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Regiospecific Functionalization of Azacalixaromatics through Copper-Mediated Aryl C–H Activation and C–O Bond Formation

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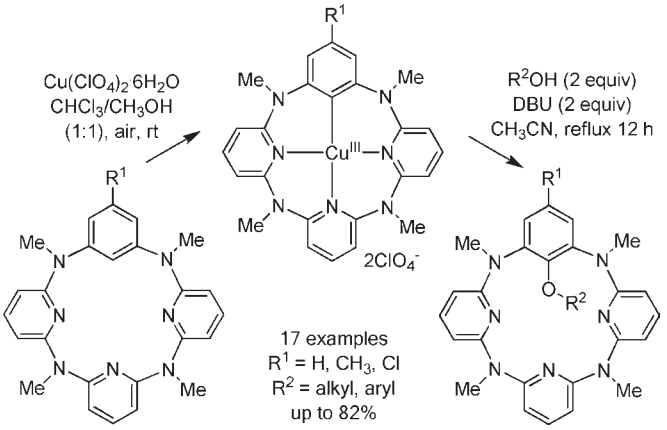
ABSTRACT



Regiospecific functionalization of tetraazacalix[1]arene[3]pyridines at the lower rim position of the benzene ring was achieved conveniently from their cross-coupling reaction with both aliphatic alcohols including chiral primary and secondary alcohols and phenol derivatives through the $Cu(ClO_4)_2$-mediated aerobic aryl C–H activation, which gave structurally well-defined aryl–Cu(III) intermediates and a subsequent C–O bond formation reaction under very mild conditions.

Heteracalixaromatics,[1] or heteroatom-bridged calixaromatics, are a new generation of macrocyclic host molecules that have gained considerable attention in recent years in the study of supramolecular chemistry. Being different from the methylene linkage in the conventional calixarenes,[2] heteroatoms such as nitrogen can adopt sp^2 and sp^3 electronic configurations to form remarkably varied conjugation systems with their adjacent aromatic rings, producing macrocycles of unique conformational structures and of fine-tunable sizes.[3−7] Furthermore, introduction of heteroatoms into the bridging positions leads to the regulation of binding ability of aromatic rings of resultant macrocyclic

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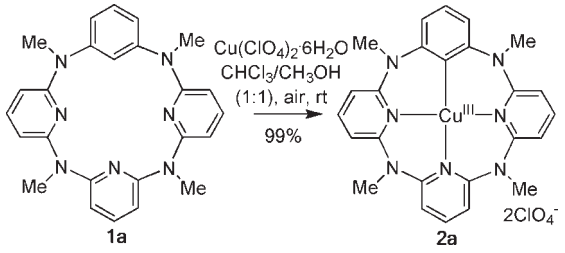
hosts.[8−10] For example, tetraazacalix[4]pyridines exhibit enhanced interactions with transition-metal ions[8] and hydrogen-bond donors,[7,9] whereas tetraoxacalix[2]arene[2]triazines form complexes with halides via anion−π interactions.[10]

The fragment coupling approach[1a−d,3,4,11] and the one-pot reaction protocol[1a−d,12] provide effective synthetic routes to heteracalixaromatics. Starting from prefunctionalized aromatic bisnucleophiles and biselectrophiles, a few functionalized heteracalixaromatics have also been synthesized.[12a,d,13−15] An attractive strategy for the construction of functionalized heteracalixaromatics, however, relies on the chemical fabrication of easily available heteracalixaromatic compounds. In other words, basic heteracalixaromatics can serve as platforms for the synthesis of sophisticated molecular architectures.[1a−d,3,12e,16] Advantageously, the "platform strategy" avoids the linear or one-directional synthesis of each individual macrocycle. It is amenable to the construction of macrocyclic heteracalixaromatic libraries. In addition, versatile chemical manipulations on both aromatic rings and bridging positions lead to the flourishing of molecular diversity. Moreover, the successful control of regio- and site-selectivities provides an enabling method for the tailor-made macrocyclic molecules.

Scheme 1. $Cu(ClO_4)_2$-Mediated Aryl C−H Activation



We[17] have discovered recently that azacalix[1]arene[3]pyridine **1a** undergoes aryl C−H bond activation efficiently with $Cu(ClO_4)_2$ under mild aerobic conditions to yield stable and structurally well-defined aryl−Cu(III) complex **2a** (Scheme 1). The aryl−Cu(III) complex **2a** reacts readily at ambient temperature with a number of nucleophiles including halides, cyanide, isothiocyanate, and carboxylates to form C−X, C−C, C−S, and C−O bonds, respectively, in almost quantitative yield. The chemistry of the well-defined aryl-Cu(III) species **3** has been studied nicely by Ribas[18] and Stalh[19] (Figure 1). It is their very recent report[20] on the C−O bond formation reaction that prompts us to disclose our study. In this paper, we present the regiospecific functionalization of azacalix[1]arene[3]pyridines by means of their cross-coupling reaction with a variety of both aliphatic alcohols including primary and secondary chiral alcohols and phenol derivatives through aryl−Cu(III) intermediates.

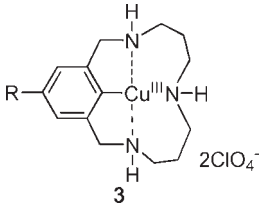


Figure 1. Aryl−Cu(III) complex pioneered by Ribas[18] and Stalh.[19]

We began our investigation with the examination of the reaction of aryl−Cu(III) complex **2a** with ethanol (2 equiv) (Table 1). Aryl−Cu(III) complex **2a** was found stable and inert toward ethanol as it was intact after refluxing in acetonitrile for 12 h (entry 1, Table 1). A trace amount of the desired C−O bond-forming product **5a** was observed when 1 equiv of an organic base such as triethylamine (entry 2, Table 1), 2,4,6-trimethylpyridine (collidine) (entry 3, Table 1), or 4-(*N,N,*-dimethylamino)pyridine (DMAP) (entry 4, Table 1) was used. To our delight, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a strong organic base,

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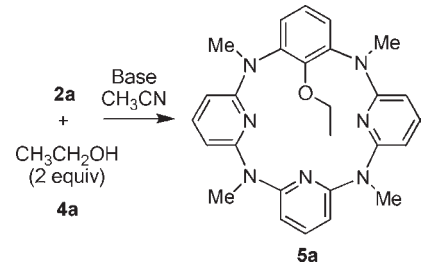
Table 1. Reaction between Aryl−Cu(III) Complex **2a** and Ethanol **4a**[a]



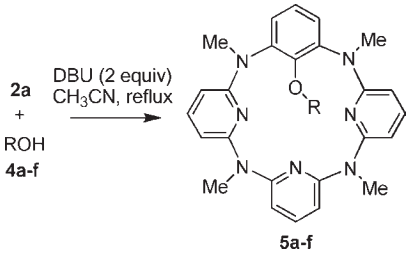
entry	base (equiv)	T (°C)	time (h)	**5a**[b] (%)
1		reflux	12	0
2	Et_3N (1)	reflux	12	trace
3	Collidine (1)	reflux	12	trace
4	DMAP (1)	reflux	12	trace
5	DBU (1)	reflux	12	47
6	DBU (2)	reflux	12	61
7	DBU (2)	reflux	24	62
8[c]	DBU (2)	reflux	12	42
9[d]	DBU (2)	reflux	12	59
10	DBU (2)	40	12	41
11	DBU (2)	rt	12	33
12	Na_2CO_3 (2)	reflux	12	trace
13	K_2CO_3 (2)	reflux	12	trace
14	NaOH (2)	reflux	12	21
15	KOH (2)	reflux	12	42
16	EtONa (2)	reflux	12	51

[a] A mixture of **2a** and ethanol (2 equiv) was reacted in acetonitrile. [b] Isolated yield. [c] Ethanol (1 equiv) was used. [d] Ethanol (1 mL) was used.

promotes the cross-coupling reaction to produce **5a** in 47% isolated yield (entry 5, Table 1). The chemical yield of **5a** was improved to 61% when 2 equiv of DBU was employed (entry 6, Table 1). Elongation of reaction time to 24 h led to 62% yield (entry 7, Table 1). The use of an excess amount of ethanol resulted in a comparable result (entry 9, Table 1), whereas equimolar ethanol led to a low yield (entry 8, Table 1). It should be noted that the identical reaction performed at a lower temperature afforded diminished yields (entries 10 and 11, Table 1). Inorganic bases showed no superiority over organic bases, as the employment of a weak inorganic base like Na_2CO_3 (entry 12, Table 1) and K_2CO_3 (entry 13, Table 1) almost did not effect the reaction, whereas NaOH (entry 14, Table 1) and KOH (entry 15, Table 1) led to the formation of **5a** only in 21% and 42%, respectively. The application of sodium ethoxide yielded **5a** in 51% (entry 16, Table 1).

Under the optimized conditions, a number of alkoxylated tetraazacalix[1]arene[3]pyridines **5b**−**f** were synthesized from aliphatic alcohols **4b**−**f**. As compiled in Table 2, all primary alcohols examined such as ethanol **4a**, methanol **4b**, benzylic alcohol **4c**, and 3-phenylprop-2-yn-2-ol **4d** underwent equally efficient coupling reaction to produce the corresponding C−O bond-forming products **5a**−**d** in 57%-68% (entries 1 to 4, Table 2), with the exception of cyclopropylmethanol **4e**, which gave **5e** in 26% (entry 5, Table 2). This is probably due to low stability of the small ring substrate under the reaction conditions. The reaction between **2a** and isopropyl alcohol **4f**, a secondary alcohol species, proceeded analogously to afford **5f** albeit in a slightly low yield (entry 6, Table 2). However, no reaction was observed for tertiary butyl alcohol **4g** (entry 7, Table 2). The outcomes indicated clearly the steric effect in the C−O bond forming reaction between aryl−Cu(III) complex **2a** and aliphatic alcohols **4**.

Table 2. Synthesis of Alkoxylated Azacalixaromatics[a]



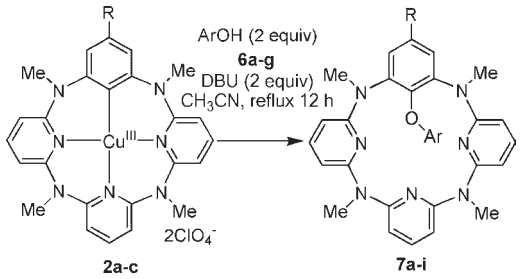
entry	**4**	ROH	**5**[b] (%)
1	**4a**	EtOH	**5a** (61)
2	**4b**	MeOH	**5b** (57)
3	**4c**	BnOH	**5c** (56)
4	**4d**	$PhC{\equiv}CCH_2OH$	**5d** (68)
5	**4e**	c-$C_3H_5CH_2OH$	**5e** (26)
6	**4f**	^{i}PrOH	**5f** (46)
7	**4g**	^{t}BuOH	**5g** (0)

[a] A mixture of **2a**, alcohol **4** (2 equiv), and DBU (2 equiv) was refluxed in acetonitrile for 12 h. [b] Isolated yield.

In the presence of DBU, aryl−Cu(III) complexes **2a**−**c** were able to react smoothly in refluxing acetonitrile with phenols **6a**−**g** tested in this study. For example, the cross-coupling reaction between **2a** and phenol **6a** and its analogues **6b**−**f** bearing either one electron-withdrawing halogen and nitro group or electron-donating methyl group at the *ortho*-, *meta*-, or *para*-position afforded diaryl ether-containing tetraazacalixaromatics **7a**−**f** in yields ranging from 50% to 82% (entries 1−6, Table 3). Disubstituted phenol derivative, 4-chloro-3-methylphenol **6g**, underwent a similar reaction to yield **7g** in 48% yield (entry 6, Table 3). Azacalix[1]arene[3]pyridine that contains a *p*-methyl (**2b**) or a *p*-chloro (**2c**) at the benzene ring is also functionalized with 4-chlorophenol **6c** effectively (entries 7 and 8, Table 3). It is worth noting that substituents such as chloro, bromo, and nitro are tolerated under reaction conditions, and they provide a useful handle for further chemical manipulations.

The facile C−O cross-coupling reaction encouraged us to explore the construction of chiral macrocycles using enantiomerically pure chiral alcohols as reactants. Thus, following the same reaction procedure, chiral tetraazacalix[1]arene[3]pyridine **8a** was obtained in

Table 3. Synthesis of Aryloxylated Azacalixaromatics **7**



entry	**2**	**6** ArOH	**7**[a] (%)
1	**2a**, R = H	**6a**, PhOH	**7a** (64)
2	**2a**, R = H	**6b**, 2-ClC_6H_4OH	**7b** (65)
3	**2a**, R = H	**6c**, 4-ClC_6H_4OH	**7c** (79)
4	**2a**, R = H	**6d**, 3-Me-C_6H_4OH	**7d** (50)
5	**2a**, R = H	**6e**, 4-Br-C_6H_4OH	**7e** (73)
6	**2a**, R = H	**6f**, 4-NO_2-C_6H_4OH	**7f** (82)
7	**2a**, R = H	**6g**, 4-Cl-3-Me-C_6H_3OH	**7g** (48)
8	**2b**, R = Me	**6c**, 4-Cl-C_6H_4OH	**7h** (78)
9	**2c**, R = Cl	**6c**, 4-Cl-C_6H_4OH	**7i** (66)

[a] Isolated yield.

46% from (*S*)-2-methylbutanol, a primary alcohol with a β-stereogenic center. The employment of (*S*)-2-phenylethanol, a secondary chiral alcohol, in the reaction with **2a** afforded chiral macrocyclic product **8b** in 35% (Figure 2).

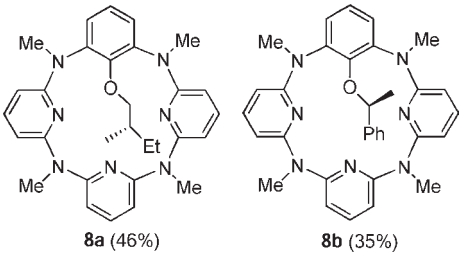
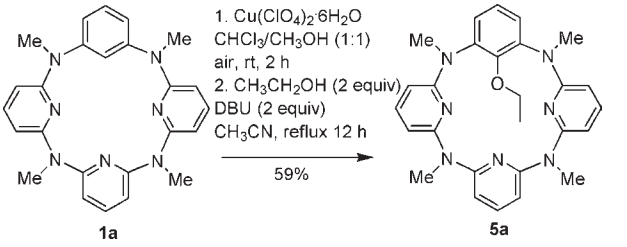


Figure 2. Chiral tetraazacalix[1]arene[3]pyridine derivatives **8**.

The synthesis of regiospecifically functionalized azacalix[1]arene[3]pyridines does not necessarily require the isolation of an aryl−Cu(III) intermediate. To demonstrate the efficacy of the copper-mediated C−O cross-coupling reaction in the synthesis of functionalized macrocyclic compound, we conducted the preparation of **5a** simply by stirring at ambient temperature a mixture of **1a** and $Cu(OCl_4)_2 \cdot 6H_2O$ in chloroform and methanol (1:1) in an open vial for 2 h followed by, after removal of solvent, refluxing the residue with ethanol (2 equiv) and DBU (2 equiv) in acetonitrile for 12 h (Scheme 2).

The structure of the functionalized azacalix[1]arene[3]pyridine products was established on the basis of their

Scheme 2. One-Pot Straightforward Synthesis of **5a**



spectroscopic data, microanalyses, and X-ray crystallography (see the Supporting Information). Figure 3 illustrates the X-ray structure of **7c**. In the crystalline state, the molecule adopts a slightly distorted 1,3-alternate conformation, with the benzene ring being almost face-to-face paralleled to its distal pyridine ring. Interestingly, the 4-chlorophenyl moiety is included in the V-shaped cleft formed by another two pyridine rings of the macrocycle. The distances of the C(8) atom to the N(2) and N(6) atoms are 3.06 and 3.28 Å, respectively.

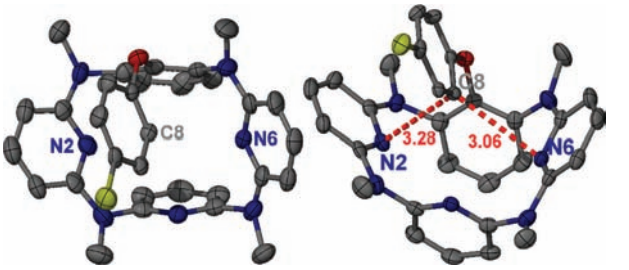


Figure 3. X-ray structure of **7c**.

In summary, we have established a straightforward and convenient method for the regiospecific functionalization of azacalix[1]arene[3]pyridines on the lower rim position of the benzene ring by means of the $Cu(ClO_4)_2$-mediated aryl C−H bond activation and subsequent C−O bond formation with a variety of aliphatic alcohols and phenols. The application of the resulting alkoxylated and aryloxylated products in molecular recognition and self-assembly is being actively pursued in this laboratory.

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Supporting Information Available. Full experimental details and characterization data; X-ray structure of **7c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.