

# Direct Synthesis of High-Valent Aryl–Cu(II) and Aryl–Cu(III) Compounds: Mechanistic Insight into Arene C–H Bond Metalation

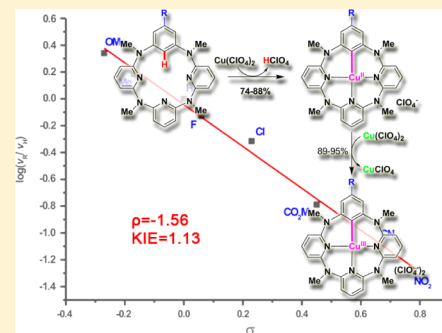
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**S** Supporting Information

**ABSTRACT:** Copper and its salts are abundant, inexpensive, and eco-friendly and have been used as the surrogates of noble metals to effect arene C–H bond activation and transformations. Despite of the recent significant progress of the study, syntheses of high-valent arylcopper(II–III) compounds are still very rare and mechanisms of copper(II)-catalyzed reactions remain elusive. With the use of azacalix[1]arene[3]pyridines as a platform, a number of arylcopper(II) compounds were synthesized efficiently from the reaction of Cu(ClO<sub>4</sub>)<sub>2</sub> under ambient conditions. The resulting aryl–Cu(II) compounds, which contain an unprecedented (substituted) phenyl–Cu(II)  $\sigma$ -bond, were stable under atmospheric conditions and can undergo facile oxidation reaction by free copper(II) ions or oxone to afford arylcopper(III) compounds in good yields. Both arylcopper(II) and arylcopper(III) compounds were characterized unambiguously by means of XRD, XPS, and NMR methods. Experimental evidence including reaction kinetics, LFER and KIE, and theoretical calculations indicated that the Cu(ClO<sub>4</sub>)<sub>2</sub>-mediated arene C–H bond activation proceeds plausibly through an electrophilic aromatic metalation pathway. The synthesis of high-valent arylcopper compounds and the reaction mechanism reported here highlight the diversity and richness of organocopper chemistry.



## INTRODUCTION

Because of natural abundance, cost effectiveness, and eco-friendliness, copper and its compounds are extensively used either as organometallic reagents or catalysts in chemical synthesis.<sup>1–4</sup> In recent years, copper salts have been applied as the surrogates of noble metals such as palladium and rhodium to catalyze or mediate various arene C–H bond activations and transformations.<sup>4–7</sup> On the basis of the directing-group strategy, for example, Yu<sup>8</sup> reported in a seminal study in 2006 that Cu(OAc)<sub>2</sub> can regioselectively catalyze arene C–H functionalizations including acetoxylation, halogenation, amination, etherification, thioetherification and cyanation of 2-arylpyridines using oxygen as a terminal oxidant at 130 °C. In 2008, Buchwald<sup>9</sup> succeeded in Cu(OAc)<sub>2</sub>-catalyzed intramolecular aryl C–H activation/C–N bond formation of amidines to synthesize benzimidazoles, while transformation of benzanilides to benzoxazoles via Cu(OTf)<sub>2</sub>-catalyzed intramolecular aryl C–H activation/C–O bond formation was realized by Nagasawa in the same year.<sup>10</sup> Since then a number of copper-catalyzed oxidative aryl C–H bond transformations have been explored to construct diverse carbon–carbon and carbon–heteroatom bonds.<sup>2–5</sup> It should be noted that, being different from the palladium-catalyzed aryl C–H bond activations in which the reaction mechanisms have been elucidated explicitly,<sup>11</sup> the mechanistic aspects of the copper-catalyzed or -mediated reactions still remain elusive. For

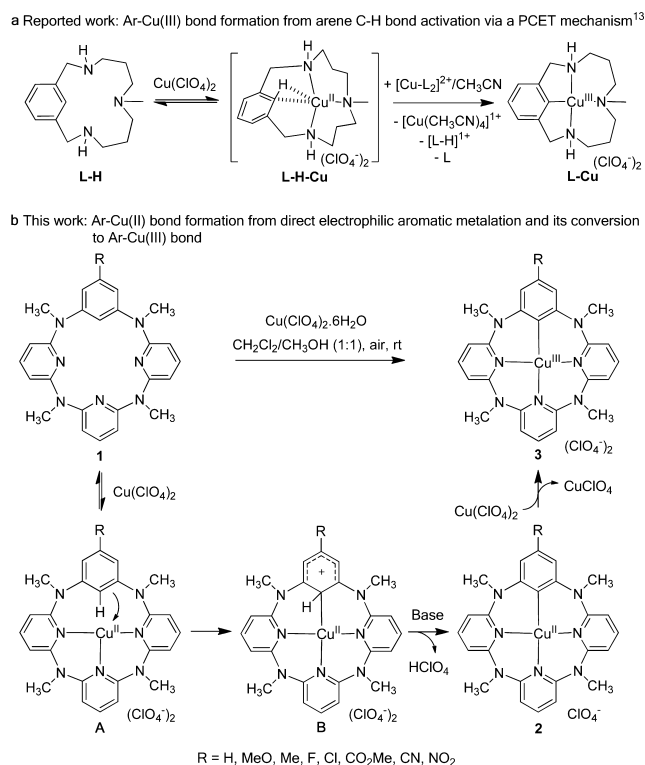
instance, varied reaction pathways including single electron transfer process,<sup>8,12</sup> organometallic reactions involving varied arylcopper intermediates,<sup>9,12</sup> and proton-coupled electron transfer (PCET) have been reported in literature.<sup>13</sup>

In the realm of organocopper chemistry, organocopper(I) compounds still dominate because of their invaluable synthetic potentials as unique nucleophilic reagents.<sup>14</sup> Indeed, a large number of aryl–Cu(I) compounds have been isolated and their intriguing molecular structures have also been unequivocally characterized by X-ray crystallography.<sup>1,2</sup> In sharp contrast, organocopper compounds in which copper is in higher oxidation states remain largely unexplored. For instance, only a few organocopper(III) complexes have been structurally well-defined<sup>5,15</sup> although organocopper(III) species are widely hypothesized as ubiquitous intermediates in organocuprate reactions and copper(I)-mediated carbon–carbon (C–C) and carbon–heteroatom (C–X) bond formation reactions.<sup>14</sup> In 2002, Hedman, Hodgson, and Lobet<sup>16</sup> reported the synthesis of a stable aryl–Cu(III) species L–Cu in about 50% yield from the reaction of a triazamacrocyclic ligand L–H and Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O under *anaerobic* conditions. Very recently, Ribas et al.<sup>13</sup> have proposed a five-step mechanism to account for the formation of aryl–Cu(III) from the Cu(II) salt-mediated arene

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C–H activation. The rate-limiting step is a facile C–H bond cleavage via a concerted proton-coupled electron transfer (PCET) process that involves a three-center, three-electron C–H...Cu<sup>II</sup> interaction of L–H–Cu (Figure 1a). We<sup>17</sup> discovered



**Figure 1.** Synthesis of Ar–Cu(III) complexes through two different reaction pathways.

serendipitously in 2009 that tetraazacalix[1]arene[3]pyridine **1a** (R = H), a member of novel macrocyclic heterocalixaromatics,<sup>18</sup> undergoes a highly efficient arene C–H bond activation with Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O under aerobic conditions to afford a stable aryl–Cu(III) complex **3a** (R = H) almost quantitatively (Figure 1b). The same aryl–Cu(III) complex has also been readily obtained from oxidative addition of a Cu(I) ion into a C–I bond of the iodobenzene moiety of azacalix[1]arene[3]pyridine.<sup>19</sup> Aryl–Cu(III) compounds have been shown to exhibit excellent reactivity toward a variety of nucleophiles under mild conditions, offering therefore powerful methods for the synthesis of diverse C–C and C–X bonds.<sup>4,17,20–23</sup>

In comparison to organocopper(III) compounds, surprisingly, very fewer divalent organocopper(II) compounds have been reported,<sup>24–32</sup> whereas Cu(II) is the most common oxidation state in inorganic and coordination chemistry. Using N-confused porphyrin derivatives, Chmielewski and Latos-Grazynski,<sup>26</sup> and Furuta<sup>30</sup> have prepared organocopper(II) complexes. Oxidation of (1*H*-pyrrol-3-yl)copper(II) leads to the formation of (1*H*-pyrrol-3-yl)copper(III) compounds.<sup>26,30,31</sup> Both (1*H*-pyrrol-3-yl)copper(II) and (1*H*-pyrrol-3-yl)Cu(III) ions are stabilized by the rest part of the constrained anionic macrocyclic ligand.<sup>26–32</sup> To the best of our knowledge, however, no structurally well-defined (substituted) phenylcopper(II) compounds have been reported in literature.

To explore the synthesis and the reactivity of high-valent organocopper compounds and get insight into the mechanism

of arene C–H activations with copper(II) salts, we embarked on the current systematic study of the reaction between azacalix[1]arene[3]pyridines **1** and Cu(ClO<sub>4</sub>)<sub>2</sub>. We report herein for the first time a simple and highly efficient synthesis of a series of aryl–Cu(II) complexes **2** under very mild conditions. The resulting products represent unprecedented examples of (substituted) phenylcopper(II) organometallic compounds (Figure 1b). Experimental studies including reaction kinetics, linear free-energy relationships (LFER) and kinetic isotope effect (KIE), combined with theoretical calculations indicate that the arene C–H bond activation would proceed through an electrophilic aromatic metalation pathway. We also demonstrated that the oxidation of such arylcopper(II) compounds, which are very stable under atmospheric oxidation conditions, by a free Cu(II) source or oxone would lead to the formation of arylcopper(III) products **3** in excellent yields (Figure 1b).

## RESULTS AND DISCUSSION

**Synthesis of Ar–Cu(II) Compounds and Their Conversion to Ar–Cu(III) Compounds.** We first surveyed the reaction between azacalix[1]arene[3]pyridine **1a** and Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O. As indicated by the results summarized in Table 1, interaction of tetraazacalix[1]arene[3]pyridine **1a** with

**Table 1.** Selective Synthesis of Ar–Cu(III) and Ar–Cu(II) Compounds

entry	1a/Cu(II)	additive (equiv)	time (h)	additive	
				2a (%) <sup>a</sup>	3a (%) <sup>a</sup>
1	1:1	-	1	-	56
2	1:1.5	-	1	-	99
3 <sup>b</sup>	1:1.5	-	1	-	60
4	3:1	-	3	38	15
5 <sup>b</sup>	3:1	-	3	80	-
6 <sup>c</sup>	1:1	collidine (1)	24	80	16
7	1:1	collidine (5)	1	85	-
8	1:1	Et <sub>3</sub> N (5)	5	84	-
9 <sup>d</sup>	1:1	-	1	-	37 <sup>e</sup>

<sup>a</sup>Isolated yield. **3a** was isolated from filtration. **2a** was obtained from the evaporation of the solvent from filtrate. <sup>b</sup>Under anaerobic conditions. <sup>c</sup>Copper(II) salt was dissolved in solvent and then added dropwise into the solution of **1a** and collidine. <sup>d</sup>Cu(OAc)<sub>2</sub> was used. <sup>e</sup>Isolated yield of acetoxy-substituted azacalix[1]arene[3]pyridine which was derived from the reaction of **3a** and acetate. Reactant **1a** was also recovered in 47% yield.

equimolar Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O in a mixture of dichloromethane and methanol (1:1) under aerobic conditions led to the precipitation of a dark purple crystalline aryl–Cu(III) complex **3a** in 56% yield as the sole product within 1 h (entry 1, Table 1). Increasing the molar ratio between **1a** and copper(II) salt from 1:1 to 1:1.5 led to the formation of **3a** quantitatively (entry 2, Table 1). In the absence of oxygen, the chemical yield of **3a** decreased to 60% along with the formation of Cu(I) product (entry 3, Table 1), indicating seemingly a disproportionation reaction of Cu(II) species to Cu(III) and Cu(I) products. Surprisingly, when copper(II) salt was added very slowly to an excess amount of **1a** (3 equiv), Ar–Cu(II) complex **2a** was formed in a moderate yield in addition to the

formation of Ar–Cu(III) product **3a** (entry 4, Table 1). Under *anaerobic* conditions, Ar–Cu(II) complex **2a** was isolated exclusively as a red crystalline solid in 80% yield (entry 5, Table 1). Assuming that the excessive azacalix[1]arene[3]pyridine **1a** may act as a soft base, collidine (2,4,6-trimethylpyridine) was employed instead of macrocycle. To our delight, in the presence of 1 equiv of collidine, reaction between **1a** and  $\text{Cu}(\text{ClO}_4)_2 \cdot \text{H}_2\text{O}$  under atmospheric conditions in 24 h gave a mixture of Ar–Cu(III) and Ar–Cu(II) compounds, and the latter was a major product (entry 6, Table 1). The Ar–Cu(II) product **2a** was obtained efficiently in 85% yield as the sole product when a large excess of collidine (5 equiv) was used (entry 7, Table 1). Triethylamine was also found to be effective albeit an elongated time was required. It should be noted that the replacement of  $\text{Cu}(\text{ClO}_4)_2$  by  $\text{Cu}(\text{OAc})_2$  did not allow the isolation of arylcopper(II) product **2a**. Instead, the reaction gave arylcopper(III) compound **3a** which underwent spontaneously reaction with acetate to afford acetoxy-substituted azacalix[1]arene[3]pyridine in 34% yield,<sup>17</sup> along with the recovery of starting macrocycle **1a** in 47% yield. The outcomes exclude a putative concerted metalation deprotonation (CMD) pathway,<sup>33</sup> which should give a high yield of arylcopper(II) product **2a**.

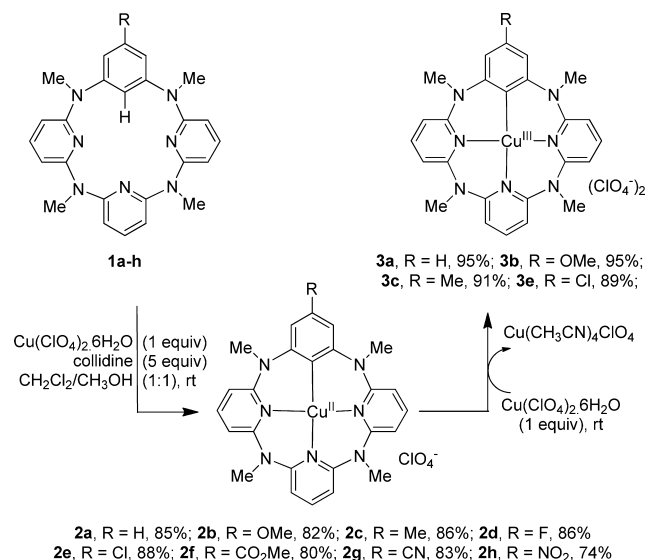
To test the generality of the synthesis, and also to study the reaction kinetics, particularly, the linear free energy relationships (*vide infra*), a number of aryl–Cu(II) complexes bearing either an electron-donating or an electron-withdrawing *para*-substituent on the benzene ring were synthesized. Under the optimized reaction conditions (entry 7, Table 1), azacalix[1]arene[2]pyridines **1b–h**, which were prepared by means of a fragment coupling approach (see Supporting Information), underwent reaction efficiently with  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  to produce the desired aryl–Cu(II) complexes **2b–h** as sole products in good yields ranging from 74% to 88% (Scheme 1). It was noteworthy that in all cases, formation of organocopper(III) compounds **3b–h** was not observed.

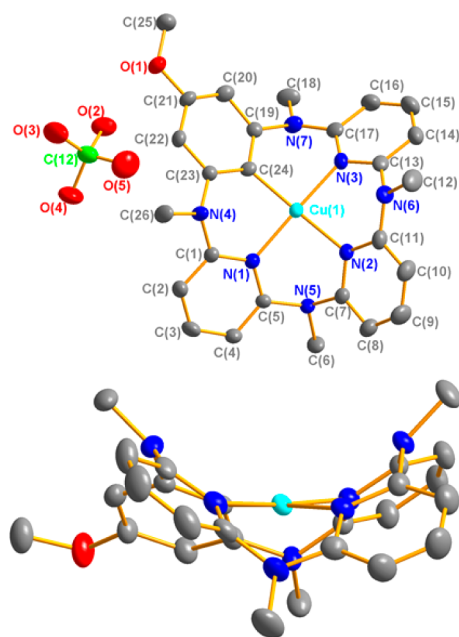
Similar to Ar–Cu(III) compounds that were prepared almost quantitatively from direct interaction of azacalix[1]arene[3]-

pyridines with  $\text{Cu}(\text{ClO}_4)_2$  under aerobic conditions<sup>17</sup> (see Table 1, entry 2), all pure Ar–Cu(II) complexes **2a–h** appear very stable. For example, no auto-oxidation and decomposition were observed when the samples were exposed to atmospheric conditions for a long time. They can not undergo self-disproportionation to Ar–Cu(III) and Ar–Cu(I) compounds either. However, in the presence of free Cu(II) ion source, Ar–Cu(II) compounds **2** can be oxidized into Ar–Cu(III) complexes **3** while the free copper(II) ion was reduced to Cu(I) species quantitatively. As shown in Scheme 1, for instance, Ar–Cu(II) complex **2a** and its analogues that contain a methoxy (**2b**), methyl (**2c**) and chloro (**2e**) group were converted efficiently into the corresponding Ar–Cu(III) complexes in excellent yields. Noticeably, the oxidation reaction of Ar–Cu(II) **2** with free Cu(II) salt was greatly facilitated when a small amount of acetonitrile was added. It was most probably due to the formation of more stable  $[\text{Cu}(\text{CH}_3\text{CN})_4]^+$  complex from the coordination of  $\text{Cu}^+$  by acetonitrile. This assumption was finally evidenced by the isolation and structural characterization of the crystalline solid  $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{ClO}_4)$ . Apparently, the existence of free Cu(II) salt was essential for the conversion of Ar–Cu(II) complex **2** to Ar–Cu(III) complex **3**. In other words, it is the free Cu(II) ion source that act as an oxidant to oxidize Ar–Cu(II) complexes **2** into Ar–Cu(III) complexes **3**. The outcomes also revealed convincingly that Ar–Cu(II) compounds are the intermediates during the course of the formation of Ar–Cu(III) from the reaction of arenes **1** and  $\text{Cu}(\text{ClO}_4)_2$  (Scheme 1). Transformation of arylcopper(II) **2** into arylcopper(III) **3** can also take place in the presence of an appropriate oxidant. For example, we found oxone, a non-nucleophilic oxidation agent, was able to oxidize **2a** at ambient temperature, producing **3a** in 89% yield within 1.5 h (Supporting Information).

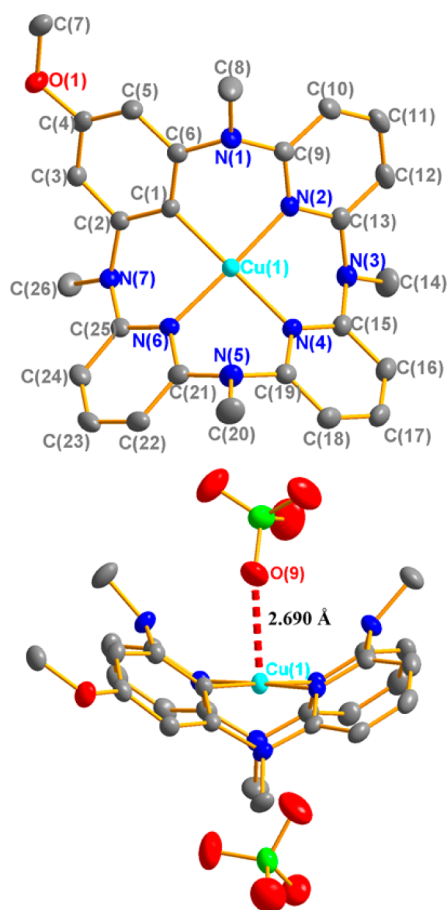
**Structure of Ar–Cu(II) and Ar–Cu(III) Complexes.** Both Ar–Cu(II) and Ar–Cu(III) compounds as synthesized are stable under atmospheric conditions, allowing their structural characterization conveniently by means of spectroscopic techniques and microanalysis. Recrystallization of Ar–Cu(II) and Ar–Cu(III) compounds gave high quality single crystals, and their molecular structures were therefore determined unambiguously based on X-ray diffraction analysis (see Supporting Information). As a representative example of Ar–Cu(II) complexes, molecular structure of **2b** is illustrated in Figure 2. It is interesting to note that the macrocyclic moiety of **2b** adopts a saddle conformation with its *p*-methoxyphenyl and three pyridine rings coordinating to copper(II) ion center in a square planar geometry. The average distance between Cu(II) center and pyridine nitrogen atoms is around 2.02 Å and the *p*-methoxyphenyl carbon–Cu(II) bond length is 1.92 Å. Notably, perchlorate counteranion does not interact with organocopper ion center. Instead, the oxygen atom of the methoxy group of another aryl–Cu(II) complex forms weak interaction with the copper(II) ion ( $d_{\text{Cu}(\text{I})-\text{O}(\text{I})} = 2.78$  Å), yielding an infinitely compacted zigzag molecular chain in the solid state (see Supporting Information). Perchlorate anions are located between the chains. Figure 3 shows the solid-state molecular structure of Ar–Cu(III) complex **3b**, which is very similar to that of Ar–Cu(II) complex **2b**. However, the average interatomic distances between pyridine-2,6-diyl nitrogen atoms and the copper(III) center in **3b** are about 1.92 Å, shorter than the Cu–N distances in **2b**. A slightly shorter bond length between *p*-methoxyphenyl carbon and copper(III) ( $d_{\text{C}(\text{I})-\text{Cu}(\text{I})} = 1.90$  Å) was also observed in **3b**. It is worth

**Scheme 1. Synthesis of Ar–Cu(II) Complexes 2 from the Reaction of 1 with  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  and Their Conversion to Ar–Cu(III) Compounds 3**





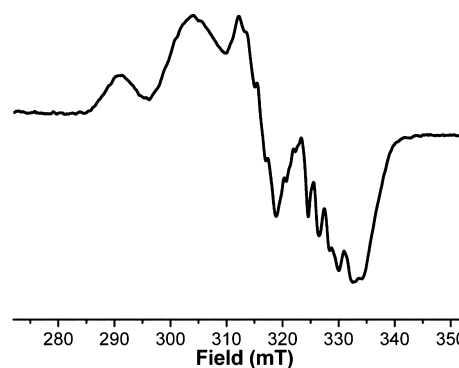
**Figure 2.** X-ray crystal structure of **2b**. Top (top) and side (bottom) views. Selected interatomic distances (Å): Cu(1)–C(24), 1.923; Cu(1)–N(1), 2.026; Cu(1)–N(2), 2.001; Cu(1)–N(3), 2.031; Cu(1')–O(1), 2.775. All hydrogen atoms are omitted for clarity.



**Figure 3.** X-ray crystal structure of **3b**. Top (top) and side (bottom) views. Selected interatomic distances (Å): Cu(1)–C(1), 1.904; Cu(1)–N(2), 1.906; Cu(1)–N(4), 1.934; Cu(1)–N(6), 1.910; Cu(1)–O(7A), 2.690. All hydrogen atoms were omitted for clarity.

addressing that, in contrast to Ar–Cu(II) complex **2b**, two perchlorate anions in complex **3b** are positioned on both sides of the square plane along the pseudo- $S_4$  axis. One of them forms weak interaction with copper(III) ion, which is evidenced by a short Cu–O distance of 2.69 Å (Figure 3).

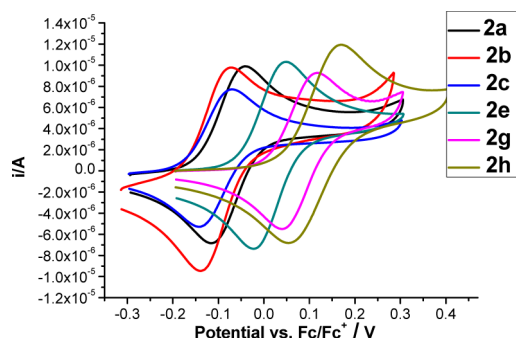
Aryl–Cu(II) compounds **2** display two strong absorption bands at around 261–270 nm and 329–331 nm in UV–visible spectra. In comparison to the electronic spectra of their parent azacalix[1]arene[3]pyridines **1**, the absorption band of Ar–Cu(II) compounds at the longer wavelength shifted about 10 nm bathochromically (see Supporting Information). Since Ar–Cu(II) complexes **2** contain unpaired electron, they gave no distinct signals in their  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. Being paramagnetic species, electron spin signals were observed in their EPR spectra. As a representative example, Figure 4 shows



**Figure 4.** EPR spectrum of **2a** (X-band, EtOH, 77 K). Experimental conditions: microwave frequency,  $\nu = 9.1177$  GHz; microwave power, 2.0 mW; modulation amplitude, 0.3 mT; modulation frequency, 100 kHz;  $g_{\perp} = 2.06$ ,  $g_{\parallel} = 2.10$ .

EPR spectrum of arylcopper(II) compound **2a** in ethanol at 77K, which appears similar to that of N-confused porphyrin-derived organocopper(II) species.<sup>26,29</sup> Organocopper(III) compounds are, however, typical diamagnetic species. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compounds thus revealed distinct proton and carbon resonance signals respectively (see Supporting Information). It is worth mentioning that, as supported by HMBC of **3a**, the benzene carbon that is  $\sigma$ -bonded to the copper ion was found to resonate at 139.7 ppm, in sharp contrast to the peak at 125.8 ppm in compound **1a** (see Supporting Information). In addition to aforementioned experimental evidence, the different oxidative states of the central copper in compounds **2** and **3** were finally verified by using X-ray photoelectron spectroscopy. In the case of Ar–Cu(II) compound **2a**, for example, the binding energy for Cu  $2p_{3/2}$  is 934.1 eV, being characteristic of a Cu(II) state. The Ar–Cu(III) compound **3a** shows a higher binding energy of 936.7 eV that is attributable to a Cu(III) state (see Supporting Information).

To shed light on the redox properties of organocopper(II) compounds **2**, their electrochemistry was investigated by means of cyclic and differential pulse voltammetry. Depicted in Figure 5 are cyclic voltammograms of organocopper(II) compounds, which gave a similar electrochemical response showing a reversible redox couple due to one-electron oxidation and reduction. The half-wave potentials measured from CV are in the range of –105 to 115 mV (Table 2). DPV measurements gave nearly identical parameters (Supporting Information). It is noteworthy that the substituent effect was clearly evidenced by



**Figure 5.** Cyclic voltammograms of compounds **2**. The potential scan rate 100 mV/s. Measurements were carried in 0.2 M TBAP/CH<sub>3</sub>CN at 293 K.

**Table 2. Redox Parameters for Arylcopper(II) Compounds 2<sup>a</sup>**

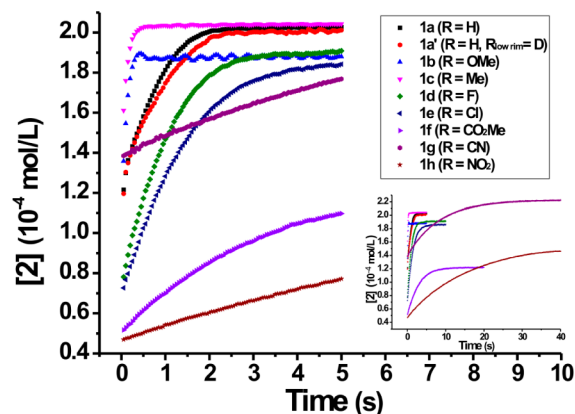
<b>2</b> (R)	$E_{pa}$ (mV)	$E_{pc}$ (mV)	$\Delta E$ (mV)	$E_{1/2}$ (mV) <sup>b</sup>
2a (H)	-42	-116	74	-79
2b (MeO)	-71	-139	68	-105
2c (Me)	-70	-135	65	-102.5
2e (Cl)	47	-24	71	11.5
2g (CN)	118	40	78	79
2h (NO <sub>2</sub> )	170	60	110	115

<sup>a</sup>Measure by CV. <sup>b</sup>Measured by DPV. All potentials are given vs Fc/Fc<sup>+</sup>.

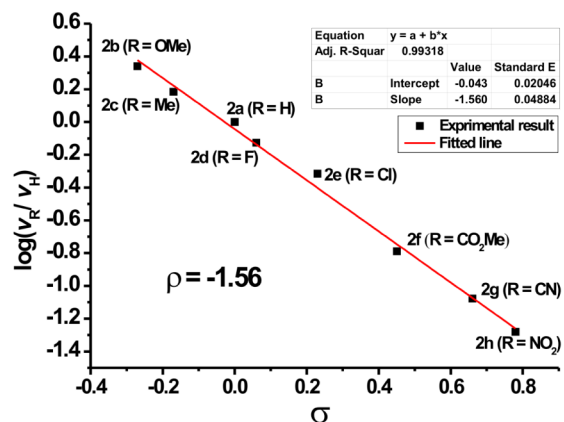
the gradual increase of half-wave potential depending on the increase of electron-withdrawing power of the *para*-substituent on the benzene ring in **2**. As we expected, arylcopper(III) compound **3a** gave a nearly same CV trace as arylcopper(II) **2a** (Supporting Information).

**Mechanistic Insight into the Arene C–H Bond Activation by Cu(ClO<sub>4</sub>)<sub>2</sub>.** The facile arene C–H bond activation with Cu(ClO<sub>4</sub>)<sub>2</sub> to form Ar–Cu(II) compounds **2** was very intriguing. To account for the direct conversion of an arene C–H bond to a phenyl–Cu(II) bond, several reaction pathways could be hypothesized. Similar to the Pd-catalyzed reactions, for instance, formation of Ar–Cu(II) might result from a concerted metalation–deprotonation,<sup>33</sup> a  $\sigma$ -bond methathesis,<sup>34</sup> and an electrophilic aromatic substitution ( $S_EAr$ ) or a direct electrophilic metalation. To shed light on the mechanism, reaction kinetics and linear free-energy relationship for the substituents on benzene ring were then investigated.

Since the reaction between azacalix[1]arene[3]pyridines **1** and Cu(ClO<sub>4</sub>)<sub>2</sub> took place very rapidly, a stopped-flow reactor was employed to study the reaction kinetics at 298 K. The concentration change of the Ar–Cu(II) products **2** was reliably determined by recording the variation of their UV–visible absorptions at 375 nm for **2a–g** or at 380 nm for **2h**, where all reactants and collidine additive in reaction have no absorption. As illustrated in Figure 6a, the use of this stop-flow reactor enabled us to monitor the reaction with a time resolution of 0.05 s as soon as the reactants were mixed in the reactor. Most of the reactions were found to reach a plateau within 3 to 5 s. Noticeably, the presence of an electron-donating group on the *para*-position of the benzene ring facilitated the formation of Ar–Cu(II) product. The stronger the electron-donating group, the richer the electron density of the benzene ring, the faster the formation of Ar–Cu(II) product. The slopes for the linear



b

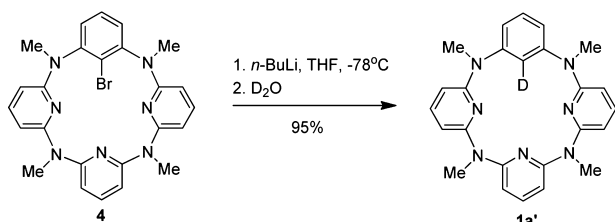


**Figure 6.** Reaction kinetics and Hammett plot. (a) Variation of concentration of aryl–copper(II) complexes **2a–h** and **2a'** with reaction time. (b) Dependence of the logarithm of the relative initial rate,  $V_R/V_H$ , on the substituent parameter  $\sigma$ .

parts of the kinetic curves at the very initials of the reactions (mostly in less than 0.2 s) were used to measure the initial reaction rates ( $V_R$ ) for the formation of Ar–Cu(II) complexes **2a–h**. The thus obtained rates ranged from  $0.077 \times 10^{-4}$  to  $3.216 \times 10^{-4} \text{ mol}\cdot\text{L}^{-1}\cdot\text{s}^{-1}$  (see Supporting Information). Significantly, the plot of  $V_R/V_H$  versus substituent parameters ( $\sigma$ )<sup>35</sup> gave a Hammett plot in Figure 6b, which shows excellent linearity with a slope of  $-1.56$ . This linear free-energy relationship for the substituents with a negative  $\rho$  value, though being smaller due to most probably the electron-donating effect of two bridging amino groups, indicates convincingly that a positive charge was created during the course of reaction between azacalix[1]arene[3]pyridines **1** and Cu(ClO<sub>4</sub>)<sub>2</sub>.

To gain a deeper insight into the reaction kinetics, we then examined the kinetic isotope effect of the C–H bond activation reaction. A deuterium-substituted azacalix[1]arene[3]pyridine **1a'** was readily prepared in 95% yield from the lithiation of the brominated azacalix[1]arene[3]pyridine **6**<sup>17,19</sup> followed by a deuteration using D<sub>2</sub>O (Scheme 2). A kinetics curve of the reaction of **1a'** was measured under the identical conditions in the stop-flow reactor (Figure 6a), from which an initial reaction rate of  $1.3 \times 10^{-4} \text{ mol}\cdot\text{L}^{-1}\cdot\text{s}^{-1}$  was obtained (Supporting Information). Comparison of the initial rate for the reaction of **1a** with that of **1a'** gave the kinetic isotope effect of  $V_H/V_D = 1.13$ . Such low primary kinetic isotope effect reflected convincingly that the C–H bond cleavage was not involved in the rate-determining step of the formation of an Ar–Cu(II)

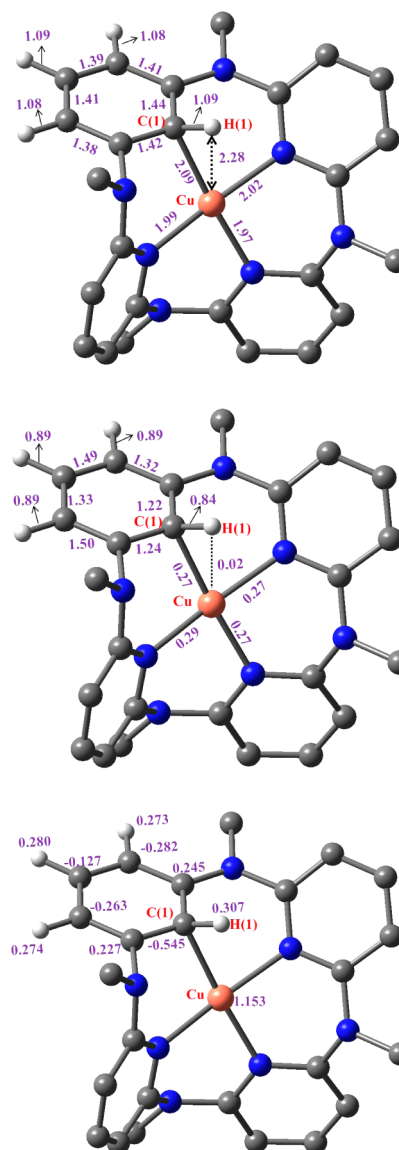
**Scheme 2. Synthesis of the Lower-Rim Deuterium-Substituted Azacalix[1]arene[3]pyridine 1a'**



compound from the reaction between azacalix[1]arene[3]pyridines **1** and  $\text{Cu}(\text{ClO}_4)_2$ .

The aforementioned outcomes of LFER, KIE and of the reaction between azacalix[1]arene[3]pyridine **1a** and  $\text{Cu}(\text{OAc})_2$  (vide supra) are suggestive of a Friedel–Crafts type metalation pathway for the formation of arylcopper(II) compounds from the reaction of azacalix[1]arene[3]pyridines **1** and  $\text{Cu}(\text{ClO}_4)_2$ . On the basis of experimental evidence, the most plausible reaction mechanism was proposed. As depicted in Figure 1, interaction between an arene-embedded macrocycle with  $\text{Cu}(\text{II})$  ion forms probably a coordination complex **A**. Directed metalation gives rise to the formation of the Wheland intermediate **B**. Deprotonative aromatization in the presence of a base furnishes the production of arylcopper(II) compound **2**. Further oxidation of arylcopper(II) **2** by a free copper(II) source or an oxidant like Oxone yields arylcopper(III) product **3**. It should be addressed that the deprotonative aromatization step is not rate-determining based on a low determined primary kinetic isotope effect ( $\text{KIE} = 1.13$ ). The process of the attack of a chelated  $\text{Cu}(\text{II})$  on the aromatic ring to form the cationic Wheland intermediate **B**, which is supported the observation of LFER with a negative  $p$ -value ( $p = -1.56$ ), is most likely the rate-controlling step.

The proposed mechanism was supported by DFT calculations at the level of B3LYP using the 6-31G(d,p) basis set<sup>36–41</sup> (Supporting Information). For the model reaction of **1a** with  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  leading to **2a**, two intermediates such as the Wheland intermediate and its complex with 2,4,6-collidine, and the transition state for the deprotonative aromatization step were identified. The optimized geometry of the Wheland intermediate shows that the macrocyclic ring adopts a twisted 1,3-alternate conformation with the interatomic distance between C(1) and Cu being 2.09 Å, whereas that between H(1) and Cu being 2.28 Å (Figure 7a). Furthermore, natural bond orbital (NBO) analysis at the same level of theory shows that the bond order between Cu and C(1) is 0.27 (Figure 7b), indicative a strong interaction between Cu and C(1). The formation of Wheland intermediate is also consistent with the decreased aromaticity of the benzene ring (HOMA indexes<sup>42</sup> are 0.77 and 0.957 for the Wheland intermediate and for **1a**, respectively) and the change of charges over the benzene ring (Figure 7c). The computed energy required for deprotonative aromatization is 20.5 kcal/mol, which is also in agreement with experimental results that the step is not rate limiting. It should be pointed out that the transition state for electrophilic attack of  $\text{Cu}(\text{II})$  on the benzene ring was not identified successfully by calculations. The reaction was hypothesized however to proceed probably via a macrocyclic- $\text{Cu}(\text{II})$   $\pi$ -complex-like transition state which has activation energy higher than 20.5 kcal/mol (Supporting Information).



**Figure 7.** Theoretical calculations with a DFT optimized Wheland intermediate with selected interatomic distances (Å) (top), selected natural bond orders from NBO analysis (middle), and natural charges on selected atoms (bottom). Color code: Cu, orange; N, blue; C, gray; H, light gray. For clarity, hydrogen atoms are omitted except for those of the benzene ring.

## CONCLUSION

In summary, we have reported for the first time the simple and efficient synthesis of a number of stable and structurally well-defined Ar– $\text{Cu}(\text{II})$  compounds from the direct reaction of macrocyclic azacalix[1]arene[3]pyridines with  $\text{Cu}(\text{ClO}_4)_2$  under very mild conditions. The Ar– $\text{Cu}(\text{II})$  products prepared represent unprecedented examples of organocopper(II) compounds that contain a (substituted) phenyl– $\text{Cu}(\text{II})$   $\sigma$ -bond. On the basis of experimental results including reaction kinetics, LFER and KIE, and theoretical calculations,  $\text{Cu}(\text{ClO}_4)_2$ -mediated arene C–H bond activation proceeds most plausibly through an electrophilic aromatic metalation pathway. Ar– $\text{Cu}(\text{II})$  compounds, which are stable under atmospheric oxidation conditions, undergo oxidation reaction with free  $\text{Cu}(\text{II})$  ions or oxone as an oxidant to afford almost quantitatively Ar– $\text{Cu}(\text{III})$  compounds. The formation and

conversion of organocopper compounds of high oxidation states along with the reaction pathways revealed from the present study would not only broaden our knowledge of organocopper chemistry, but also provide a new strategy in the design of copper-catalyzed C–H bond activation and transformations.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Detailed experimental procedures; characterization of all products; X-ray crystallographic files of **2b**, **2g**, and **3g**; XPS of **2a** and **3a**; DPV of **2**; CV and DPV of **3a**;  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of products; DFT calculations. 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 interest.

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## ■ REFERENCES

- (1) *The Chemistry of Organocopper Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons Ltd.: Chichester, West Sussex, 2009.
- (2) Van Koten, G.; Pérez, P. J.; Liebeskind, L. S. *Organometallics* **2012**, *31*, 7631–7633.
- (3) Allen, A. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozłowski, M. C. *Chem. Rev.* **2013**, *113*, 6234–6458.
- (4) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062–11087.
- (5) Casitas, A.; Ribas, X. *Chem. Sci.* **2013**, *4*, 2301–2318.
- (6) *C-H Activation*; Yu, J.-Q., Shi, Z., Eds. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, Heidelberg, 2010; Vol. 292.
- (7) Chen, B.; Hou, X.-L.; Li, Y.-X.; Wu, Y.-D. *J. Am. Chem. Soc.* **2011**, *133*, 7668–7671.
- (8) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791.
- (9) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932–1934.
- (10) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411–6413.
- (11) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802.
- (12) Suess, A. M.; Ertern, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797–9804.
- (13) Ribas, X.; Calle, C.; Poater, A.; Casitas, A.; Gómez, L.; Xifra, R.; Parella, T.; Benet-Buchholz, J.; Schweiger, A.; Mitrikas, G.; Solà, M.; Llobet, A.; Stack, T. D. P. *J. Am. Chem. Soc.* **2010**, *132*, 12299–12306.
- (14) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *114*, 2339–2372.
- (15) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177–185.
- (16) Ribas, X.; Jackon, D. A.; Donnadiou, B.; Mahia, J.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2991–2994.

- (17) Yao, B.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Chem. Commun.* **2009**, 2899–2901.
- (18) Wang, M.-X. *Acc. Chem. Res.* **2012**, *45*, 182–195.
- (19) Wang, Z.-L.; Zhao, L.; Wang, M.-X. *Org. Lett.* **2012**, *14*, 1472–1475.
- (20) (a) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196–9197. (b) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068–12073.
- (21) (a) Casitas, A.; Canta, M.; Sola, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* **2011**, *133*, 19386–19392. (b) Casitas, A.; Ribas, X. *Chem. Sci.* **2013**, *4*, 2301–2318.
- (22) (a) Wang, Z.-L.; Zhao, L.; Wang, M.-X. *Org. Lett.* **2011**, *13*, 6560–6563. (b) Yao, B.; Wang, Z.-L.; Zhang, H.; Zhao, L.; Wang, D.-X.; Wang, M.-X. *J. Org. Chem.* **2012**, *77*, 3336–3340. (c) Zhang, H.; Zhao, L.; Wang, D.-X.; Wang, M.-X. *Org. Lett.* **2013**, *15*, 3836–3839.
- (23) (a) Wang, Z.-L.; Zhao, L.; Wang, M.-X. *Chem. Commun.* **2012**, *48*, 9418–9420. (b) Zhang, H.; Zhao, L.; Wang, D.-X.; Wang, M.-X. *Org. Lett.* **2013**, *15*, 3836–3839.
- (24) Kinoshita, I.; Wright, L. J.; Kubo, S.; Kimura, K.; Sakata, A.; Yano, T.; Miyamoto, R.; Nishioka, T.; Isobe, K. *Dalton, Trans.* **2003**, 1993–2003.
- (25) Miyamoto, R.; Santo, R.; Matsushita, T.; Nishioka, T.; Ichimura, A.; Teki, Y.; Kinoshita, I. *Dalton Trans.* **2005**, 3179–3186.
- (26) Chmielewski, P. J.; Latos-Grażyński, L.; Schmidt, I. *Inorg. Chem.* **2000**, *39*, 5475–5482.
- (27) Grzegorzczek, N.; Pawlicki, M.; Szterenber, L.; Latos-Grażyński, L. *J. Am. Chem. Soc.* **2009**, *131*, 7224–7225.
- (28) Furuta, H.; Maeda, H.; Osuka, A. *J. Am. Chem. Soc.* **2000**, *122*, 803–807.
- (29) Furuta, H.; Ishizuka, T.; Osuka, A.; Uwatoko, Y.; Ishikawa, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2323–2325.
- (30) Maeda, H.; Osuka, A.; Ishikawa, Y.; Aritome, I.; Hisaeda, Y.; Furuta, H. *Org. Lett.* **2003**, *5*, 1293–1296.
- (31) Maeda, H.; Ishikawa, Y.; Matsuda, T.; Osuka, A.; Furuta, H. *J. Am. Chem. Soc.* **2003**, *125*, 11822–11823.
- (32) Maeda, H.; Osuka, A.; Furuta, H. *J. Am. Chem. Soc.* **2003**, *125*, 15690–15691.
- (33) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.
- (34) Garcia-Cuadrado, D.; Braga, A. A.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067.
- (35) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.
- (36) Frisch, M. J.; et al. *Gaussian 03*, Revision D.02; Gaussian, Inc.; Wallingford, CT, 2004.
- (37) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
- (38) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
- (39) Stevens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627.
- (40) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matasunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347–1363.
- (41) Reed, A. E.; Curtis, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899–926.
- (42) Krygowski, T. M.; Cyrański, M. K. *Chem. Rev.* **2001**, *101*, 1385–1419.