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Synthesis of Functionalized Azacalix[1]arene[3]pyridine Macrocycles from Cu(II)-Mediated Direct Amination Reactions of Arene through High Valent Arylcopper(III) Intermediates

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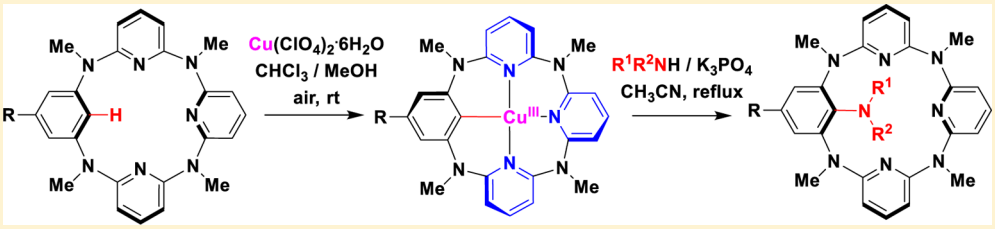
Supporting Information



ABSTRACT: Mediated by $Cu(ClO_4)_2$ in the presence of K_3PO_4 under mild conditions, azacalix[1]arene[3]pyridines underwent arene C−H bond amination with a number of sulfonamides, imides, and saccharin to afford the diverse C−N bond forming products. Based on different reactivity between arylcopper(II) and arylcopper(III) compounds toward nitrogen nucleophiles, the reaction proceeded most likely through arene C−H bond metalation via reactive arylcopper(III) intermediates and their binding to nitrogen anions which were derived from deprotonation of acidic N−H bonds of nitrogen nucleophiles of pK_a (DMSO) < 17.5 followed by reductive elimination. The study not only provides a convenient and straightforward access to functionalized heteracalixaromatics that are not readily obtained by other means but also enriches our understanding of high valent organocopper chemistry.

INTRODUCTION

Heteracalixaromatics, or heteroatom bridged calix(het)arenes, are powerful and versatile macrocyclic host molecules in supramolecular chemistry.[1] Formation of different conjugation systems between bridging heteroatoms of varied electronic configurations and various adjacent constitutional (het)-aromatic rings results in diverse heteracalixaromatics of tunable macrocyclic cavity and electronic features. They are able to recognize both charged species such as transition metal ions,[2] organometallic clusters,[3] anions of different geometries, shapes, and volumes,[4] and electron-neutral guests.[5] Applications in the fabrication of metal organic frameworks,[6] liquid crystals,[7] CO_2-absorbents,[8] anion responsive vesicles,[9] stationary phase,[10] and organic catalysts[11] have been demonstrated.

The fragment coupling strategy,[1,12] which has been used most frequently in academia, produces the diversity-orientated construction of heteracalixaromatics employing simple and cheap commodity chemicals. The one-pot reaction between aromatic dinucleophiles and dielectrophiles provides an operationally simple approach to highly symmetric macrocycles.[1,13] While both the fragment coupling strategy and the one-pot reaction approach also permit the synthesis of functionalized heteracalixaromatics providing the prefunctionalized starting materials are utilized, postmacrocyclization chemical manipulations constitute a more powerful and efficient protocol to generate tailor-made functional macrocycles.[1,12b,14] For example, selective halogenation of azacalix[4]pyrimidines leads to inherently chiral macrocycles that are used as excellent probes to elucidate the conformational structures of heteracalix[4]-aromatics in solution.[15] The Vilsmeier−Haack reaction of azacalixpyridines, on the other hand, proceeds in a selective fashion, affording the formylated macrocycles that are valuable platforms for sophisticated molecular architectures.[16]

Recently, we have discovered that arene C−H bond activation emerges as a very useful and practical means to functionalize heteracalixaromatics.[17] Catalyzed or mediated by a copper(II) salt, azacalix[1]arene[3]pyridines undergo efficient arene C−H bond transformations with a number of nucleophiles ranging from alkyl and alkynyl lithium reagents to 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] We have also shown that the arene C−H bond activation with copper(II) generates initially the arylcopper(II) compounds through electrophilic cupration of arenes. Subsequent oxidation of arylcopper(II) compounds by free copper(II) ion affords arylcopper(III) intermediates[19] which undergo a cross-coupling reaction with nucleophiles to form new chemical bonds.[17,18] To

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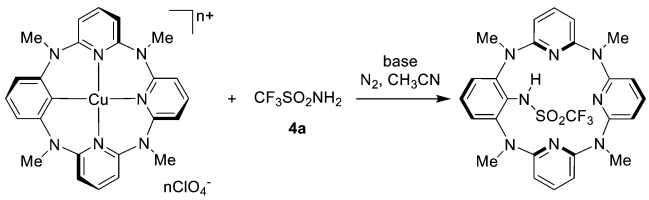
understand the reactivity of arylcopper(II) and arylcopper(III) organometallics, to further explore the synthetic utility of the Cu(II)-mediated arene C−H activation/transformation and also to obtain functionalized heteracalixaromatics that are not easily accessible by other methods, we undertook the current study. We report herein the Cu(II)-mediated arene amination reactions of azacalix[1]arene[3]pyridines with nitrogen nucleophiles, revealing the structurally well-defined arylcopper(III) compounds as reactive intermediates to cross-couple with the conjugate bases of acidic N−H reactants.

Copper-catalyzed or mediated C−H bond aminations have been attracting growing interest since Yu reported the first example of $Cu(OAc)_2$-mediated regioselective arene C−H bond amination of 2-phenylpyridine with $TsNH_2$ in 2006.[20] Some successful intermolecular and, especially, intramolecular C−N bond formation reactions from direct copper-catalyzed and mediated C−H bond functionalization using varied nitrogen sources have been documented.[21] Interestingly, different reaction mechanisms involving radicals, high valent organocopper complexes, and nitrenes as intermediates have been hypothesized.[20,21] It is worth noting that by using stable and structurally well-defined arylcopper(III) compounds which are derived from the reaction of a Cu(II) salt with *m*-phenylene-embedded azacrown ethers,[22] Stahl has demonstrated convincingly that arylcopper(III) compounds are able to react with nitrogen nucleophiles.[23]

RESULTS AND DISCUSSION

Stable and structurally well-defined macrocyclic arylcopper(II) **2** and arylcopper(III) compounds **3** were readily synthesized in high yields from the reaction of azacalix[1]arene[3]pyridines **1** with $Cu(ClO_4)_2$ under controlled conditions.[17,19] To understand the reactivity of arylcopper(II) **2** and arylcopper(III) compounds **3**, we commenced our study with the examination of their reaction with trifluoromethanesulfonamide **4** (Table 1).

Table 1. Development of the Reaction of Arylcopper Complex 2a and 3a with Trifluoromethanesulfonamide 4a



2a, n = 1, PhCu(II)
3a, n = 2, PhCu(III)

5a

entry	2a or 3a	4 (equiv)	base (equiv)	temp (°C)	time (h)	5a (%)[a]
1	**2a**	1.5	K_3PO_4 (1.5)	30	12	5
2	**2a**	1.5	K_3PO_4 (1.5)	60	6	20
3	**2a**	1.5	K_3PO_4 (1.5)	reflux	6	32
4	**3a**	1.5	K_3PO_4 (1.5)	30	12	27
5	**3a**	1.5	K_3PO_4 (1.5)	60	6	43
6	**3a**	1.5	K_3PO_4 (1.5)	reflux	6	67
7	**3a**	1.5	K_3PO_4 (1.5)	reflux	12	52
8	**3a**	1.5	K_3PO_4 (1.5)	100	6	57
9	**3a**	2.0	K_3PO_4 (2.0)	reflux	12	57
10	**3a**	4.0	K_3PO_4 (4.0)	reflux	12	46
11	**3a**	1.5	Cs_2CO_3 (1.5)	reflux	18	37
12	**3a**	1.5	DBU (1.5)	reflux	18	34

[a]Isolated yield.

The reaction of **2a** and **3a** with **4** was performed in acetonitrile under the protection of nitrogen (Table 1) since the cross-coupling reactions between arylcopper compounds and nucleophiles are reported to proceed smoothly in acetonitrile.[17] In the presence of K_3PO_4 (1.5 equiv) as a base, both arylcopper(II) and arylcopper(III) compounds were able to react with **4a** to give the C−N bond forming product **5a**. Notably, the arylcopper(III) complex **3a** exhibited greater reactivity than arylcopper(II) analog **2a**, as the former reactant afforded a much high yield of **5a** under the identical conditions (entries 1−6, Table 1). A good yield of **5a** was thus obtained in 6 h from reaction of **3a** with **4a** in refluxing acetonitrile (entry 6, Table 1). It was also noticeable that elongating the reaction period to 12 h or increasing the reaction temperature to 100 °C in a sealed tube slightly deteriorated the yield of **5a** (entries 7 and 8, Table 1). The employment of an excess amount of reactant **4a** and K_3PO_4 did not further increase the yield (entries 9 and 10). It should also be addressed that the replacement of K_3PO_4 by Cs_2CO_3 and DBU diminished the yield considerably (entries 11 and 12, Table 1). Under all reaction conditions scrutinized, in addition to desired product **5a**, the parent azacalix[1]arene[3]pyridine **1a** was also obtained from unreacted **3a** after workup (Supporting Information).

Under the optimized conditions, the scope of the cross-coupling reaction between arylcopper(III) complexes **3** with nitrogen nucleophiles **4** was tested. As summarized in Table 2, in addition to trifluoromethanesulfonamide **4a**, other sulfonamides such as methanesulfonamide **4b** and arene sulfonamides **4c−e** reacted analogously with **3a** to form the corresponding products **5b−e** in 56%−76% yields (entries 2−5, Table 2). Phthalimide **4f** also acted as a good reaction partner to high valent organocopper(III) complexes. Under the identical basic conditions, all arylcopper(III) complexes **3a−d** cross-coupled with phthalimide **4f** effectively to afford the products **5f−i** in the yields ranging from 56% to 67% (entries 6−9, Table 2). Maleimide **4g** reacted similarly with **3a** albeit the conversion was low, affording product **5j** in 37% yield (entry 10, Table 2). It should be pointed out that, in contrast to sulfonamides and imides, very low reactivity of carboxamides was observed. For example, no C−N bond forming product was observed at all when the reactions between arylcopper(III) compound **3a** and benzamide **4h** and acetamide **4i** were attempted (entries 11 and 12, Table 2).

Pleasingly, arylcopper(III) compounds exhibited excellent reactivity toward saccharin (*o*-benzoic sulfimide) **4j**. The cross-coupling reaction between **3a** and **4j** proceeded highly efficiently within 4 h. Interestingly, two C−N bond forming products **5m** and **5m′** and one C−O bond forming product **6** were obtained in 41%, 21%, and 11% yield, respectively (Scheme 1). The former two compounds **5m** and **5m′** are apparently a pair of conformers both derived from the desired C−N bond cross-coupling reaction while the latter product **6** was stemmed from the unexpected C−O bond cross-coupling reaction.

The structure of all resulting products was elucidated on the basis of spectroscopic data. To establish the structure beyond any ambiguity, and also to shed light on the conformation of these novel macrocycles, high quality single crystals of products **5a**, **5f**, **5j**, **5m**, **5m′**, and **6** were cultivated and their structures were determined by X-ray diffraction analysis. As depicted in Figures 1−4 and Figures S1−S6 (Supporting Information), all macrocyclic compounds yield the analogous slightly distorted 1,3-alternate conformation in the solid state with a N- (**5**) or an

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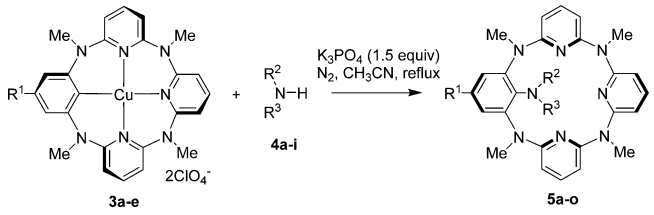
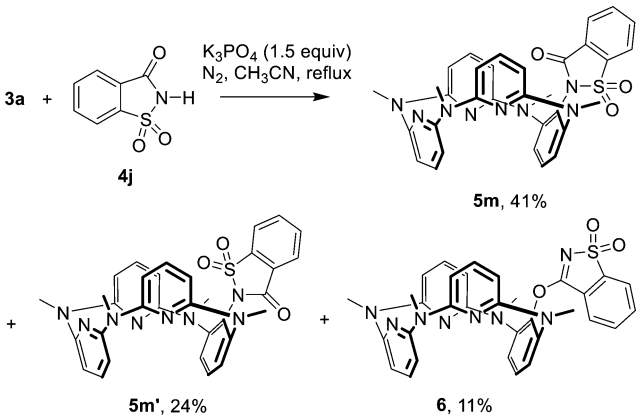
Table 2. Reaction of Arylcopper(III) Compounds 3 with Nitrogen Nucleophiles 4



entry	3	R^1	4	R^2R^3NH	pK_a[a]	time (h)	5	%[b]
1	**3a**	H	**4a**	$CF_3SO_2NH_2$	9.7	6	**5a**	67
2	**3a**	H	**4b**	$MeSO_2NH_2$	17.5	24	**5b**	56
3	**3a**	H	**4c**	$PhSO_2NH_2$	16.1	10(24)	**5c**	75(76)
4	**3a**	H	**4d**	$4\text{-}MeC_6H_4SO_2NH_2$	16.3	24	**5d**	75
5	**3a**	H	**4e**	$4\text{-}ClC_6H_4SO_2NH_2$	14.7	24	**5e**	76
6	**3a**	H	**4f**	phthalimide	13.4	24	**5f**	66
7	**3b**	Me	**4f**	phthalimide	13.4	24	**5g**	67
8	**3c**	Cl	**4f**	phthalimide	13.4	24	**5h**	65
9	**3d**	CN	**4f**	phthalimide	13.4	24	**5i**	56
10	**3a**	H	**4g**	maleimide	–	24	**5j**	37
11	**3a**	H	**4h**	$PhCONH_2$	23.3	24	**5k**	–
12	**3a**	H	**4i**	CH_3CONH_2	25.5	24	**5l**	–

[a] pK_a values in DMSO are obtained from iBonD database.[24] [b] Isolated yield.

Scheme 1. Reaction of Arylcopper(III) Compound 3a with Saccharin 4j



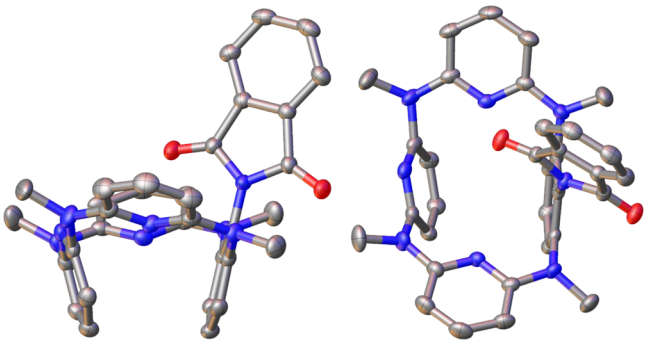


Figure 1. X-ray molecular structure of **5f** with side (left) and top views (right).

O-substituent (**6**) being at the lower rim position of the benzene ring. While the benzene ring is almost face-to-face parallel to its distal pyridine ring, the remaining two pyridine rings tend to be procumbent on the plane defined roughly by four bridging nitrogen atoms. The bond lengths of the bridging nitrogens to the carbon atoms of their adjacent procumbent pyridine rings are shorter than those to the carbons of nearly perpendicularly aligned aromatic rings (see captions in Figures S1–S6 in Supporting Information), suggesting the formation of stronger conjugation systems in the former cases. It is also evident that phthalimide and maleimide are orthogonal to the benzene ring, with nearly half of the substituent located inside the cavity while the other half outside the cavity (Figures 1 and 2). Most astonishingly, the introduced planar heterocyclic ring

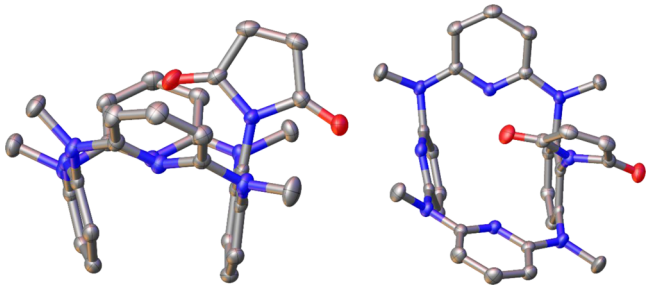


Figure 2. X-ray molecular structure of **5j** with side (left) and top views (right).

substituent of saccarin adopts two different orientations. It results in therefore two isolable conformers **5m** and **5m′** in which the carbonyl moiety is in and out of the V-shaped cleft of heteracalixaromatics, respectively (Figures 3 and 4).

The ^1H and ^{13}C NMR spectra of all acquired aminated azacalix[1]arene[3]pyridine derivatives **5** are also worth addressing. Each of the macrocyclic compounds gave a single set of proton and carbon signals at room temperature. However, the protons of maleimide group in **5j** showed a pair of doublets at 6.49 and 6.26 ppm with a coupling constant of 5.96 Hz in its ^1H NMR spectrum (Figure 5a). In its ^{13}C NMR spectrum, four carbon peaks were observed for the maleimide moiety (Figure 5b). The results indicated explicitly the nonequivalence of the maleimide substituent. Similar nonequivalent proton and carbon resonance signals were also evidenced for the phthalimide group in macrocyclic products

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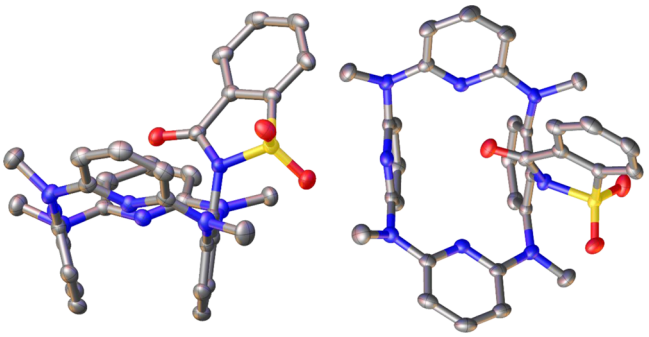

Figure 3. X-ray molecular structure of **5m** with side (left) and top views (right).

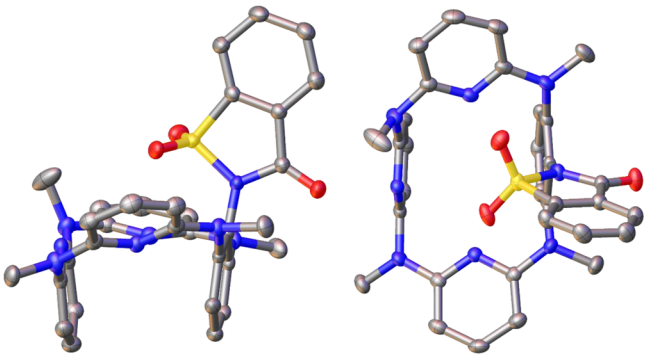

Figure 4. X-ray molecular structure of **5m′** with side (left) and top views (right).

5f–i (see Supporting Information). These NMR spectral features were in good agreement with the 1,3-alternate conformational structure in solution. In other words, because of the rigidity of the macrocyclic conformation, the newly formed C–N bonds between the arene moiety and large, planar phthalimide and maleimide could not rotate freely at room temperature relative to the NMR time scale. As a consequence, the protons and carbons of substituents inside and outside of the cavity experience different shielding or deshielding effects. As an extreme example, the cross-coupling reaction between **3a** and saccharin **4j**, a structurally unsymmetric nitrogen nucleophile, afforded two stable conformational isomers **5m** and **5m′** in solution that were even separated easily with silica gel column chromatography at room temperature. Not unexpectedly, upon heating to 140 °C, either pure in-conformer **5m** (the carbonyl is located inside the cavity) or out-conformer **5m′** (the carbonyl is positioned outside the cavity) underwent interconversion to yield an equilibrium mixture of **5m** and **5m′** in a ratio of 2:3 due to most probably accelerated bond rotation and macrocyclic ring inversion, a process being readily monitored and measured by means of ^{1}H NMR spectroscopy (Figures S7 and S8). The aforementioned outcomes demonstrated again that heteracalix[4]aromatics adopt predominantly the 1,3-alternate conformation in both the crystalline state and in solution.[15]

To gain deep insight into the reaction mechanism and also to understand the reaction outcomes of different nitrogen nucleophiles examined in the study, the correlation of the acidity of N–H reactants **4** with their reactivity was attempted.

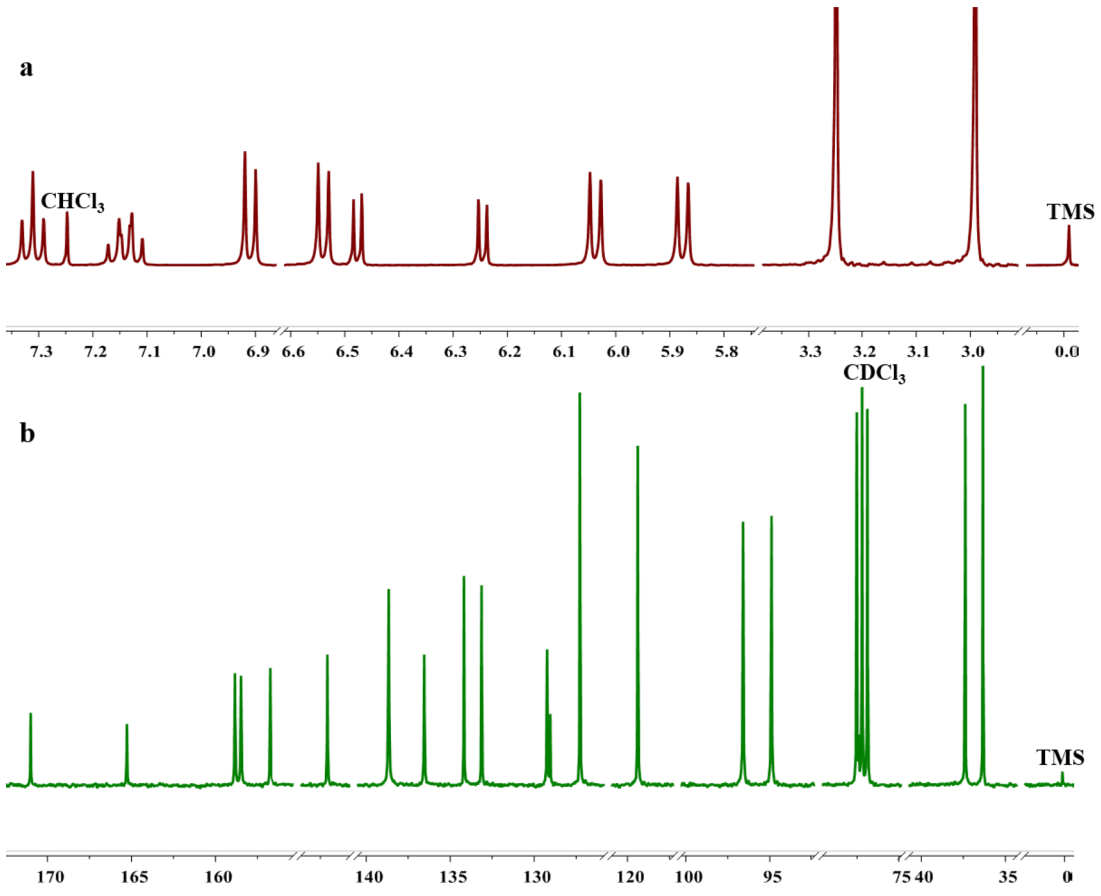

Figure 5. ^{1}H and ^{13}C NMR spectra of **5j** at room temperature.

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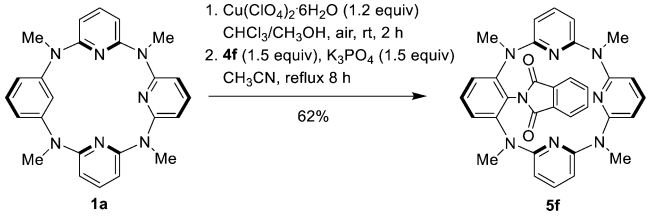
Remarkably, the nitrogen nucleophiles with pK_a smaller than 17.5 were able to react with arylcopper(III) in the presence of K_3PO_4. This has been exemplified by the observation of the reaction of the substrates including sulfonamides **4a−e** (pK_a < 17.5), phthalimide **4f** (pK_a 13.4) and saccharin **4j** (pK_a 4.0). As pK_a values in DMSO, which are tabulated in Table 2, revealed, the more acidic an N−H bond, the more reactive the nitrogen nucleophile. N−H components with pK_a values that were higher than 23.3, however, led to no effective reaction as benzamide **4h** (pK_a 23.3) and acetamide **4i** (pK_a 25.5) did not cross-couple with an arylcopper(III) intermediate **3a**. The dependence of the reactivity of nitrogen nucleophiles on the acidity of N−H bonds under basic conditions implicated an initial deprotonation step to form anion species. Subsequent binding to the copper(III) center followed by reductive elimination furnishes the C−N bond formation products **5**. Our discovery concurred with the results reported by Stahl who investigated the reaction of the azacrown ether stabilized arylcopper(III) complexes with nitrogen nucleophiles.[23]

It is worth mentioning that the synthesis of functionalized azacalix[1]arene[3]pyridine macrocycles **5** does not necessarily require the preparation and purification of arylcopper(III) complexes **3**. In other words, they can be synthesized directly and conveniently from the Cu(II)-mediated arene C−H bond amination reaction of parent macrocycles. To demonstrate the practicability of the method, a one-pot reaction was executed (Scheme 2). Thus, the treatment of azacalix[1]arene[3]-

Scheme 2. Synthesis of 5f from the Cu(II)-Mediated Arene C−H Bond Amination of 1a with Phthalimide 4f in a One-Pot Reaction Manner



pyridine **1a** with 1.2 equiv of $Cu(ClO_4)_2·6H_2O$ in a mixture of chloroform and methanol at ambient temperature under aerobic conditions led to the formation of arylcopper(III) **3a**. Further reaction with phthalimide **4f** in the presence of K_3PO_4 after replacement of solvent by acetonitrile resulted in the formation of product **5f** in 62% yield.

CONCLUSION

We have developed a method of the copper(II)-mediated arene C−H bond amination of azacalix[1]arene[3]pyridine macrocycles with various nitrogen nucleophiles under mild basic conditions. The reaction proceeded consecutively through arene C−H bond metalation via arylcopper(III) intermediates and their binding to the conjugated bases of acidic N−H nucleophiles, that were derived from deprotonation of the N−H bond of nitrogen nucleophiles of pK_a (DMSO) < 17.5, followed by reductive elimination. The method provided a facile and straightforward approach to diverse functionalized heteracalixaromatics that are not readily obtainable by other synthetic means. We have also demonstrated that the stable and structurally well-defined arylcopper(II) and arylcopper(III) compounds are valuable and unique molecular tools facilitating the mechanistic study of copper-mediated cross-coupling reactions. Applications of functionalized macrocycles in supramolecular science and of high valent organocopper complexes in the study of organometallic reactions are being actively pursued in this laboratory, and the results will be disclosed in due course.

EXPERIMENTAL SECTION

General Procedure for the Reaction of Arylcopper(III) Complexes 3a−d with Nitrogen Nucleophiles 4a−g: Synthesis of Aminated Azacalix[1]arene[3]pyridines 5a−j. Under nitrogen protection, a mixture of arylcopper(III) complexes **3a−d** (0.2 mmol), nitrogen nucleophiles **4a−g** (0.3 mmol), and K_3PO_4 (64 mg, 0.3 mmol) in dry CH_3CN (8 mL) was refluxed for a period of time (Table 2). After cooling to ambient temperature, the mixture was filtrated through a Celite pad. The filtration cake was washed with 30 mL of DCM, and the resulting filtrate was concentrated. The residue was mixed with a saturated aqueous solution of EDTA (20 mL) and then was extracted with DCM (2 × 20 mL). The combined organic layer was washed with brine (20 mL) and then dried with anhydrous Na_2SO_4. After removal of solvent, the residue was chromatographed on a silica gel column (100−200 mesh) using a mixture of petroleum ether and acetone (v/v from 30:1 to 10:1 for **5a−e** or 1:1 for **5f−j**) as mobile phase to give pure products **5a−j**. The products are fully characterized by spectroscopic data which are listed below.

5a (76 mg, 67% yield): white solid, mp 283−284 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, J = 8.2 Hz, 2H), 7.24 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 7.8 Hz, 2H), 6.55 (d, J = 7.8 Hz, 2H), 6.14 (d, J = 8.2 Hz, 2H), 6.11 (d, J = 8.2 Hz, 2H), 4.98 (s, br, 1H), 3.27 (s, 6H), 3.16 (s, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.5 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 158.9, 156.7, 147.6, 139.5, 137.9, 131.0, 130.0, 125.7, 120.3, 119.3 (q, J = 321.4 Hz), 96.4, 96.3, 39.7, 36.7; IR (KBr, cm^{-1}) ν 3436, 1601, 1577, 1564, 1476, 1449, 1425, 1403. HRMS (ESI-ion trap) calcd for $C_{26}H_{26}F_3N_8O_2S$ [M + H]$^+$ 571.1846. Found 571.1838. A high quality single crystal suitable for X-ray diffraction analysis was obtained by slow evaporation of solvents of a solution of **5a** in a mixture of *n*-hexane, DCM, and acetone at room temperature.

5b (58 mg, 56% yield): white solid, mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, J = 8.0 Hz, 2H), 7.11 (t, J = 7.8 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 6.87 (d, J = 7.8 Hz, 2H), 6.55 (d, J = 7.3 Hz, 2H), 6.10 (d, J = 7.8 Hz, 2H), 6.06 (d, J = 8.2 Hz, 2H), 5.56 (s, 1H), 3.27 (s, 6H), 3.17 (s, 6H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 158.9, 156.9, 145.2, 139.5, 137.8, 134.6, 127.6, 126.5, 120.6, 95.9, 95.2, 42.9, 38.9, 36.3; IR (KBr, cm^{-1}) ν 3340, 1597, 1578, 1561, 1479, 1424. HRMS (ESI-ion trap) calcd for $C_{26}H_{29}N_8O_2S$ [M + H]$^+$ 517.2129. Found 517.2119.

5c (87 mg, 75% yield): white solid, mp 222−223 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53−7.48 (m, 3H), 7.39−7.34 (m, 4H), 7.15−7.09 (m, 3H), 6.84 (d, J = 7.8 Hz, 2H), 6.37 (d, J = 7.8 Hz, 2H), 6.18 (d, J = 7.8 Hz, 2H), 5.73 (d, J = 8.2 Hz, 2H), 3.16 (s, 6H), 2.84 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.6, 158.4, 156.4, 145.4, 142.8, 138.9, 137.4, 132.8, 131.4, 128.6, 127.7, 126.0, 125.2, 118.4, 96.8, 96.6, 38.7, 36.5; IR (KBr, cm^{-1}) ν 3317, 1595, 1578, 1562, 1479, 1446, 1423, 1416. HRMS (ESI-ion trap) calcd for $C_{31}H_{31}N_8O_2S$ [M + H]$^+$ 579.2285. Found 579.2275.

5d (111 mg. 75% yield): white solid, mp 239 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.2 Hz, 2H), 7.33 (t, J = 8.0 Hz, 2H), 7.05−7.10 (m, 2H), 7.01 (d, J = 7.8 Hz, 2H), 6.82 (d, J = 8.0 Hz, 2H), 6.49 (d, J = 7.8 Hz, 2H), 6.08 (d, J = 7.8 Hz, 2H), 5.91 (s, 1H), 5.70 (d, J = 8.2 Hz, 2H), 3.28 (s, 6H), 2.97 (s, 6H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 158.9, 156.7, 145.8, 141.8, 140.0, 139.0, 137.7, 134.2, 129.0, 127.8, 126.3, 125.9, 120.2, 95.9, 38.9, 36.6, 21.6; IR (KBr, cm^{-1}) ν 3290, 2911, 1579, 1479, 1423. HRMS (ESI-ion trap) calcd for $C_{32}H_{32}N_8O_2S$: [M + H]$^+$ 593.2447. Found: 593.2433.

5e (117 mg, 76% yield): white solid, mp 208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.7 Hz, 2H), 7.36 (t, J = 8.0 Hz, 2H), 7.17(d, J = 8.2 Hz, 2H), 7.08 (d, t, J = 7.8 Hz, J = 2.3 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 6.49 (d, J = 7.8 Hz, 2H), 6.10 (d, J = 8.2 Hz, 2H), 6.00 (s, 1H), 5.71 (d, J = 8.2 Hz, 2H), 3.28 (s, 6H), 2.97 (s, 6H); ^{13}C

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NMR (100 MHz, $CDCl_3$) δ 159.1, 158.9, 156.7, 145.5, 141.3, 139.2, 137.8, 137.5, 134.0, 128.6, 127.9, 127.2, 126.2, 120.3, 96.0, 95.8, 38.8, 36.6; IR (KBr, cm^{-1}) ν 3446, 2906, 1578, 1477, 1424. HRMS (ESI-ion trap) calcd for $C_{31}H_{29}ClN_8O_2S$: $[M + H]^+$ 613.1901. Found: 613.1896.

5f (75mg, 66% yield): yellow solid, mp 245−246 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76−7.74 (m, 1H), 7.60−7.52 (m, 3H), 7.23−7.16 (m, 4H), 6.94 (d, J = 7.8 Hz, 2H), 6.59 (d, J = 7.3 Hz, 2H), 6.01 (d, J = 8.2 Hz, 2H), 5.77 (d, J = 7.8 Hz, 2H), 3.29 (s, 6H), 3.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 162.9, 159.1, 158.3, 156.9, 147.2, 138.5, 136.9, 133.8, 133.1, 132.4, 131.9, 129.7, 129.3, 127.3, 123.8, 122.8, 120.0, 96.3, 94.9, 37.4, 36.5; IR (KBr, cm^{-1}) ν 1720, 1596, 1575, 1561, 1468, 1446, 1419. HRMS (ESI-ion trap) calcd for $C_{33}H_{29}N_8O_2$ $[M + H]^+$ 569.2408. Found 569.2394. A high quality single crystal suitable for X-ray diffraction analysis was obtained by slow evaporation of solvents of a solution of **5f** in a mixture of *n*-hexane, DCM, and acetone at room temperature.

5g (78 mg, 67% yield): yellow solid, mp 228−229 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 6.6, 2.1 Hz, 1H), 7.58−7.51 (m, 3H), 7.25−7.18 (m, 3H), 6.76 (s, 2H), 6.61 (d, J = 7.8 Hz, 2H), 6.00 (d, J = 7.8 Hz, 2H), 5.76 (d, J = 8.2 Hz, 2H), 3.29 (s, 6H), 2.99 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 162.9, 159.1, 158.2, 156.8, 146.6, 138.7, 138.4, 135.8, 133.6, 133.0, 132.3, 131.8, 128.0, 126.6, 123.6, 122.6, 119.3, 96.2, 94.8, 37.2, 36.4, 21.3; IR (KBr, cm^{-1}) ν 1730, 1711, 1574, 1561, 1472, 1464, 1420. HRMS (ESI-ion trap) calcd for $C_{34}H_{31}N_8O_2$ $[M + H]^+$ 583.2565. Found 583.2554.

5h (78 mg, 65% yield): yellow solid, mp 257−258 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.3 Hz, 1H), 7.62−7.55 (m, 3H), 7.47 (t, J = 7.8 Hz, 1H), 7.23 (t, J = 8.0 Hz, 2H), 6.94 (s, 2H), 6.75−6.60 (2H), 6.04 (d, J = 8.2 Hz, 2H), 5.78 (d, J = 7.8 Hz, 2H), 3.30 (s, 6H), 2.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 162.8, 159.0, 158.1, 156.6, 148.1, 138.7, 136.7, 134.0, 133.9, 133.3, 132.2, 131.8, 128.6, 127.9, 123.9, 122.9, 119.7, 96.8, 95.1, 37.2, 36.4; IR (KBr, cm^{-1}) ν 1729, 1712, 1572, 1470, 1422. HRMS (ESI-ion trap) calcd for $C_{33}H_{28}ClN_8O_2$ $[M + H]^+$ 603.2018. Found 603.2009.

5i (66 mg, 56% yield): yellow solid, mp >300 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.3 Hz, 1H), 7.64−7.56 (m, 3H), 7.48 (t, J = 7.8 Hz, 1H), 7.23 (t, J = 8.0 Hz, 2H), 7.23 (s, 2H), 6.67 (d, J = 7.8 Hz, 2H), 6.06 (d, J = 7.8 Hz, 2H), 5.80 (d, J = 7.8 Hz, 2H), 3.29 (s, 6H), 3.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 162.4, 159.2, 158.1, 156.4, 148.5, 138.9, 136.9, 134.9, 134.2, 133.5, 132.1, 131.6, 131.1, 124.0, 123.1, 119.5, 118.4, 112.8, 97.4, 95.3, 37.0, 36.5; IR (KBr, cm^{-1}) ν 2225, 1731, 1712, 1577, 1565, 1469, 1421. HRMS (ESI-ion trap) calcd for $C_{34}H_{28}N_9O_2$ $[M + H]^+$ 594.2361. Found 594.2351.

5j (38 mg, 37% yield): yellow solid, mp 252−253 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, J = 7.8 Hz, 2H), δ 7.16 (t, J = 8.0 Hz, 1H), δ 7.14 (t, J = 7.6 Hz, 1H),, 6.92 (d, J = 7.8 Hz, 2H), 6.55 (d, J = 7.8 Hz, 2H), 6.49 (d, J = 6.0 Hz, 1H), 6.26 (d, J = 6.4 Hz, 1H), 6.05 (d, J = 7.8 Hz, 2H), 5.89 (d, J = 7.8 Hz, 2H), 3.26 (s, 6H), 3.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 165.2, 158.8, 158.5, 156.7, 147.0, 138.6, 136.5, 134.1, 133.1, 129.2, 129.0, 127.2, 119.4, 96.6, 94.9, 37.4, 36.3; IR (KBr, cm^{-1}) ν 1717, 1577, 1561, 1466, 1447. HRMS (ESI-ion trap) calcd for $C_{29}H_{27}N_8O_2$ $[M + H]^+$ 519.2252. Found 519.2242. A high quality single crystal suitable for X-ray diffraction analysis was obtained by slow evaporation of solvents of a solution of **5j** in a mixture of DCM and acetone at room temperature.

Reaction of 3a with Saccharin 4j. Following the aforementioned general procedure, the reaction of **3a** (171 mg, 0.25 mmol) with saccharin **4j** (69 mg, 0.375 mmol) afforded, after silica gel column chromatography elution with a mixture of petroleum ether and acetone (v/v from 10:1 to 3:1), products **5m**, **5m′**, and **6**. Their characterization data are listed as follows.

5m (62 mg, 41% yield): yellow solid, mp 290−291 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 7.3 Hz, 1H), 7.70 (td, J = 8.0, 0.8 Hz, 1H), 7.62 (td, J = 7.6, 0.9 Hz, 1H), 7.29 (t, J = 7.8 Hz, 2H), 7.23 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 7.8 Hz, 2H), 6.58 (d, J = 7.3 Hz, 2H), 6.05 (d, J = 7.8 Hz, 2H), 5.92 (d, J = 8.2 Hz, 2H), 3.28 (s, 6H), 3.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 157.9, 157.4, 155.3, 148.7, 138.4, 138.0, 136.8, 133.8, 133.7, 130.2, 128.0, 127.3, 125.6, 120.2, 119.2, 96.5, 96.3, 39.4, 36.5; IR (KBr, cm^{-1}) ν 2905, 1759, 1578, 1467, 1421, 1339, 1183. HRMS (ESI-ion trap) calcd for $C_{32}H_{29}N_8O_3S$: $[M + H]^+$ 605.2078. Found: 605.2059. A high quality single crystal suitable for X-ray diffraction analysis was obtained by diffusing *n*-hexane vapor into the solution of **5m** in DCM.

5m′ (36 mg, 24% yield): yellow solid, mp 289−290 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 1H), 7.70 (m, 2H), 7.60 (m, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.26 (m, 2H), 7.00 (d, J = 7.2 Hz, 2H), 6.58 (d, J = 6.9 Hz, 2H), 6.08 (d, J = 7.8 Hz, 2H), 5.90 (d, J = 7.3 Hz, 2H), 3.27 (s, 6H), 3.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 158.6, 158.5, 148.3, 138.4, 137.4, 134.6, 133.4, 131.1, 129.8, 128.1, 126.2, 124.8, 121.2, 119.7, 96.2, 94.9, 37.1, 36.5; IR (KBr, cm^{-1}) ν 2906, 1728, 1577, 1463, 1422,1365, 1302. HRMS (ESI-ion trap) calcd for $C_{32}H_{29}N_8O_3S$: $[M + H]^+$ 605.2078. Found: 605.2054. A high quality single crystal suitable for X-ray diffraction analysis was obtained by diffusing *n*-hexane vapor into the solution of **5m′** in DCM.

6 (17 mg, 11% yield): yellow solid, mp 262−263 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.8 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.29−7.24 (m, 3H), 7.14 (t, J = 7.8 Hz, 1H), 6.96 (d, J = 7.8 Hz, 2H), 6.66 (d, J = 7.3 Hz, 2H), 6.07 (d, J = 8.2 Hz, 2H), 5.84 (d, J = 8.2 Hz, 2H), 3.29 (s, 6H), 3.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 158.8, 158.9, 158.4, 156.8, 147.2, 143.4, 139.9, 138.9, 137.9, 133.9, 133.3, 127.2, 125.9, 124.5, 121.4, 120.3, 95.9, 95.4, 38.2, 36.6; IR (KBr, cm^{-1}) ν 2927, 1578, 1561, 1470, 1173. HRMS (ESI-ion trap) calcd for $C_{32}H_{29}N_8O_3S$: $[M + H]^+$ 605.2078. Found: 605.2056. A high quality single crystal suitable for X-ray diffraction analysis was obtained by diffusing *n*-hexane vapor into the solution of **6** in DCM.

One-Pot Cu(II)-Mediated Reaction of Azacalix[1]arene[3]-pyridine 1a with Phthalimide 4f. Azacalix[1]arene[3]pyridine **1a** (85 mg, 0.2 mmol) and $Cu(ClO_4)_2{\cdot}6H_2O$ (89 mg, 0.24 mmol) were mixed in chloroform (4 mL) and methanol (4 mL). The reaction mixture was allowed to stir for 2 h at room temperature under air. After removal of solvent under vacuum, the residue was mixed with phthalimide **4f** (44 mg, 0.3 mmol) and K_3PO_4 (64 mg, 0.3 mmol) in dry acetonitrile (8 mL). The resulting mixture was refluxed for 8 h. Workup followed the same procedure as that for the reaction between **3** and **4f** affording product **5f** (71 mg, 62%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01448.

X-ray structure of **5a** (CIF)
X-ray structure of **5f** (CIF)
X-ray structure of **5j** (CIF)
X-ray structure of **5m** (CIF)
X-ray structure of **5m′** (CIF)
X-ray structure of **6** (CIF)
^1H and ^{13}C NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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