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Functionalization of Azacalixaromatics by Cu(II)-Catalyzed Oxidative Cross-Coupling Reaction between the Arene C−H Bond and Boronic Acids

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Supporting Information

ABSTRACT: Catalyzed by $Cu(ClO_4)_2{\cdot}6H_2O$ under mild aerobic conditions using air as the oxidant, azacalix[1]arene[3]pyridines underwent a highly efficient oxidative cross-coupling reaction with a large number of aryl-, alkenyl-, and alkylboronic acids to afford diverse functionalized macrocycles. Stoichiometric reactions of an arylboronic acid with isolated and structurally well-defined high valent organocopper compounds indicated the involvement of arylcopper(II) rather than arylcopper(III) species as an organometallic intermediate in catalysis.

Heteracalixaromatics are versatile and useful synthetic macrocyclic receptors in supramolecular chemistry.[1] Because of the formation of different conjugation systems between bridging heteroatoms and various adjacent constitutional (het)aromatic rings, heteracalixaromatics give tunable macrocyclic cavity with varied electronic features. For example, azacalix[*n*]pyridines have been reported to form complexes with transition-metal ions,[2] organometallic clusters,[3] and fullerenes,[4] while oxacalix[2]arene[2]triazines are able to recognize anions of different geometries and volumes through anion−π interactions.[5] Extensive applications such as the fabrication of MOFs,[6] LCs,[7] vesicles,[8] organic catalysts,[9] and materials for CO_2 fixation[10] and the stationary phase[11] have also been documented in the literature.

Heteracalixaromatics are now readily accessible by means of a few efficient synthetic methods. The most frequently used methods involve the stepwise fragment coupling approach[1,12] and the one-pot reaction strategy,[1,13] both starting from simple and cheap commodity chemicals. While the one-pot synthetic reaction is limited to the preparation of symmetric macrocycles, the fragment-coupling approach permits the synthesis of both unsymmetric and functionalized heteracalixaromatics with excellent designability. Notably, post-macrocyclization chemical manipulations on both aromatic subunits and heteroatom linkages offer an effective and alternative protocol to construct tailor-made functional macrocycles.[1,12b,14−16] One remarkable functionalization of postmacrocyclization, for instance, is based on our recent discovery of an intriguing arene C−H bond activation process.[17] Catalyzed or mediated by a copper(II) salt, azacalix[1]arene[3]pyridines undergo efficient arene C−H bond transformations with a wide range of nucleophiles including alkyl- and alkynyllithium reagents, alkali metal halides, alkyl and aryl alcohols, sodium azide, cyanide, and thiocyanate to yield the corresponding carbon−carbon and carbon−heteroatom bond-forming products.[17,18] The arene C−H bond activation with copper(II) has been revealed to proceed through initially the electrophilic cupration of arenes, generating arylcopper(II) compounds. After oxidation by free copper(II) ion, arylcopper(II) intermediates were converted into arylcopper(III) compounds,[19] which undergo cross-coupling reactions with nucleophiles to form new chemical bonds.

To continue our study on novel macrocyclic receptors[1,20] and high valent organocopper chemistry,[17−19] we have been exploring the copper-catalyzed C−H bond reaction of azacalixaromatics with boronic acids. Reported herein are the syntheses of diverse functional azacalix[1]arene[3]pyridine derivatives from highly efficient copper(II)-catalyzed oxidative cross-coupling reaction between arene C−H bonds and aryl-, alkenyl-, and alkylboronic acids under mild aerobic conditions without using any other oxidants.

Copper-catalyzed C−H bond activation and functionalization have attracted great attention since Yu's seminal work in 2006.[21] A few intermolecular and intramolecular C−C and C−X (X = heteroatoms) bond formation reactions have been achieved from direct copper-catalyzed and mediated C−H bond transformations.[22] However, a literature survey shows that oxidative cross-coupling reactions between arenes and boronic acids and their derivatives under copper catalysis are very rare.[23−25] Dai, Yu, et al.[24] showed that *N*-arylbenzamides bearing an oxazoline directing group are able to undergo $Cu(OAc)_2$-catalyzed oxidative aromatic C−H coupling reaction with arylBpins. The reaction, which requires Ag_2O (1.5 equiv) as an oxidant and an excess amount of Na_2CO_3 (2 equiv) and KOAc (2 equiv) as

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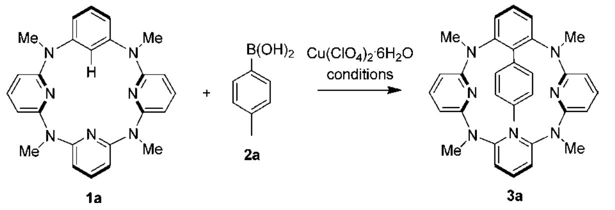
bases, leads to *ortho*-arylation products. Very recently, a similar copper-mediated *ortho*-arylation of *N*-(quinolin-8-yl)benzamides with arylboronic acids was disclosed.[25] No copper-catalyzed cross-coupling reactions of arenes with alkenyl- and alkylboronic acids have been reported.

We began our study by scrutinizing the reaction of azacalix[1]arene[3]pyridine **1a** with *p*-tolylboronic acid **2a** using a stoichiometric amount of $Cu(ClO_4)_2{\cdot}6H_2O$. In the presence of 1 equiv of collidine in DMF, no reaction took place at ambient temperature (entry 1, Table 1). The reaction was effected at an elevated temperature (entries 2 and 3, Table 1). When the temperature was increased to 100 °C, a full conversion was achieved within 1 h to afford product **3a**. Encouraged by the results, we then investigated a catalytic cross-coupling reaction using 20 mol % of copper(II) salt under basic conditions. Screening of bases ranging from collidine to Et_3N, DIPEA, DBU, and K_2CO_3 did not give satisfactory results in hot DMF or 1,4-dioxane, with chemical yields of **3a** hardly exceeding 70% (entries 4−11, Table 1). The reaction was substantially retarded by $HClO_4$ (entry 12, Table 1). Pleasingly, further optimization by varying the reaction temperatures and solvents led to a highly efficient catalytic reaction. Under the catalysis of $Cu(ClO_4)_2{\cdot}6H_2O$ in DMSO at 80 °C, the cross-coupled product **3a** was yielded quantitatively in 1.5 h (entry 13, Table 1). The reaction proceeded equally well when a smaller amount of Et_3N (0.5−0.1 equiv) was used (entries 14−16, Table 1). In the absence of Et_3N, however, the reaction became very sluggish and gave an appallingly low yield of **3a** after 48 h (entry 17, Table 1). Noticeably, the catalyst loading could be lowered to 10−5 mol % or even to 1 mol % although an elongated reaction time was required (entries 18−20, Table 1). The combination of $Cu(ClO_4)_2{\cdot}6H_2O$ (20 mol %) as a catalyst and triethylamine (0.2 equiv) as a base in DMSO stood out as the optimal conditions (entry 15, Table 1). Finally, the reaction was not influenced by the presence of water (entry 21, Table 1), and it proceeded efficiently with the use of oxygen in air as an oxidant (entry 22, Table 1), highlighting the general and excellent applicability of this catalytic reaction.

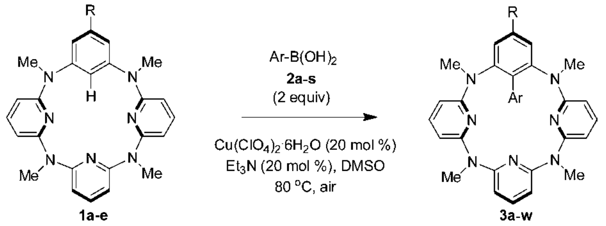
Table 1. Cu(II)-Catalyzed Reaction of 1a with 2a[a]



entry	Cu^{2+} (mol %)	additive (equiv)	solvent	temp (°C)	time (h)	**3a**[b] (%)
1	100	collidine (1)	DMF	rt	24	0
2	100	collidine (1)	DMF	60	20	80
3	100	collidine (1)	DMF	100	0.5	91
4	20	collidine (1)	DMF	100	24	53
5	20	Et_3N (1)	DMF	100	12	71
6	20	DIPEA (1)	DMF	100	12	73
7	20	DBU (1)	DMF	100	24	14
8	20	K_2CO_3 (1)	DMF	100	24	20
9	20	Et_3N (1)	DMF	80	24	75
10	20	Et_3N (1)	DMF	60	72	51
11	20	Et_3N (1)	dioxane	80	24	<1
12	20	$HClO_4$ (1)	DMF	100	5	18
13	20	Et_3N (1)	DMSO	80	1.5	quant
14	20	Et_3N (0.5)	DMSO	80	2	quant
15	20	Et_3N (0.2)	DMSO	80	3	quant
16	20	Et_3N (0.1)	DMSO	80	12	98
17	20	Et_3N (0)	DMSO	80	48	41
18	10	Et_3N (0.2)	DMSO	80	4	94
19	5	Et_3N (0.2)	DMSO	80	15	80
20	1	Et_3N (0.2)	DMSO	80	48	29
21[c]	20	Et_3N (0.2)	DMSO	80	2	quant
22[d]	20	Et_3N (0.2)	DMSO	80	3	quant
23[e]	20	Et_3N (0.2)	DMSO	80	20	92
24[f]	20	Et_3N (0.2)	DMSO	80	24	18

[a] A mixture of **1a** (0.1 mmol) and **2a** (0.2 mmol) in a specified solvent (4 mL) was stirred under oxygen (balloon). [b] Isolated yield. [c] Water (5 equiv) was added. [d] Reaction was carried under atmospheric conditions using air as an oxidant. [e] 1 equiv of **2a** was used. [f] The reaction was performed under N_2.

Table 2. Cu(II)-Catalyzed Reaction of 1a−e with 2a−s



entry	1	R	2	Ar	time (h)	3[a] (%)
1	**1a**	H	**2a**	4-Me-C_6H_4	3	**3a** (99)
2	**1a**	H	**2b**	Ph	2.5	**3b** (90)
3	**1a**	H	**2c**	4-$MeOC_6H_4$	2	**3c** (99)
4	**1a**	H	**2d**	4-PhC_6H_4	2	**3d** (99)
5	**1a**	H	**2e**	4-ClC_6H_4	3	**3e** (96)
6	**1a**	H	**2f**	4-BrC_6H_4	9	**3f** (97)
7	**1a**	H	**2g**	4-NCC_6H_4	7.5	**3g** (90)
8	**1a**	H	**2h**	4-$HCOC_6H_4$	20	**3h** (97)
9	**1a**	H	**2i**	3-MeC_6H_4	4.5	**3i** (99)
10	**1a**	H	**2j**	3-ClC_6H_4	3.5	**3j** (99)
11	**1a**	H	**2k**	3-BrC_6H_4	3	**3k** (93)
12	**1a**	H	**2l**	2-MeC_6H_4	2	**3l** (74) + **3l′** (22)
13	**1a**	H	**2m**	2-ClC_6H_4	6	**3m** (34) + **3m′** (37)
14	**1a**	H	**2n**	2-BrC_6H_4	8	**3n** (32) + **3n′** (35)
15[b]	**1a**	H	**2o**	2,6-$Me_2C_6H_3$	24	**3o** (30)
16	**1a**	H	**2p**	1-naphthyl	4	**3p**(62) + **3p′** (22)
17	**1a**	H	**2q**	2-naphthyl	5	**3q** (87)
18	**1a**	H	**2r**	3-thienyl	12	**3r** (65)
19	**1a**	H	**2s**	3-pyridinyl	24	**3s** (0)[c]
20	**1b**	MeO	**2a**	4-MeC_6H_4	2	**3t** (98)
21	**1c**	Me	**2a**	4-MeC_6H_4	2.5	**3u** (95)
22	**1d**	Cl	**2a**	4-MeC_6H_4	3.5	**3v** (99)
23	**1e**	CN	**2a**	4-MeC_6H_4	4	**3w** (99)

[a] Isolated yield. [b] Reaction temperature was 100 °C. [c] Starting material **1a** (86%) was recovered after reaction.

With optimized conditions in hand, we next examined the generality of this Cu(II)-catalyzed reaction with respect to the arylboronic acid substrates. As illustrated in Table 2, irrespective of the nature of a substituent at the para or meta position of the arylboronic acids **2a−k**, a very high yield over 90% was achieved all the time (entries 1−11, Table 2). The copper(II) catalysis displayed tolerance toward functional groups including bromo, cyano, and formyl, although a longer reaction time was necessary owing to most probably the lower reactivity of these boronic acids **2f−h** (entries 6−8, Table 2). A comparable yield was obtained from the reaction of 2-tolylboronic acid **2l** (entry 12, Table 2), whereas the yield decreased notably when arylboronic acids bearing an ortho chloro and bromo were employed (entries 13 and 14, Table 2). Sterically hindered substrate 2,6-dimethylphenylboronic acid **2o** gave only a moderate yield of cross-coupled product **3o** after a lengthy reaction period (entry 15, Table 2). Both 1- and 2-naphthylboronic acids **2p** and **2q** underwent cross-coupling reaction readily with **1a** to form products **3p** and **3q**, respectively, in good yields (entries 16 and 17, Table 2). It is noteworthy that 3-thienylboronic acid **2r** reacted smoothly with **1a** to afford 3-thienyl-containing azacalixarene **3r** (entry 18, Table 2), whereas no reaction at all was observed for 3-pyridinylboronic acid **2s** (entry 19, Table 2) probably due to the coordination of pyridine of **2s** to copper ion that inhibits the cross-coupling reaction. It is also important to emphasize that arene moieties **1a−e** bearing either a electron-donating or electron-withdrawing group were able to undergo reaction with arylboronic acids under copper(II) catalysis. The electron-rich arenes reacted faster than the electron-deficient ones. In all cases, biaryl products **3t−w** were obtained in excellent yields (entries 20−23, Table 2).

Interestingly, while the reaction of most of the arylboronic acids yielded one product, the reaction of ortho-substituted phenylboronic acids **2l−n** and 1-naphthylboronic acid **2p** resulted in the formation of two separable products (entries 12−14 and 16, Table 2). X-ray molecular structures of **3p** and **3p′** as depicted in Figure 1 revealed that there was actually an in-isomer and out-isomer pair. Virtually no interconversion between in-isomer and out-isomer was observed after either sample was heated at 180 °C for 10 h in DMSO. The outcomes concurred with a previous study[15] that azacalix[4]arenes adopt a shape-persistent 1,3-alternate conformation both in solid state and in solution phase.

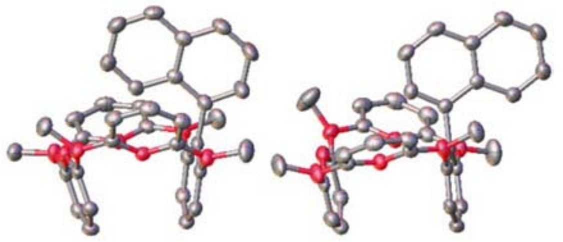
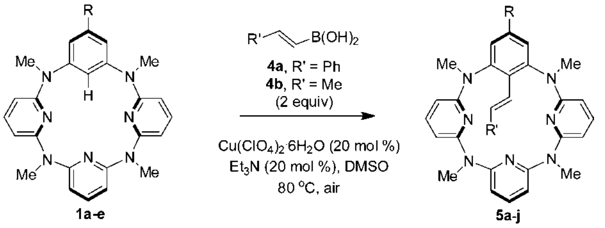


Figure 1. X-ray molecular structures of in-isomer **3p** (left) and out-isomer **3p′** (right).

Table 3. Cu(II)-Catalyzed Reaction of 1a−e with 4a and 4b



entry	**1**	R	**4**	Ar	time (h)	**5**	yield[a] (%)
1	**1a**	H	**4a**	Ph	8	**5a**	80
2	**1b**	MeO	**4a**	Ph	2	**5b**	94
3	**1c**	Me	**4a**	Ph	5	**5c**	91
4	**1d**	Cl	**4a**	Ph	10	**5d**	86
5	**1e**	CN	**4a**	Ph	24	**5e**	82
6	**1a**	H	**4b**	Me	2	**5f**	91
7	**1b**	MeO	**4b**	Me	1.5	**5g**	99
8	**1c**	Me	**4b**	Me	1.5	**5h**	92
9	**1d**	Cl	**4b**	Me	2	**5i**	98
10	**1e**	CN	**4b**	Me	4	**5j**	84

[a] Isolated yield.

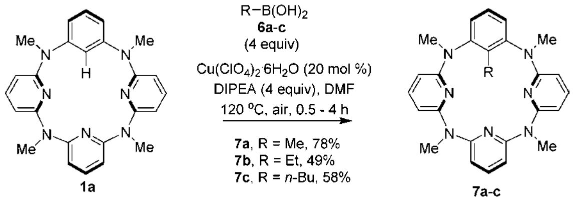
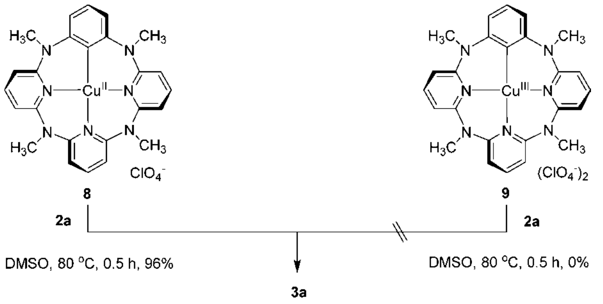


Figure 2. Cu(II)-catalyzed reaction of **1a** with **6a−c**.

The Cu(II)-catalyzed oxidative cross-coupling reaction was readily extended to both alkenyl and alkyl boronic acid substrates, which had never been accomplished. Results compiled in Table 3 showed clearly that all azacalix[1]arene[3]pyridines **1a−e** underwent reaction with (*E*)-styrylboronic acid **4a** and (*E*)-prop-1-enylboronic acid **4b** under the identical conditions to furnish the formation of olefinated macrocyclic products **5a−j** in good to excellent yields (Table 3). No isomerization of carbon−carbon double bond was observed during the course of the reaction. In addition to arylation and alkenylation, we were delighted to find the Cu(II)-catalysis was also applicable to alkylation of arene employing alkylboronic acids as cross-coupling reagents (Figure 2). Since alkylboronic acids **6a−c** were less reactive than aryl and alkenyl boronic acids, slightly forceful reaction conditions were needed. In the presence of an excess amount of DIPEA (4 equiv), the cross-coupling reaction between **1a** and **6a−c** at 120 °C in DMF proceeded effectively to afford the corresponding alkylarene compounds **7a−c**. To the best of our knowledge, this is probably the first example of the cross-coupling reaction between arenes and aryl-, alkenyl-, and alkylboronic acids catalyzed by a copper(II) salt using air as the oxidant.

The copper(II)-catalyzed and mediated coupling reaction between aromatic C−H bond and arylboron reagents was proposed previously to proceed through intuitive arylcopper(III) intermediates.[24,25] Taking advantage of having structurally well-defined arylcopper(II) (**8**) and arylcopper(III) (**9**) complexes in hand,[17−19] we tested the stoichiometric reaction of *p*-tolylboronic acid **2a** with respective organocopper compounds **8** and **9** under the otherwise identical catalytic reaction conditions. As illustrated in Figure 3, an almost quantitative yield (96%) was obtained from the reaction of arylcopper(II) **8**. In stark contrast, arylcopper(III) compound **9** did not react with *p*-tolylboronic acid **2a**. Although the mechanism of the oxidative coupling reaction between aromatic C−H bond and boronic acids under copper catalysis awaits further study, the controlled stoichiometric reactions depicted in Figure 3 excluded convincingly the involvement of an arylcopper(III) intermediate.

In summary, we have developed an efficient method for the synthesis of diverse functionalized azacalix[1]arene[3]pyridine derivatives by means of copper(II)-catalyzed oxidative arene C−H coupling reaction with boronic acids. The method was applicable to aryl-, alkenyl-, and alkylboronic acids under aerobic conditions. The application of acquired novel macrocycles



8

9

Figure 3. Reactions of **2a** with **8** and **9**.

in supramolecular chemistry and the investigation of the mechanistic aspect of the copper catalysis are being actively studied. The results will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02530.

Detailed experimental procedures, characterization data for products, X-ray crystallographic data for **3p** and **3p′**, ^{1}H and ^{13}C NMR spectra of products (PDF)
X-ray structure of **3p** (CIF)
X-ray structure of **3p′** (CIF)

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Notes

The authors declare no competing financial interest.

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