcd for $C_{37}H_{32}N_{10}$: C, 72.06; H, 5.23; N, 22.71. Found: C, 72.18; H, 5.30; N, 22.42.

5h. (20 h, white solid, 48.6 mg, 80% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, *J* = 8.0, 2H), 7.36 (t, *J* = 7.7, 1H), 7.28 (m, 2H), 6.86−6.81 (m, 3H), 6.73 (d, *J* = 7.8, 2H), 6.34 (d, *J* = 7.9, 2H), 5.64 (m, 2H), 1.41 (s, 18H) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.4, 153.3, 153.1, 138.8, 137.2, 135.9, 133.7, 127.8, 123.9, 121.5, 107.1, 104.0, 81.7, 28.1 ppm; IR (KBr) 3363(m), 2129(m), 1706(s), 1606(s), 1454(s), 1154(m), 1320(s), 1156(s); ESI-MS (*m/z*) 609.4 $[M + H]^+$, 631.4 $[M + Na]^+$, 647.3 $[M + K]^+$. Anal. Calcd for

$C_{31}H_{32}N_{10}O_4$: C, 61.17; H, 5.30; N, 23.01. Found: C, 60.98; H, 5.43; N, 22.58.

5i. (20 h, white solid, 60.5 mg, 88% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (t, *J* = 8.0, 1H), 7.49 (t, *J* = 7.9, 1H), 7.44 (t, *J* = 7.8, 1H), 7.38−7.33 (m, 2H), 7.09 (d, *J* = 8.5, 1H), 6.81 (d, *J* = 7.7, 1H), 6.73 (d, *J* = 8.5, 1H), 6.72 (d, *J* = 7.7, 1H), 6.43 (d, *J* = 7.8, 1H), 6.34 (d, *J* = 7.8, 2H), 5.60 (s, 1H), 5.57 (s, 1H), 1.43−1.41 (m, 18H) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.1, 155.2, 153.4, 153.1, 153.06, 152.97, 139.2, 139.0, 137.5, 137.1, 132.63, 132.60, 129.3, 127.1, 122.0, 121.9, 121.3, 107.4, 104.2, 104.0, 81.87, 81.85, 28.2 ppm; IR (KBr) 3364(m), 2111(s), 1706(s), 1603(s), 1452(m), 1317(s), 1155(s). HRMS (ESI-TOF) calcd. for $C_{31}H_{32}BrN_{10}O_4^+$ $(M + H)^+$ 687.1786. Found: 687.1786.

Reaction of 3a and Sodium Azide. **3a** (0.1 mmol) and sodium azide (0.2 mmol) were stirred in a mixture of acetonitrile (2 mL)/dichloromethane (1 mL)/water (0.2 mL) at room temperature under aerobic conditions for 0.5 h, which led to, after the same workup procedure as **5**, the isolation of **5a** in 99% yield. Following the same reaction procedure, the reaction of **2a** (0.1 mmol) with sodium azide (0.2 mmol) for 1 h gave **5a** in 22% yield.

Synthesis of 6. Under hydrogen atmosphere (balloon), a mixture of **5a** (0.1 mmol, 45.7 mg), and Pd/C catalyst (5 mg, 5%) in methanol (10 mL) was stirred at room temperature for 10 h. After filtration through a Celite pad, the filtrate was concentrated to give pure product **6** as a white solid (43.0 mg, 99%): mp 237−238 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (t, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 2H), 6.57 (d, *J* = 7.7 Hz, 2H), 6.54 (dd, J_1 = 7.2 Hz, J_2 = 8.2 Hz, 1H), 6.07 (d, *J* = 8.1 Hz, 2H), 6.04 (d, *J* = 8.9 Hz, 2H), 3.27 (s, 6H), 3.13 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.1, 158.7, 156.7, 142.7, 139.2, 137.5, 134.9, 126.2, 120.5, 117.5, 95.4, 94.6, 37.6, 36.1 ppm; IR (KBr) 1576(s), 1473(s), 1420(s), 1370(m), 1342(w), 1275(w), 1152(m), 769(m); ESI-MS (*m*/*z*) 439.3 $[M + H]^+$, 461.3 $[M + Na]^+$, 477.3 $[M + K]^+$. Anal. Calcd for $C_{25}H_{26}N_8$: C, 68.47; H, 5.98; N, 25.55. Found: C, 68.50; H, 6.00; N, 25.45.

Synthesis of 7. A mixture of **5a** (0.2 mmol, 93 mg) and dimethyl acetylenedicarboxylate (0.8 mmol, 96 mL) was refluxed for 15 h in 1,4-dioxane (10 mL) under nitrogen. After removal of solvent, the residue was chromatographed on a silica gel column eluted with a mixture of petroleum ether and acetone (v:v = 7:1) to give product **7** (65 mg, yield 54%) as a white solid: mp 205−206 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 120 °C) δ 7.36 (m, 3H), 7.22 (t, *J* = 6.4 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 2H), 6.48 (d, *J* = 7.8 Hz, 2H), 6.17 (d, *J* = 7.8 Hz, 2H), 5.94 (d, *J* = 7.8 Hz, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.18 (s, 6H), 2.84 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, d_6-DMSO, 120 °C) δ 159.4, 157.9, 157.7, 156.3, 143.4, 138.1, 136.5, 136.1, 131.1, 130.0, 125.4, 117.5, 97.4, 96.1, 52.3, 51.4, 36.6, 35.6; IR (KBr, cm^{-1}) ν 1732, 1577,1474,1420; Anal. Calcd (%) for $C_{31}H_{30}N_{10}O_4$: C, 61.38; H, 4.98; N, 23.09. Found: C, 61.14; H, 4.90; N, 22.87. HRMS (ESI) calcd. for $C_{31}H_{31}N_{10}O_4^+$ $(M + H)^+$: 607.2524. Found: 607.2510.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21132005, 21121004), the Ministry of Science and Technology (2011CB932501), Tsinghua University, and the Chinese Academy of Sciences for financial support.

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