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Divergence between Organometallic and Single-Electron-Transfer Mechanisms in Copper(II)-Mediated Aerobic C−H Oxidation

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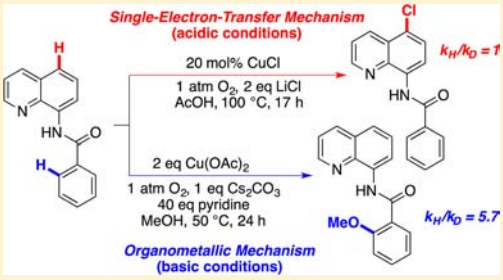
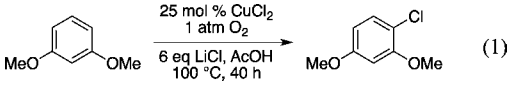
Supporting Information

ABSTRACT: Copper(II)-mediated C−H oxidation is the subject of extensive interest in synthetic chemistry, but the mechanisms of many of these reactions are poorly understood. Here, we observe different products from Cu^{II}-mediated oxidation of *N*-(8-quinolinyl)benzamide, depending on the reaction conditions. Under basic conditions, the benzamide group undergoes directed C−H methoxylation or chlorination. Under acidic conditions, the quinoline group undergoes nondirected chlorination. Experimental and computational mechanistic studies implicate an organometallic C−H activation/functionalization mechanism under the former conditions and a single-electron-transfer mechanism under the latter conditions. This rare observation of divergent, condition-dependent mechanisms for oxidation of a single substrate provides a valuable foundation for understanding Cu^{II}-mediated C−H oxidation reactions.



INTRODUCTION

Copper(II) catalyzes a wide variety of aerobic C−H oxidation reactions.[1] Many of these transformations involve electron-rich substrates that undergo initial one-electron oxidation by Cu^{II}. Examples include oxidative dimerization of naphthol,[2] oxychlorination of phenols and other electron-rich arenes (eq 1),[3,4]



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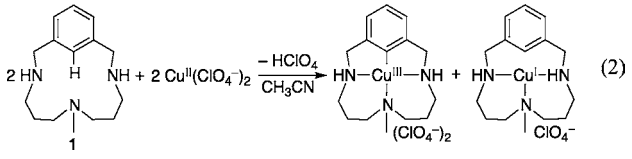
and cross-dehydrogenative coupling reactions of aromatic and benzylic amines.[1b,5] Yu and co-workers proposed a similar single-electron-transfer (SET) mechanism for chelate-directed, aerobic oxidative functionalization of 2-phenylpyridines (Scheme 1),[6] and support for this mechanism was obtained from the lack of a kinetic isotope effect (KIE).[7]

Numerous other Cu-catalyzed aerobic C−H oxidation reactions, including chelated-directed and nondirected examples, have been reported for which the mechanism of C−H activation is not well established.[8] Many of these reactions appear similar to those catalyzed by Pd and other noble metals, and we considered whether some of these aerobic oxidation reactions could involve organometallic intermediates. Stoichiometric C−H activation by Cu^{II} had been identified for macrocyclic substrates,[9] including the triazamacrocyclic arene **1**, reported by Ribas et al. (eq 2).[10,11] Several of these studies



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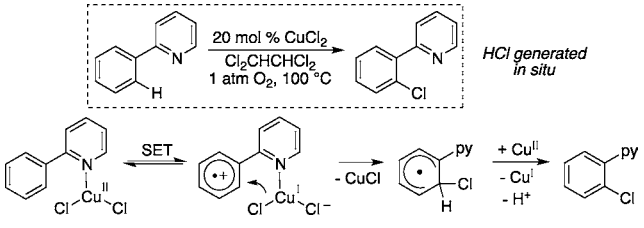
revealed an unusual Cu^{II} disproportionation pathway that yields aryl-Cu^{III} and Cu^{I} products, as shown in eq 2. We recently demonstrated the relevance of this reactivity to catalytic C−H oxidation by showing that Cu^{II} salts, $CuBr_2$ and $Cu(ClO_4)_2$ catalyze aerobic oxidation of the arene C−H bond in **1** to C−O and C−N bonds in the presence of methanol and pyridone, respectively (eq 3).[12] An aryl-Cu^{III} species, which undergoes facile C−O or C−N reductive elimination to afford the functionalized product,[13] was directly observed and established as a kinetically competent intermediate. This work provided the first direct evidence for an organometallic pathway in Cu-catalyzed aerobic C−H oxidation.

The proof-of-principle studies depicted in eq 3 have an important caveat: the macrocyclic nature of the substrate could

Scheme 1. Proposed SET Mechanism for Oxidative Chlorination of 2-Phenylpyridine



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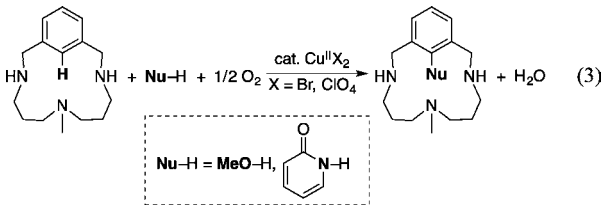
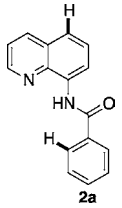


artificially stabilize the aryl-Cu^{III} intermediate and enforce an otherwise-unfavorable organometallic pathway. In order to explore the potential role of organometallic intermediates with a less biased substrate, we investigated the reactivity of substrate **2a**, which features an amidoquinoline directing group first used by Daugulis and co-workers in Pd-catalyzed C–H functionalization reactions.[14,15] Here, we show that substrate **2a** exhibits divergent reactivity in Cu^{II}-mediated C–H functionalization, depending on the reaction conditions. Directed C–H oxidation occurs under basic conditions, while nondirected oxidation of the quinoline ring occurs under acidic conditions. Experimental and computational mechanistic studies provide fundamental insights into the organometallic and SET pathways that give rise to these distinct outcomes. These results have important implications for the ongoing development of Cu^{II}-catalyzed aerobic oxidation reactions.



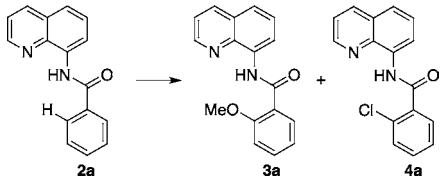
RESULTS AND DISCUSSION

Cu^{II}-Mediated C–H Oxidation of *N*-(8-quinolinyl)-benzamide under Different Conditions. Our investigation of the reactivity of **2a** was initiated by evaluating Cu^{II}-catalyzed C–H oxidation conditions similar to those reported previously. No reaction was observed under the conditions used for oxidative methoxylation of the triazamacrocyclic arene **1** (cf. eq 3; Table 1, entry 1). Addition of a stoichiometric base (Cs_2CO_3) to the reaction resulted in small quantities of product **3a**, arising from methoxylation of the *ortho* position of the benzamide (entry 2). The yield of **3a** could be increased up to 56% by employing 2 equiv of $Cu(OAc)_2$ as the Cu^{II} source. No difunctionalization of the arene was observed under these conditions, and the presence of O_2 enabled a somewhat higher yield relative to anaerobic reaction conditions (entries 3 and 4). Use of $CuCl_2$ resulted in a mixture of methoxylation and chlorination products **3a** and **4a** (entries 5 and 6). Control experiments suggest that the **3a** formed under these conditions arises from direct C–H methoxylation, not C–H chlorination followed by methoxide substitution of chloride in **4a**. Subjection of **4a** to the oxidative methoxylation conditions in entry 3 resulted in near-complete recovery of **4a** with no formation of **3a**.

These product yields are not sufficiently high to be synthetically useful, but they provide clear evidence for directed C–H oxidation, mediated by Cu^{II}. Control experiments show that the product inhibits the reaction. For example, when a 1:1 mixture of **2a**:**3a** was combined under the conditions of entry 3 (Table 1), the quantity of **3a** increased only 8.6% after 5 h, whereas use of **2a** alone affords a 25% yield of **3a** over the same time period. Analogous product inhibition has been reported for Cu-catalyzed amination of 2-phenylpyridine.[8a]

The reactivity of **2a** was then evaluated under conditions similar to those used for the oxidative chlorination of electron-rich arenes (cf. eq 1). In the presence of 1 atm O_2 and 2 equiv LiCl in AcOH at 100 °C, catalytic CuCl or $CuCl_2$ promoted chlorination of **2a**. In contrast to the methoxylation results described above, the product arose from chlorination of the quinoline ring (**5a**), not the benzamide ring (Table 2). Higher yields were obtained with CuCl rather than $CuCl_2$ (entries 1 and 2), and no conversion was observed under these conditions in the absence of Cu (entries 3 and 4). The reactivity with $CuCl_2$ was nearly identical to that of CuCl when an equal amount of LiOAc (20 mol %) was included in the reaction mixture (entries 2 and 5). This effect is attributed to the role of a Brønsted base to promote substrate binding to the Cu center: The use of a Cu^{I} catalyst precursor generates an equivalent of base in situ upon reaction with O_2 to afford H_2O_2 or H_2O.[16]

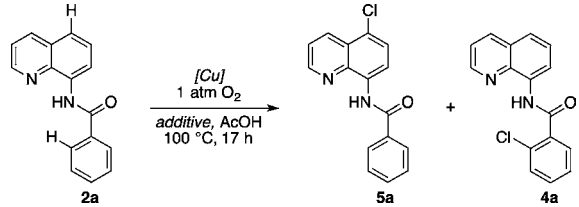
Table 1. Directed C–H Methoxylation of the Benzamide[a]



entry	[Cu]	base (1 equiv)	atm (1 atm)	% **3a**	% **4a**
1[b]	10 mol % $Cu(ClO_4)_2{\cdot}6H_2O$	none	O_2	0.0	n/a
2[b]	10 mol % $Cu(ClO_4)_2{\cdot}6H_2O$	Cs_2CO_3	O_2	18	n/a
3[c]	**2 equiv $Cu(OAc)_2$**	**Cs_2CO_3**	**O_2**	**56**	**n/a**
4[c]	2 equiv $Cu(OAc)_2$	Cs_2CO_3	N_2	46	n/a
5[d]	1 equiv $CuCl_2$	Na_2CO_3	O_2	31	10.8
6[d]	2 equiv $CuCl_2$	Na_2CO_3	O_2	2.0	41.2

[a]Yields determined by ^{1}H NMR spectroscopy. [b]Conditions: 50 mM **2a**, 5 mM [Cu], 0 or 50 mM base, 1 mL MeOH, 60 °C, 17 h. [c]50 mM **2a**, 100 mM [Cu], 50 mM base, 1 mL 5.2:1 MeOH/pyridine, 50 °C, 24 h. [d]50 mM **2a**, 50 or 100 mM [Cu], 50 mM base, 1 mL MeOH, 50 °C, 17 h.

Table 2. C–H Chlorination of the Quinoline[a]



entry	[Cu]	additive	% **5a**	% **4a**
1	20 mol % $CuCl_2$	2 equiv LiCl	34	0.0
2	**20 mol % CuCl**	**2 equiv LiCl**	**81**	**2.1**
3	none	none	0.0	0.0
4	none	2 equiv LiCl	0.0	0.0
5	**20 mol % $CuCl_2$, 20 mol % LiOAc**	**2 equiv LiCl**	**88**	**0.0**

[a]Yields determined by ^{1}H NMR spectroscopy. Conditions: 50 mM **2a**, 10 mM [Cu], 100 mM LiCl in 1 mL AcOH, 1 atm O_2, 100 °C, 17 h.

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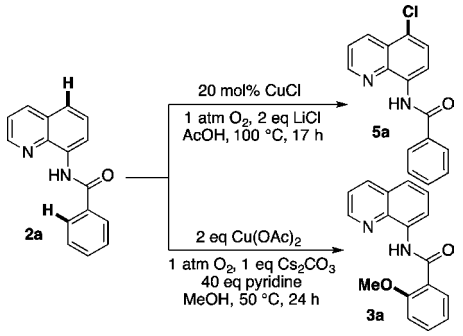
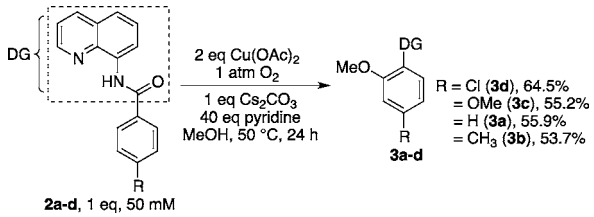
Scheme 2. Divergent Reactivity in Cu^{II}-Mediated C−H Oxidation of 2a



Overall, these observations, summarized in Scheme 2, highlight an unusual condition-dependent selectivity for Cu^{II}-mediated C−H oxidation. With these empirical data in hand, we turned our attention to understanding the mechanistic basis for these observations.

Mechanistic Study of Cu^{II}-Mediated C−H Oxidation of the Benzamide Ring. In order to gain further insight into the methoxylation reaction, substrates with electronically varied substituents on the benzamide ring were prepared (**2a−d**, Scheme 3). Initial rates were measured for the $Cu(OAc)_2$-

Scheme 3. Cu^{II}-Mediated Methoxylation from Methanol to Yield Substituted Anisoles



promoted methoxylation of these substrates (Table S6), and faster rates were observed with substrates bearing electron-withdrawing groups. A Hammett plot using σ_{meta} parameters reveals a small, but distinct, positive slope reflecting this electronic effect (ρ = 0.6 ± 0.1; Figure 1).

When the reaction is performed in CH_3OD, no deuterium is incorporated into the recovered starting material or the product (Scheme 4a), suggesting that C−H activation is irreversible. Kinetic isotope effects were obtained by an intramolecular competition experiment (Scheme 4b) and by comparison of

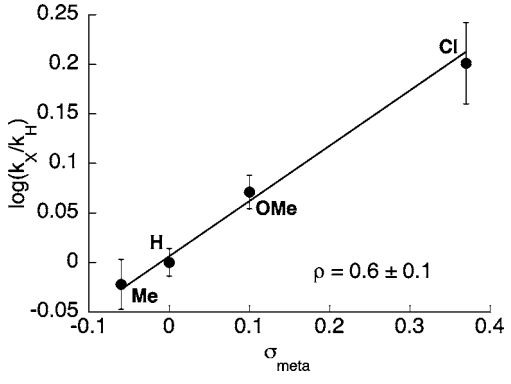
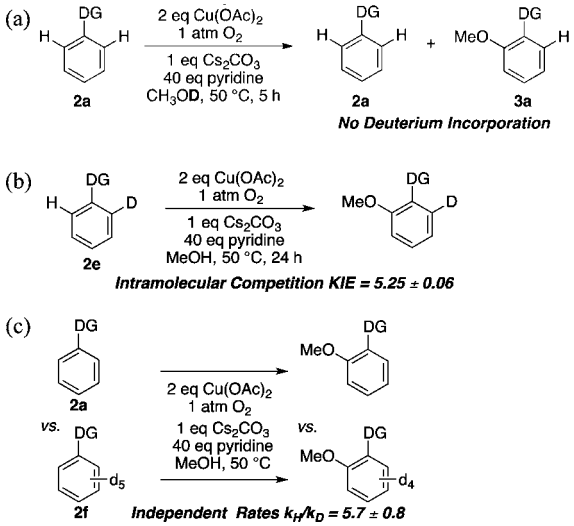


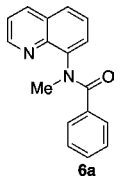
Figure 1. Hammett plot from initial rates of **2a−d** methoxylation.

Scheme 4. Deuteration and Isotope Effect Experiments for the Benzamide C−H Methoxylation Reaction



the independent rates of the H- and D-labeled substrates (Scheme 4c). Reaction of the monodeuterated substrate **2e** led to an 84:16 ratio of product isotopologues, favoring reaction of the C−H bond (KIE = 5.25 ± 0.06). A similar KIE was obtained from the comparison of the initial rates of **2a** and the aryl-d_5 substrate **2f** (KIE = 5.7 ± 0.8; Scheme 4c).

When the *N*-methyl substrate **6a** was submitted to the reaction conditions, no C−H functionalization was observed after 24 h. Most of the starting material was recovered cleanly, together with an approximately 20% yield of methyl benzoate arising from methanolysis of the tertiary amide (Table S3).



Mechanistic Study of Cu-Catalyzed C−H Chlorination of the Quinoline Ring. When the quinoline chlorination reaction was performed in CD_3CO_2D, no deuterium incorporation was observed in the recovered starting material or the product (Scheme 5a). This result indicates that cleavage of the C−H bond is irreversible. Kinetic isotope effects were obtained by an intermolecular competition experiment and by comparing the independent rates of the H- and D-labeled substrates. A 1:1 mixture of **2a** and the dideuterated substrate **2g** was submitted to the reaction conditions for 30 min, resulting in ∼5% product yield (Scheme 5b). Analysis of the H/D ratio at the 7-position of the quinoline revealed a nearly equal mixture of isotopes, corresponding to a KIE of 1.04 ± 0.05. Independent reactions of **2a** and **2g** exhibit nearly identical time courses (Figure S9), corresponding to a KIE ∼ 1 (Scheme 5c).

Coordination of **2a** to Cu^{II} as an amidate prior to chlorination, even under these acidic conditions, is supported by the lack of reaction of the *N*-methyl substrate **6a**. This substrate is fully recovered after 17 h under the standard reaction conditions. This observation aligns with our interpretation of the beneficial effect of a Brønsted base on the chlorination reaction (Table 2, entry 5).

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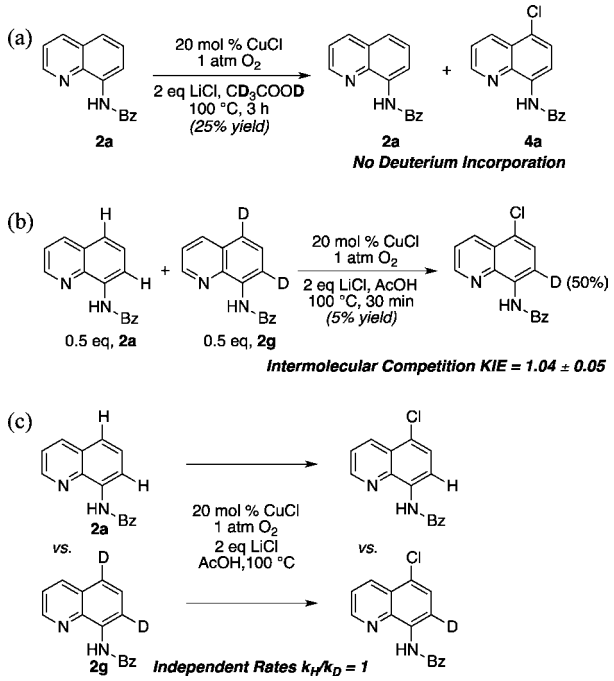
Scheme 5. Deuteration and Isotope Effect Experiments for the Quinolinyl C−H Chlorination Reaction



Preliminary Mechanistic Assessment. The results outlined above show that Cu^{II}-mediated C−H oxidation of **2a** affords different products and exhibits significantly different mechanistic features under different reaction conditions. On the basis of literature precedents (see Introduction), we attribute these results to the operation of organometallic and SET C−H functionalization pathways for the benzamide methoxylation and quinoline chlorination, respectively.

The positive Hammett slope observed for chelate-directed methoxylation of the benzamide ring (Figure 1) is inconsistent with an SET mechanism, which strongly favors electron-rich substrates.[17] Organometallic C−H activation reactions also typically favor electron-rich substrates, albeit to a lesser extent than SET reactions.[18] Several studies of Pd^{II}-mediated C−H activation, however, show that some of these reactions can proceed more rapidly with electron-deficient substrates.[19] For example, Fagnou and Gorelsky demonstrated C−H arylation reactions of pyridine *N*-oxides that proceed via rate-limiting C−H activation (k_H/k_D = 3.3) and exhibit a positive Hammett slope (ρ = 1.53).[19f] These results have been interpreted within the framework of a "concerted metalation-deprotonation" (CMD) mechanism in which C−H activation involves simultaneous electrophilic activation of the arene and deprotonation of the C−H bond. A positive Hammett slope can be observed for reactions in which C−H deprotonation contributes strongly to the transition state, and this pathway is consistent with the large KIE that we observe in the Cu^{II}-mediated C−H methoxylation reaction (KIE ∼ 5−6).

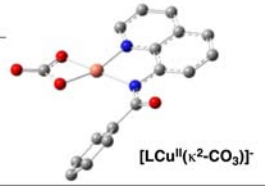
The nonchelate-directed chlorination of the quinoline ring of **2a** is consistent with SET reactivity. No KIE is observed for this reaction (KIE ∼ 1), and the regioselectivity is consistent with the electronic directing effect of benzamide nitrogen. Deprotonation of the amide group (i.e., upon coordination to the Cu center) would enhance this electronic effect. Similar electronic effects have been observed in SET-based chlorination of other electron-rich arenes.[3,4]

These considerations provided the basis for the use of density functional theory (DFT) calculations to gain further insights into both of the proposed mechanisms.

Computational Analysis of an Organometallic Pathway for Cu^{II}-Mediated C−H Oxidation. DFT methods were used to assess the energetic viability of an organometallic C−H functionalization pathway originating from the Cu^{II}-**2a** complex. The calculations were performed at the M06-L level of density functional theory,[20] incorporating solvation effects via the appropriate SMD continuum solvation model[21] (see Supporting Information for details). A number of Cu^{II} complexes bearing the 8-amidoquinoline ligand were optimized to evaluate the relative energies of possible ground-state structures (Table 3). The square-planar carbonate complex

Table 3. Calculated Stability of Possible Cu-2a Complexes under the Benzamide C−H Methoxylation Conditions

Species	Relative ΔG (kcal/mol)
$[LCu^{II}(\kappa^2\text{-}CO_3)]^-$	0.0
$[LCu^{II}(OMe)_2]^-$	6.2
$[LCu^{II}(\kappa^2\text{-}CO_3)py]^-$	6.9
$[LCu^{II}(\kappa^2\text{-}OAc)]$	16.6
$[LCu^{II}(\kappa^2\text{-}OAc)py]$	18.0



$[LCu^{II}(\kappa^2\text{-}CO_3)]^-$ (**I**) (L = deprotonated **2a**) was the most stable structure identified. Species in which the carbonate was replaced with an acetate ligand, methoxide ligands, or five-coordinate structures with a coordinated pyridine ligand were less stable.

Starting from the $[LCu^{II}(\kappa^2\text{-}CO_3)]^-$complex **I**, a C−H activation pathway was identified that proceeds via transition state **I-TS** (Scheme 6). In this mechanism, formation of the aryl-Cu^{II} complex **II** involves deprotonation of the arene C−H bond by the carbonate ligand with concomitant Cu−C bond formation, analogous to the CMD pathways that have been elaborated for Pd^{II}-mediated C−H activation.[19] The activation free energy ($\Delta G^{\ddagger}$) for this step is 25.9 kcal/mol, which compares very favorably to the experimental $\Delta G^{\ddagger}$ of ∼26 kcal/mol calculated from the reaction half-life (9−24 h) at 50 °C. The computed KIE for this step (k_H/k_D = 4.9) is also very similar to the experimental value (k_H/k_D = 5.7). The $[LCu^{II}(OMe)_2]^-$ complex is 6.2 kcal/mol less stable than the carbonate complex (Table 3), but this species mediates C−H activation with a barrier of only 20.4 kcal/mol (Figure S10). This comparatively low barrier is consistent with a beneficial effect of the basic methoxide ligand in the CMD C−H activation step. The net activation free energy of 26.6 kcal/mol, which accounts for the ground-state destabilization of this complex, is only slightly higher than the pathway involving the carbonate complex **I**. An analogous pathway involving the acetate complex $LCu^{II}(\kappa^2\text{-}OAc)$ is significantly higher in energy (net $\Delta G^{\ddagger}$ = 45.5 kcal/mol), largely because the acetate complex starts 16.6 kcal/mol higher in energy than the carbonate complex (Table 3).

The energetics of one-electron oxidation of the aryl-Cu^{II} complex **II** to an aryl-Cu^{III} complex were evaluated by considering possible Cu^{II}/Cu^{I} redox couples. A number of plausible Cu^{II} and Cu^{I} species that could be present in the reaction solution were examined (Table 4). Assuming ligand exchange in solution is facile, the most stable Cu^{II} and Cu^{I} species, $Cu^{II}(py)_2(CO_3)$ and $Cu^{I}(py)(OMe)$, provide the

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Scheme 6. Calculated Mechanism for the Cu^{II}-Mediated Benzamide C−H Methoxylation Reaction

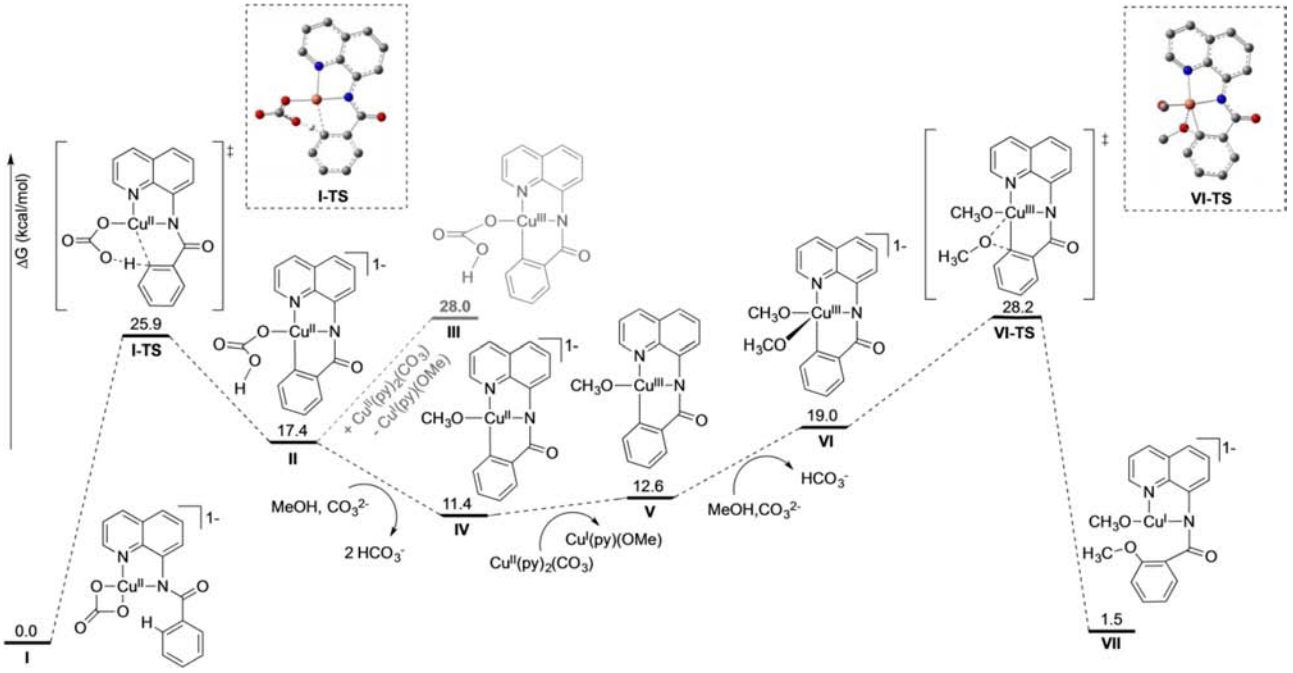


Table 4. Redox Couples Calculated for Oxidation of Aryl-Cu^{II} to Aryl-Cu^{III} in the Benzamide C−H Methoxylation Reaction in Methanol

$[Cu^{II}]$		$[Cu^{I}]$	
(Cu^{II}, CO_3^{2-}, 2 MeOH, 2 OAc^-, 2 py)	relative ΔG (kcal/mol)	(Cu^{I}, CO_3^{2-}, 2 MeOH, 2 OAc^-, 2 py)	relative ΔG (kcal/mol)
$Cu^{II}(py)_2(CO_3)$	0.0	$Cu^{I}(py)(OMe)$	0.0
$Cu^{II}(py)_2(OMe)_2$	4.2	$Cu^{I}(py)(OAc)$	7.4
$Cu^{II}(py)(CO_3)$	4.3	$Cu^{I}(py)(HCO_3)$	10.2
$Cu^{II}(OMe)_2(MeOH)_2$	8.5	$Cu^{I}(py)_2(OAc)$	11.6
$Cu^{II}(MeOH)_2(CO_3)$	8.7	$Cu^{I}(py)(OAc)_2^-$	13.3
$Cu^{II}(OMe)(HCO_3)(py)_2$	14.5	$Cu^{I}(MeOH)(OAc)$	16.7
$Cu^{II}(OMe)(HCO_3)(MeOH)_2$	15.1	$Cu^{I}(MeOH)_2(CO_3)^-$	21.1
$Cu^{II}(py)_2(OAc)_2$	16.4	$Cu^{I}(MeOH)_2(OAc)$	25.5
$Cu^{II}(MeOH)_2(OAc)_2$	16.7		
$Cu^{II}(py)(MeOH)(OAc)_2$	18.0		

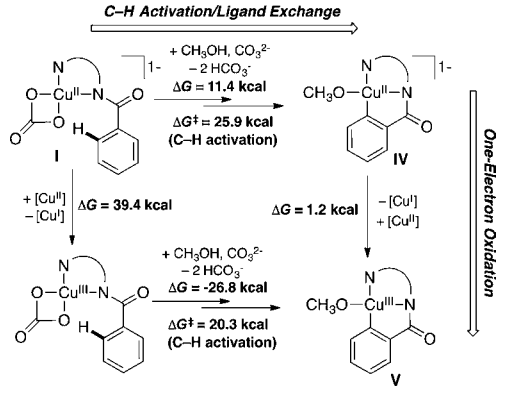
relevant equilibrium redox couple for oxidation of aryl-Cu^{II} to aryl-Cu^{III}.

Oxidation of aryl-Cu^{II} complex **II**, which has a bicarbonate ligand, is energetically disfavored (**III**, ΔG = 28.0 kcal/mol relative to **I**; Scheme 6). Exchange of the bicarbonate ligand with methoxide to form **IV**, however, is favorable, and subsequent oxidation of **IV** to afford aryl-Cu^{III} species **V** is uphill by only 1.2 kcal/mol. These observations can be rationalized by the ability of the methoxide ligand to stabilize Cu^{III} relative to a bicarbonate ligand.

Reductive elimination from the 4-coordinate Cu^{III}(aryl)-(OMe) complex **V** was found to be prohibitive (Figure S11, $\Delta G^{\ddagger}$ = 44.2 kcal/mol). The five-coordinate dimethoxide complex **VI** is energetically accessible, however, and reductive elimination from this species is more favorable (Scheme 6, $\Delta G^{\ddagger}$ = 28.2 kcal/mol relative to **I**). This observation suggests that the reactive methoxide nucleophile enters the coordination sphere following oxidation of Cu^{II} to Cu^{III}. This sequence may vary with other substrates, for example, with those lacking the conformational constraints of the chelating ligand. The reductive elimination transition state **VI-TS** is similar in energy to the C−H activation transitions state **I-TS**. The calculated pathway is consistent with the experimental observation of rate-limiting C−H activation given the expected accuracy of the computational model. Uncertainties in the computed energies derive in part from the relative pK_a values of methanol and carbonate, and they may be amplified by the multiple deprotonations of MeOH by carbonate that are performed along the reaction path.

C−H activation by Cu^{III} was also considered (Scheme 7, lower pathway)[22] and found to have an activation barrier 5.6 kcal/mol lower in energy than the corresponding Cu^{II}-mediated step ($\Delta G^{\ddagger}_{Cu(III)}$ = 20.3 kcal/mol). Nevertheless, this pathway is strongly disfavored by the highly unfavorable energy for oxidation of the Cu^{II} center to Cu^{III} (ΔG = 39.4 kcal/mol) prior to C−H activation. A concerted proton-coupled electron-transfer process cannot be excluded on the basis of our results,

Scheme 7. Cu^{II} vs Cu^{III} C−H Activation Mechanisms



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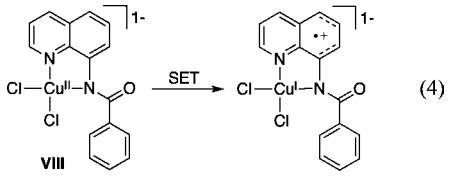
but the computational data presented here are consistent with a stepwise Cu^{II}-mediated C−H activation step followed by one-electron oxidation: **I** → **IV** → **V** (Schemes 6 and 7).

Computational Analysis of a SET Pathway for Cu^{II}-Mediated C−H Oxidation. Chlorination of the quinoline ring takes place under conditions similar to those for reactions that have been proposed to proceed by an SET mechanism. Our initial studies probed the possibility of an intramolecular SET step in complex **VIII** (eq 4), similar to that illustrated in



(4)

Scheme 1. The product corresponds to an electronic excited state of the ground-state species, and the energy of this state was evaluated by performing TD-DFT calculations. The lowest-energy internal SET product arises from transfer of a β-spin electron from a mixture of two doubly occupied orbitals, one associated with the chloride lone pairs (GS-A) and the other with quinoline π electrons (GS-B), to the singly occupied orbital localized on Cu (i.e., $d_{x^2-y^2}$) (Figure 2 and Table S7).

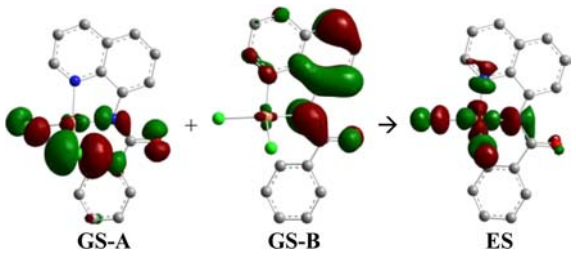


Figure 2. The lowest excited-state doublet derives from excitation of a beta electron from the nominally doubly occupied HOMO-1 (GS-A) and HOMO (GS-B), contributing with equal weight, into the singly occupied SOMO (ES). The resulting excited state is 31.4 kcal/mol above the ground state, corresponding to a photon energy of 909.4 nm.

The excitation energy for this transition is 31.4 kcal/mol. Because chlorination of the aromatic ring would add a further energy barrier, however, we considered whether an intermolecular SET process might exist that provides access to a lower energy pathway.

Various Cu^{II}/Cu^{I} redox couples were considered for the intermolecular SET reaction (Table 5). $Cu^{II}Cl_2(AcOH)_2$ and $Cu^{I}Cl_2^-$ were the lowest-energy Cu^{II} and Cu^{I} species identified and were used to calculate the energy of the SET step. One-electron oxidation of **VIII** to the Cu^{II} complex **IX**, bearing a radical-cation amidoquinoline ligand, is thermodynamically uphill by 8.6 kcal/mol (Scheme 8). This step is analogous to the Cu^{II} disproportionation step that affords the aryl-Cu^{III} species in the organometallic mechanism (i.e., **IV** → **V** in Scheme 6); however, in the present case, ligand oxidation is favored over oxidation of the Cu center based on analysis of the computed spin and charge densities.

Table 5. Redox Couples Calculated for the Oxidation of Cu^{II} to Aryl-Radical-Cation-Ligated Cu^{II} Complex during Quinoline C−H Chlorination in Acetic Acid

$[Cu^{II}]$		$[Cu^{I}]$	
(Cu^{II}, 4Cl^-, 2 AcOH)	relative ΔG (kcal/mol)	(Cu^{I}, 4Cl^-, 2 AcOH)	relative ΔG (kcal/mol
$Cu^{II}(Cl)_2(AcOH)_2$	0.0	$Cu^{I}Cl_2^-$	0.0
$Cu^{II}Cl_3(AcOH)^-$	1.6	$Cu^{I}Cl_2(AcOH)^-$	2.0
$Cu^{II}Cl_4^{2-}$	4.0	$Cu^{I}Cl(AcOH)$	10.4
$Cu^{II}Cl_2(AcOH)$	5.9	$Cu^{I}Cl(AcOH)_2$	11.9
$Cu^{II}Cl_2$	18.6	$Cu^{I}Cl$	20.3

This 8.6 kcal/mol thermodynamic barrier for the SET step is much lower than the excitation energy for the intramolecular SET described above, and it is also much lower than one-electron oxidation of the noncoordinated neutral substrate **2a** (ΔG = 31.0 kcal/mol; eq 5). The latter observation shows that coordination of the substrate to Cu^{II} as an amidate ligand greatly facilitates intermolecular SET.

(5)

Various pathways were considered for chlorination of the radical-cation complex **IX**. The lowest barrier was obtained from a process involving chlorine-atom transfer from $CuCl_2$, with explicit modeling of an equivalent of chloride and acetic acid (Scheme 8). This step proceeds via transition state **IX-TS** and exhibits an activation energy of $\Delta G^{\ddagger}$ = 29.8 kcal/mol. Deprotonation of the resulting Wheland-type intermediate **X** affords the quinoline chlorination product **XI**. The overall barrier for this computed pathway exhibits good agreement with the estimated experimental barrier of ∼30 kcal/mol derived from the reaction half-life at 100 °C (8.5−17 h; energy estimated based on a pseudo first-order reaction). The computed KIE for this step, k_H/k_D = 0.91 is also similar to the value determined experimentally (k_H/k_D = 1).

The similarity between the experimental and computed barriers is almost certainly fortuitous, considering the nature of our redox-couple calculation. For example, it is possible that more stable Cu^{II} species may be present in solution than those found in Table 5, thereby increasing the thermodynamic barrier for the SET step. A considerably more sophisticated treatment of aggregates and specific solvation effects would be required to assess this point further, but we consider it unlikely that such results would increase the energies of the species in Scheme 8 by more than 3 or 4 kcal/mol, which is within the limits of the expected uncertainty for these calculations.

Reasons for the Mechanistic Divergence under Different Reaction Conditions. The experimental and computational results described above provide several insights that can account for the change in mechanism and product selectivity under different reaction conditions. Carbonate is an important additive in the benzamide C−H methoxylation reaction (Table 1), and the computational results draw attention to at least two important roles for carbonate. First, a basic ligand is essential for activation of the arene C−H bond by an organometallic CMD mechanism. Acetate could also perform such a role, but carbonate (or methoxide, Figure S10) appears to be much more effective, probably owing to its higher basicity. Second, the carbonate dianion is a good ligand that stabilizes Cu^{II} and Cu^{III} species relative to complexes with

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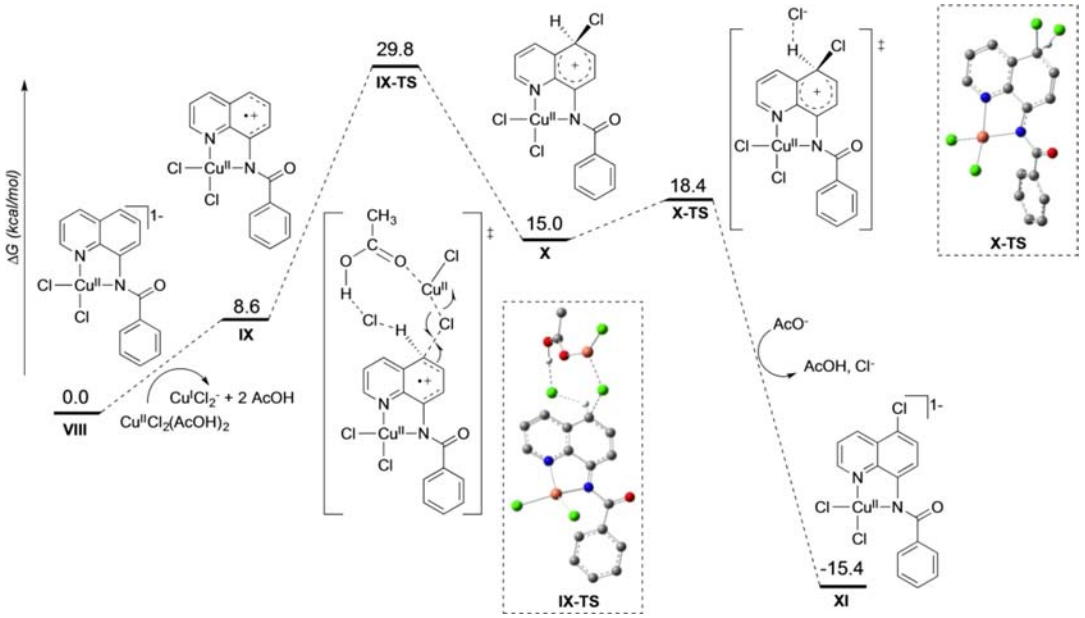
Scheme 8. Calculated Mechanism for the Cu^{II}-Mediated Quinoline C−H Chlorination Reaction



acetate or bicarbonate ligands (cf. Table 3 and Scheme 6). This effect is particularly important to access the aryl-Cu^{III} intermediate that can undergo facile C−O bond formation.

The carbonate ligand properties that favor organometallic C−H oxidation disfavor SET C−H oxidation. Specifically, coordination of carbonate to Cu^{II} will lower the Cu^{II}/Cu^{I} reduction potential and disfavor SET from the aromatic substrate. The acidic reaction conditions associated with chlorination of the quinoline ring lack strong donor ligands, and Cu^{II} will be present in the form of more-oxidizing halide species. Redox couples were computed for various Cu species to provide further insight into this issue. As shown in Table 6,

Table 6. Computed Redox Potentials of Species Available in Acidic and Basic Reaction Conditions

redox couples	ΔG (kcal/mol)	E (V) vs NHE
Acidic Conditions:		
$Cu^{II}Cl_2(AcOH)_2 + e^- \rightarrow Cu^{I}Cl_2^- + 2AcOH$	−102.8	0.18
VIII + $e^- \rightarrow$ **IX**	−111.4	0.55
Basic Conditions:		
$Cu^{II}(py)_2CO_3 + CH_3OH + e^- \rightarrow Cu^{I}(py)(OCH_3) + py + HCO_3^-$	−80.2	−0.80
III + $e^- \rightarrow$ **II**	−90.7	−0.34
V + $e^- \rightarrow$ **IV**	−81.4	−0.75

the Cu^{II}/Cu^{I} reduction potentials computed for the major species present under acidic and basic reaction conditions (the top redox couple in each category) differ by nearly 1 V. While these redox potentials have considerable uncertainty, the qualitative trend is clear: acidic conditions are much more amenable to SET-based oxidation of electron-rich substrates.

CONCLUSIONS

In summary, we have identified an unusual switch in mechanism and product identity in Cu^{II}-mediated C−H oxidation of the amidoquinoline substrate **2a**. The experimental and computational results are consistent with a switch between organometallic and SET-based C−H oxidation pathways upon changing from basic to acidic reaction conditions. The presence of a Brønsted basic ligand on the Cu^{II} center facilitates C−H activation by an organometallic mechanism, while acidic conditions enhance the Cu^{II} reduction potential, thereby favoring SET. The results of this study show that a macrocyclic chelate (as in **1**; eq 2) is not required to achieve organometallic C−H activation by Cu^{II}. The experimental and computational results highlight the proton-transfer component associated with Cu^{II}-mediated C−H activation. On the basis of this insight, it seems reasonable to speculate that Cu^{II}-catalyzed oxidations of substrates containing acidic C−H bonds follow pathways analogous to the organometallic pathway shown in Scheme 6. Many precedents for C−H oxidations of this type, including reactions with alkynes and various aromatic heterocycles, are accomplished with substrates that lack directing groups altogether. Collectively, these insights provide a valuable foundation for continued efforts to expand the scope of Cu-catalyzed aerobic C−H oxidation reactions.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization, additional data, and computational data. 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) (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062−11087. (b) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381−3430. (c) Punniyamurthy, T.; Rout, L. *Coord. Chem. Rev.* **2008**, *252*, 134−154. (d) Gamez, P.; Aubel, P. G.; Driessen, W. L.; Reedijk, J. *Chem. Soc. Rev.* **2001**, *30*, 376−385. (e) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780−1824.

(2) (a) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857−898. (b) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327−3359. (c) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540−548. (d) Kočovský, P.; Vyskočil, Š.; Smrčina, M. *Chem. Rev.* **2003**, *103*, 3212−3245. (e) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, *1992*, 503−517. (f) Wang, H. *Chirality* **2010**, *22*, 827−837.

(3) (a) Menini, L.; Gusevskaya, E. V. *Chem. Commun.* **2006**, 209−211. (b) Menini, L.; Gusevskaya, E. V. *Appl. Catal., A* **2006**, *309*, 122−128. (c) Menini, L.; Parreira, L. A.; Gusevskaya, E. V. *Tetrahedron Lett.* **2007**, *48*, 6401−6404. (d) Menini, L.; da Cruz Santos, J. C.; Gusevskaya, E. V. *Adv. Synth. Catal.* **2008**, *350*, 2052−2058.

(4) Yang, L.; Lu, Z.; Stahl, S. S. *Chem. Commun.* **2009**, *45*, 6460−6462.

(5) For leading references, see: (a) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317−5325. (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335−344. (c) Li, C.-J.; Li, Z. *Pure Appl. Chem.* **2006**, *78*, 935−945. (d) Li, Z.; Bohle, D. S.; Li, C.-J. *P. Natl. Acad. Sci.* **2006**, *103*, 8928−8933.

(6) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790−6791.

(7) The mechanism was further supported by analogy to Co^{III}-promoted arene C−H oxidation: Kochi, J. K.; Tang, R. T.; Bernath, T. *J. Am. Chem. Soc.* **1973**, *95*, 7114−7123.

(8) For an extensive review of such reactions, see ref 1a. For selected examples, see: (a) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842−843. (b) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932−1934. (c) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411−6413. (d) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833−835. (e) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052−17053. (f) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607−1610. (g) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178−5180. (h) Mizuhara, T.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2009**, 3413−3415. (i) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28−29. (j) Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 2415−2418. (k) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, *132*, 13217−13219. (l) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2358−2361. (m) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158−4162. (n) Guru, M. M.; Punniyamurthy, T. *J. Org. Chem.* **2012**, *77*, 5063−5073. (o) Ding, S.; Yan, Y.; Jiao, N. *Chem. Commun.* **2013**, *49*, 4250−4252.

(9) For leading references, see: (a) Furuta, H.; Maeda, H.; Osuka, A. *J. Am. Chem. Soc.* **2000**, *122*, 803−807. (b) Chmielewski, P. J.; Latos-Grażyński, L.; Schmidt, I. *Inorg. Chem.* **2000**, *39*, 5475−5482. (c) Furuta, H.; Ishizuka, T.; Osuka, A.; Uwatoko, Y.; Ishikawa, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2323−2325. (d) Maeda, H.; Ishikawa, Y.; Matsuda, T.; Osuka, A.; Furuta, H. *J. Am. Chem. Soc.* **2003**, *125*, 11822−11823. (e) Pawlicki, M.; Kańska, I.; Latos-Grażyński, L. *Inorg. Chem.* **2007**, *46*, 6575−6584.

(10) (a) Ribas, X.; Jackson, D. A.; Donnadieu, B.; Mahía, J.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2991−2994. (b) Xifra, R.; Ribas, X.; Llobet, A.; Poater, A.; Duran, M.; Solà, M.; Stack, T. D. P.; Benet-Buchholz, J.; Donnadieu, B.; Mahía, J.; Parella, T. *Chem.—Eur. J.* **2005**, *11*, 5146−5156. (c) 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.

(11) For a related macrocyclic arene, see: Yao, B.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Chem. Commun.* **2009**, *45*, 2899−2901.

(12) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068−12073.

(13) For fundamental studies of the C−O/C−N reductive elimination reactions, see: (a) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196−9197. (b) Huffman, L. M.; Casitas, A.; Font, M.; Canta, M.; Costas, M.; Ribas, X.; Stahl, S. S. *Chem.—Eur. J.* **2011**, *17*, 10643−10650.

(14) For leading references, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074−1086.

(15) The first application of this ligand to Cu-mediated C−H functionalization (non-aerobic) was reported recently: Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237−18240.

(16) For a similar beneficial catalytic effect arising from in situ generation of a base upon aerobic oxidation of Cu^{I} in alcohol oxidation reaction, see: Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 2357−2367.

(17) For example, in Cu-catalyzed oxidative chlorination (ref 4), benzene, toluene, and anisole do not react, while dimethoxybenzene, which is significantly more electron-rich, does react. As another example, the reaction of PhOAc is 1000-fold faster than PhO_2CCF_3 in Co^{III}-mediated oxidative trifluoroacetoxylation (ref 7), which is proposed to proceed via SET.

(18) For a comparison of the electronic effects of "electrophilic" C−H activation by Pd^{II} and other more-classical electrophiles, see: Stock, L. M.; Tse, K.-t.; Vorvick, L. J.; Walstrum, S. A. *J. Org. Chem.* **1981**, *46*, 1757−1759.

(19) See, for example: (a) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.* **1985**, *14*, 2629−2638. (b) Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115−3118. (c) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754−13755. (d) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066−1067. (e) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848−10849. (f) Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749−823. (g) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180−8189. (h) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315−1345. (i) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658−668.

(20) Zhao, Y.; Truhlar, D. G. *J. Chem. Phys.* **2006**, *125*, 194101−194118.

(21) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.

(22) C−H activation by Cu^{III} has been proposed in the presence of hypervalent iodine reagents: (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172−8174. (b) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593−1597. (c) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996−6005. (d) Chen, B.; Hou, X.-L.; Li, Y.-X.; Wu, Y.-D. *J. Am. Chem. Soc.* **2011**, *133*, 7668−7671.