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Construction of $C_{aryl}-C_{alkynyl}$ Bond from Copper-Mediated Arene–Alkyne and Aryl Iodide–Alkyne Cross-Coupling Reactions: A Common Aryl-Cu^{III} Intermediate in Arene C–H Activation and Castro–Stephens Reaction

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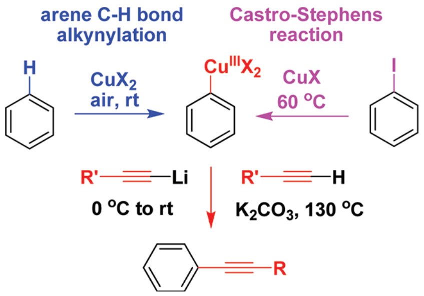
ABSTRACT



Both copper(II)-mediated oxidative C–H bond activation and oxidative addition of copper(I) into a C–I bond produced an identical and structurally well-defined aryl-Cu(III) intermediate. The cross-coupling reaction of an aryl-Cu(III) intermediate with both terminal alkynes at an elevated temperature and alkynyllithium reagents under mild conditions led effectively to the formation of a $C_{aryl}-C_{alkynyl}$ bond. An alternative mechanism has been proposed for the Castro–Stephens reaction.

The C–H bond activation of aromatic compounds using cost-efficient and eco-benign copper salts has received considerable attention in recent years.[1] Since Yu's seminal work of $Cu(OAc)_2$-catalyzed arene C–H functionalization of 2-arylpyridines in 2006,[2] a number of copper salt catalyzed and mediated intramolecular and intermolecular aryl C–H bond transformations including C–X (X = halogen, N, O, and S) and $C_{aryl}-C_{aryl}$ bond formations have been reported, either employing the directing-group strategy or starting with activated aromatic reactants.[3] Despite the burgeoning of copper salt catalyzed and mediated aryl C–H bond activations and transformations, understanding the reaction mechanism remains largely elusive and challenging. For instance, reaction processes involving single electron transfer[2] and organocopper intermediates of varied oxidative states[3b,p–s] have been hypothesized. Although organocopper(III) intermediates have been widely proposed in Cu-catalyzed reactions,[4–6] well-defined organocopper(III) compounds are scarcely reported.[7–9] Hedman, Hodgson, and Llobet et al.[7] reported in 2002 the aryl-Cu(III) complexes **A** (Scheme 1) from the reaction of triazamacrocyclic ligands and $Cu(ClO_4)_2 \cdot 6H_2O$ under *anaerobic* conditions.[7a] The resulting aryl-Cu(III) complexes **A** have been shown very recently by Stahl[7b,10,11] and Ribas[7b,11] to react with heteroatom nucleophiles to form C–N, C–O, and carbon–halogen bonds.

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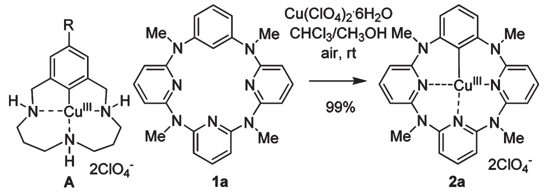
Heteracalixaromatics, the heteroatom-bridged calixaromatics, are a new generation of functional macrocyclic host molecules in supramolecular chemistry.[12] The diverse macrocycles from the combination of heteroatoms and (hetero)aromatic rings, combined with tunable conformations and cavities of varied electronic features owing to the nature of the bridging heteroatoms and their ability to form different conjugation systems with adjacent (hetero)aromatic components, render heteracalixaromatics highly versatile in the recognition of various electron-neutral and charged guest species and in the construction of supramolecular assemblies. We[8] have reported recently that azacalix[1]arene[3]pyridine **1a** undergoes highly efficient aryl C−H bond activation with $Cu(ClO_4)_2 \cdot 6H_2O$ under mild *aerobic* conditions to form a stable aryl-Cu(III) compound **2a** quantitatively (Scheme 1). At ambient temperature, aryl-Cu(III) **2a** reacts very rapidly with diverse nucleophilic reagents including halides,[8] various carboxylates,[8] cyanide,[8] thiocyanate,[8] and both aliphatic and aromatic alcohols,[13] enabling therefore the efficient functionalization of arene C−H bonds. To shed light on the reactivity of highly valent organocopper compounds and to explore applications of aryl-Cu(III) complexes in the synthesis of tailor-made functional heteracalixaromatics, we undertook the current C−C cross-coupling reaction study. We report herein the unprecedented $C_{aryl}-C_{alkynyl}$ bond formation from the cross-coupling of arenes with alkynyllithium reagents via the structurally well-defined aryl-Cu(III) intermediates. We also demonstrate for the first time that the Castro−Stephens reaction, the Cu(I)-mediated coupling between aryl halides and terminal alkynes, proceeds via an arylcopper(III) intermediate, suggesting an alternative reaction pathway in addition to a believed copper(I)-involved four-center transition state.

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



We initiated our study with examination of the reaction between pure aryl-Cu(III) species **2a** and (phenylethynyl)lithium **3a** (Table 1). At ambient temperature, the reaction proceeded smoothly in THF to afford the desired cross-coupling product **4a** in 28% yield, along with the isolation of azacalix[1]arene[3]pyridine **1a** in 47% yield and a trace amount of 1,4-diphenylbuta-1,3-diyne **5a**, which formed most likely from the homocoupling of alkyne (entry 1, Table 1). The yield of **4a** was then improved to 54% when 2 equiv of **3a** were used (entry 2, Table 1). A further increase of the ratio of **3a** over **1a** only gave rise to a marginal increase of the chemical yield of **4a** (entries 5 and 6, Table 1). Short reaction times led to a decrease in the formation of **4a** (entry 3, Table 1), while a longer reaction period did not affect the yield (entry 4, Table 1). The reaction was not very sensitive to low temperatures (entries 7 and 8, Table 1), whereas an elevated temperature had a detrimental effect on the reaction (entry 9, Table 1). It is interesting to note that oxygen did not interfere with the cross-coupling as the reaction exposed to oxygen (1 atm) proceeded equally well to produce **4a** in a comparable yield, albeit the oxidative atmosphere facilitated the formation of homocoupling product **5a** from **3a** (entry 10, Table 1). The use of other solvents such as 1,4-dioxane, diethyl ether, 1,2-dimethoxyethane, and toluene resulted in lower yields (see Supporting Information (SI)).

Under the optimized conditions, the generality of the cross-coupling reaction of the aryl-Cu(III) species with alkynyllithiums was investigated. We were pleased to find that all alkynyllithiums **3b**−**i** tested underwent reaction with aryl-Cu(III) compounds **2a**−**c** to give products **4b**−**m** in 34−87% yields (Table 2). As assembled in Table 2, for

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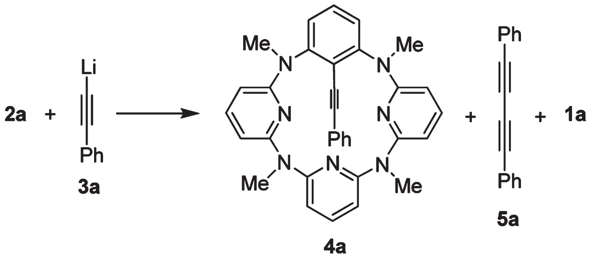
example, alkynyllithium reagents bearing a benzene ring that is substituted by an electron-donating or -withdrawing group (entries 1–3, Table 2), a 2-thienyl moiety (entry 4, Table 2), or an aliphatic substituent such as a (cyclohexyl)-methyl (entry 5, Table 2) and *tert*-butyl group (entry 6, Table 2) reacted effectively with **2a** to afford the corresponding products **4b**–**g**. The reaction of [(trimethylsilyl)-ethynyl]lithium **3h** with **2a** proceeded equally efficiently to yield **4h** in 59% yield (entry 7, Table 2). Aryl-Cu(III) complexes containing a *para*-methyl (**2b**) or chloro group (**2c**) were also good substrates in the cross-coupling reaction with **3b** and **3h**, with moderate to good yields of the products **4i**–**l** being obtained (entries 8–11). The reaction of [(4′-ethynylbiphenyl-4-yl)ethynyl]lithium **3i** with aryl-Cu(III) complex **2a** was also effective, resulting in the formation of functionalized macrocycle **4m**, albeit in a slightly lower yield (entry 12, Table 2).

Table 1. Optimization of Reaction between **2a** and **3a**[a]

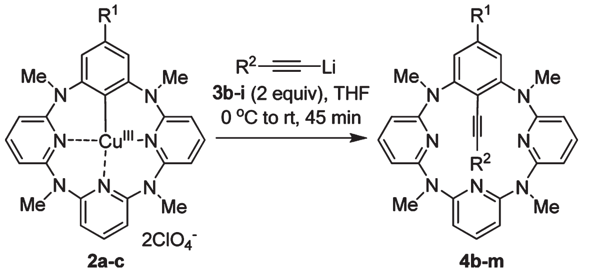


entry	2a:3a	temp	**4a** (%)	**5a** (%)	**1a** (%)
1	1:1	0 °C → rt	28	3	47
2	1:2	0 °C → rt	54	19	26
3[b]	1:2	0 °C → rt	49	17	29
4[c]	1:2	0 °C → rt	53	18	27
5	1:3	0 °C → rt	58	11	21
6	1:4	0 °C → rt	56	13	30
7	1:2	−40 °C	48	11	32
8	1:2	0 °C	50	12	32
9	1:2	0 °C → 60 °C	24	15	42
10[d]	1:2	0 °C → rt	53	27	28

[a] To a solution of **2a** (0.5 mmol) in THF at 0 °C was added a solution of **3a** in THF. After 10 min, the reaction mixture was kept stirring at room temperature for 45 min. All yields are isolated yields. [b] Reaction time was 30 min. [c] Reaction time was 23 h. [d] Under O_2 (1 atm) atmosphere.

To demonstrate the simplicity and practicality of copper salt mediated aryl C–H bond activation and functionalization, tandem aryl C–H activation and C_{aryl}–$C_{alkynyl}$ bond formation reactions were conducted. Without isolation and purification of aryl-Cu(III) complex **2a**, direct aryl C–H activation of azacalix[1]arene[3]pyridine **1a** with $Cu(ClO_4)\cdot 6H_2O$ in an open vial followed by, after removal of solvent, treatment with (phenylethynyl)lithium **3a** in THF furnished **4a** in 51% yield (Scheme 2).

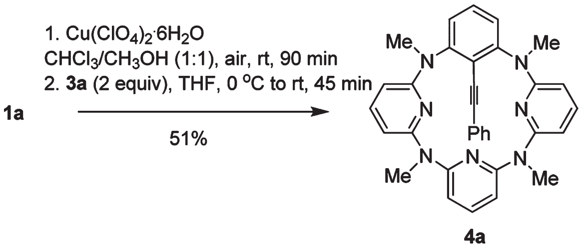
Table 2. Cross-Coupling Reaction between **2** and **3**



entry	reactant **2**	reactant **3**	**4** (%)[a]
1	**2a** (R^1 = H)	**3b** (R^2 = 4-*t*-Bu-C_6H_4)	**4b** (71)
2	**2a** (R^1 = H)	**3c** (R^2 = 4-MeO-C_6H_4)	**4c** (43)
3	**2a** (R^1 = H)	**3d** (R^2 = 4-F-C_6H_4)	**4d** (50)
4	**2a** (R^1 = H)	**3e** (R^2 = 2-thienyl)	**4e** (56)
5	**2a** (R^1 = H)	**3f** (R^2 = *c*-$C_6H_{11}CH_2$)	**4f** (41)
6	**2a** (R^1 = H)	**3g** (R^2 = *t*-Bu)	**4g** (66)
7	**2a** (R^1 = H)	**3h** (R^2 = Me_3Si)	**4h** (59)
8	**2b** (R^1 = Me)	**3b** (R^2 = 4-*t*-Bu-C_6H_4)	**4i** (75)
9	**2b** (R^1 = Me)	**3h** (R^2 = Me_3Si)	**4j** (58)
10	**2c** (R^1 = Cl)	**3b** (R^2 = 4-*t*-Bu-C_6H_4)	**4k** (87)
11	**2c** (R^1 = Cl)	**3h** (R^2 = Me_3Si)	**4l** (51)
12	**2a** (R^1 = H)	**3i** (R^2 = EBP[b])	**4m** (34)

[a] Isolated yield. [b] EBP = 4′-ethynylbiphenyl-4-yl.

Scheme 2. One-Pot Synthesis of **4a**



It is worth mentioning that, to the best of our knowledge, the above results represent the first example of C–C bond formation mediated by an isolable Cu(III) species.[14] This novel and unique C_{aryl}–$C_{alkynyl}$ bond formation reaction is also reminiscent of the seemingly relevant Castro–Stephens reaction between aryl halides and terminal alkynes,[15] which is mediated by Cu(I) salts. The mechanism of this designated name reaction has long been believed to proceed through a vague four-centered transition state.[16] Discovery of the high reactivity of arylcopper(III) complexes toward alkynyllithiums led us to investigate the alternative pathway of the Castro–Stephens reaction. As depicted in Scheme 3,

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(14) CuI-catalyzed benzylation of pentafluorobenzene with benzyl bromide was reported in ref 3s, and $Cu(acac)_2$-catalyzed allylation of electron-deficient arenes with ally phosphates was reported in ref 3w.

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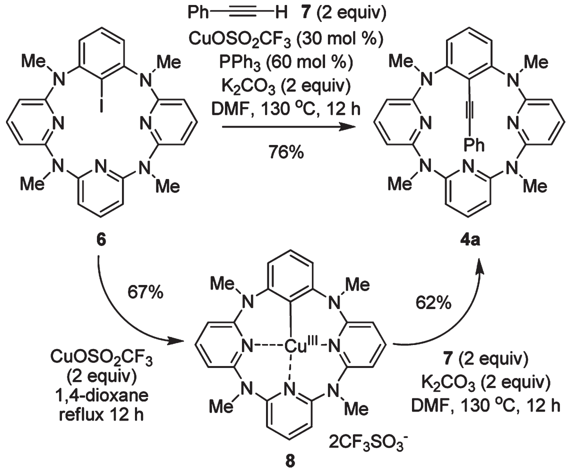
in the presence of a substoichiometric amount of CuOSO$_2$CF$_3$ under typical Castro–Stephens reaction conditions, reaction of iodobenzene compound **6**[8] with ethynylbenzene **7** afforded cross-coupling product **4a** in 76% yield. Significantly, interaction of iodo-substituted azacalix[1]arene[3]pyridine **6**[8] with a Cu(I) salt produced a highly valent organocopper product aryl-Cu^{III}[OSO$_2$CF$_3$]$_2$ **8** in 67% yield. The same aryl-Cu^{III}[CF$_3$SO$_3^-$]$_2$ compound **8** was also obtained readily from straightforward arene C–H bond activation of **1a** with Cu(OSO$_2$CF$_3$)$_2$. The aryl-Cu^{III}[CF$_3$SO$_3^-$]$_2$ complex **8** exhibited identical reactivity as the aryl-Cu^{III}[ClO$_4^-$]$_2$ complex **2a** toward alkynyllithium **3a**, yielding **4a** in 58% yield (see SI). Very pleasingly, treatment of aryl-Cu^{III}[OSO$_2$CF$_3$]$_2$ intermediate **8** with ethynylbenzene **7** under Castro–Stephens reaction conditions led to the formation of the C_{aryl}–C_{sp} bond in 62% yield (Scheme 3). On the basis of aforementioned evidence, it seems that the Castro–Stephens reaction proceeds most probably through an oxidative addition of Cu(I) into the C–I bond to form an arylcopper(III) intermediate. It allowed us to propose an alternative reaction mechanism involving Cu(I)/Cu(III) in addition to a long believed Cu(I)-involved four-center transition state.[16]

Scheme 3. Castro–Stephens Reaction via an Aryl–Cu(III) Intermediate **8**



All products including aryl-Cu(III) complex **8** were fully characterized by means of spectrocopic data. X-ray structures of **4e** and **4h** show a 1,3-alternate conformation of the azacalixarene ring (see SI).

In conclusion, we have demonstrated that copper(II) salt mediated aryl C–H bond activation of azacalix[1]arene[3]pyridines under mild aerobic conditions produced aryl-Cu(III) complexes, which underwent effective cross-coupling reactions with alkynyllithium reagents to form the C_{aryl}–$C_{alkynyl}$ bond. The method provides a general and unique synthetic route to regiospecifically alkynylated azacalixaromatics, which can serve as a springboard to various tailor-made functional macrocyclic host molecules, very useful in the study of supramolecular chemistry (results will be reported elsewhere). We have also shown for the first time experimental evidence that the Castro–Stephens reaction of aryl iodide embedded in azacalix[1]arene[3]pyridine proceeds through oxidative addition of Cu(I) into the C–I bond to form the same structurally well-defined arylcopper(III) intermediate, which subsequently undergoes a cross-coupling reaction with terminal alkynes to produce a C_{aryl}–$C_{alkynyl}$ bond forming product. Though in-depth studies are badly needed, the outcomes may also imply that aryl-Cu(III) species are genuine intermediates in Cu-catalyzed or -mediated carbon–carbon and carbon–heteroatom bond formation reactions. Studies on the copper salt catalyzed aryl C–H bond activation and diverse chemical bond forming reactions with a broad substrate scope are being actively pursued in this laboratory.

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Supporting Information Available. Experimental details and characterization data, X-ray structures of **4e** and **4h** (CIFs). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.