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Computational Explorations of Mechanisms and Ligand-Directed Selectivities of Copper-Catalyzed Ullmann-Type Reactions

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Abstract: Computational investigations of ligand-directed selectivities in Ullmann-type coupling reactions of methanol and methylamine with iodobenzene by β-diketone- and 1,10-phenanthroline-ligated Cu^{I} complexes are reported. Density functional theory calculations using several functionals were performed on both the nucleophile formation and aryl halide activation steps of these reactions. The origin of ligand-directed selectivities in N- versus O-arylation reactions as described in a previous publication (*J. Am. Chem. Soc.* **2007**, *129*, 3490−3491) were studied and explained. The selectivities observed experimentally are derived not from initial Cu^{I}(nucleophile) complex formation but from the subsequent steps involving aryl halide activation. The arylation may occur via single-electron transfer (SET) or iodine atom transfer (IAT), depending on the electron-donating abilities of the ligand and nucleophile. Mechanisms involving either oxidative addition/reductive elimination or σ-bond metathesis are disfavored. SET mechanisms are favored in reactions promoted by the β-diketone ligand; N-arylation is predicted to be favored in these cases, in agreement with experimental results. The phenanthroline ligand promotes O-arylation reactions via IAT mechanisms in preference to N-arylation reactions, which occur via SET mechanisms; this result is also in agreement with experimental results.

Introduction

Ullmann and Goldberg first reported the coupling of C−C and C−N bonds by copper complexes more than a century ago.[1] Until recently, these protocols remained underutilized because of limitations such as low yields, limited scope, and lack of selectivity. However, recent reports have generated renewed interest in Ullmann-type reactions in both academic and industrial settings by demonstrating the use of chelating ligands such as β-diketones,[2,3] 1,2-diamines,[4] phenanthrolines,[5,6] bipyridines,[7] α-amino acids,[8] and others.[9−14] Increased activity and broadened substrate scope have been achieved by using these ligands in combination with bases such as K_3PO_4, Cs_2CO_3, and K_2CO_3 in copper-catalyzed arylations.

Building on preliminary studies demonstrating copper-catalyzed N- and O-arylation reactions of β-amino alcohols,[15] the Buchwald group recently investigated ligand effects on the selectivities of related reactions. The β-diketone ligand **5** promoted the formation of N-arylated products in Cu^{I}-catalyzed reactions of 5-amino-1-pentanols with iodoarenes in *N*,*N*-dimethylformamide (DMF), but O-arylated products were formed in toluene by switching to the 1,10-phenanthroline ligand, **6** (Scheme 1).[16] β-Diketone **5** typically promoted N-arylation over O-arylation in >20:1 ratio; the phenanthroline ligand, **6**, typically promoted the formation of a 16:1 ratio of O-arylated product to N-arylated product. A recent examination

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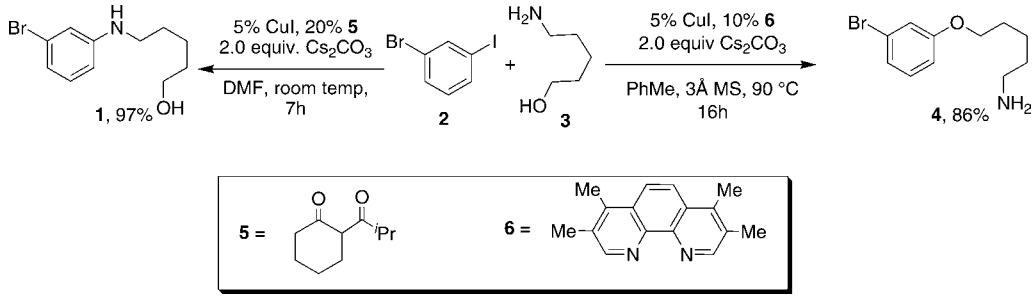
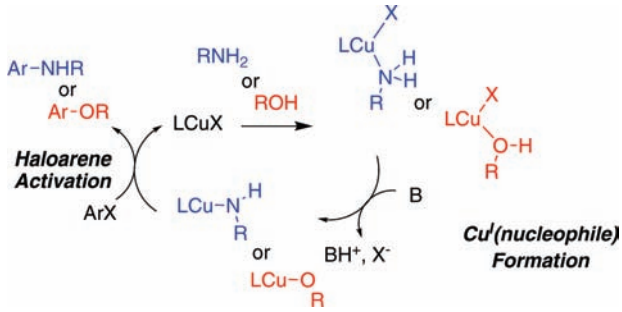
Scheme 1



Scheme 2



demonstrated that O-selective reactions also occur with picolinic acid and *N*,*N*′-dimethylcyclohexane-1,2-diamine (CyDMEDA).[17]

The proposed catalytic cycle is shown in Scheme 2. The Cu^{I}(nucleophile) complex is formed via coordination of the alcohol or the amine with the Cu^{I}(halide) and subsequent elimination of hydrogen halide. The Cu^{I}(nucleophile) complex then reacts with aryl halide to give the arylated products and regenerate the Cu^{I}(halide) catalyst. It was proposed[16] that ligands influence whether the alcohol or the amine substituent becomes coordinated to the ligated Cu^{I}(halide) and whether the O-bound or N-bound nucleophiles are more acidic. The pK_a of the alcohol bound to (phenanthroline)Cu^{I} is presumably much lower than that of the bound amine, thereby leading to the favored formation of the (phenanthroline)Cu^{I}(methoxide) complex and, eventually, to O-arylation. In contrast, the electrophilicity of Cu^{I} is lowered by the anionic β-diketone ligand; this presumably disfavors binding of the alcohol and increases the affinity of the amine for Cu^{I}. Deprotonation of the bound amine leads to the formation of the N-arylated product.

Alternatively, the selectivity differences might arise in the step involving arene activation and coupling with the coordinated nucleophile. This study differentiates between these proposals.

The formation of ligated Cu^{I}(nucleophile) complexes in Ullmann-type reactions has recently been studied experimentally;[18,19] the formation of the ligated Cu^{I}(nucleophile) complex and subsequent product are highly dependent on the concentration of the chelating ligand. Cu^{I} is multiply ligated by the nucleophile at low ligand concentrations; aryl halide activation occurs only after formation of the LCu^{I}(nucleophile) species at intermediate ligand concentrations.[18,19] The catalytic activity is diminished at higher ligand concentrations.

A computational study by Guo and co-workers[20] showed the intermediacy of the LCu^{I}(nucleophile) complexes versus other potential copper species in the coupling of aryl halides with amides. This investigation confirmed that the concentration of the LCu^{I}(nucleophile) complex far exceeds concentrations of other potential copper species. Additionally, the barrier for oxidative addition of the aryl halide to the LCu^{I}(nucleophile) complex is lower than the barriers for reactions involving other complexes. Computational investigations by Tye and coworkers[19] showed that the reaction of PhI with LCu^{I}(nucleophile) has a lower barrier for oxidative addition than do the reactions with other potential Cu^{I} complexes.

These reports demonstrate that reactions catalyzed by Cu^{I} proceed via the initial formation of a Cu^{I}(nucleophile) species, but there is no consensus on the mechanisms of subsequent steps involving aryl halide activation. Possible mechanisms based on early work by Kochi,[21] Whitesides,[22] Johnson,[23] and Cohen[24] are summarized in Scheme 3. The most widely accepted mechanism involves oxidative addition of the Cu^{I}(nucleophile) complex to the aryl halide, leading to the formation of a Cu^{III} intermediate (Scheme 3a). An alternative proposal involves single-electron transfer (SET) from the Cu^{I}(nucleophile) complex to the aryl halide, resulting in the formation of a radical pair comprising the radical anion of the aryl halide and a Cu^{II} species (i.e., an $S_{RN}1$ mechanism) (Scheme 3b). This radical pair could be directly converted into products or could form the Cu^{III} intermediate after a subsequent SET step (Scheme 3c). An atom transfer mechanism involving transfer of the halide atom from the aryl halide has also been postulated (Scheme 3d). A recent study has suggested that a four-centered σ-bond metathesis mechanism (Scheme 3e) could occur.[25] A mechanism involving nucleophilic aromatic substitution via a π-complexed organocuprate intermediate has also been proposed,[26] but there is scant experimental evidence to support this hypothesis.

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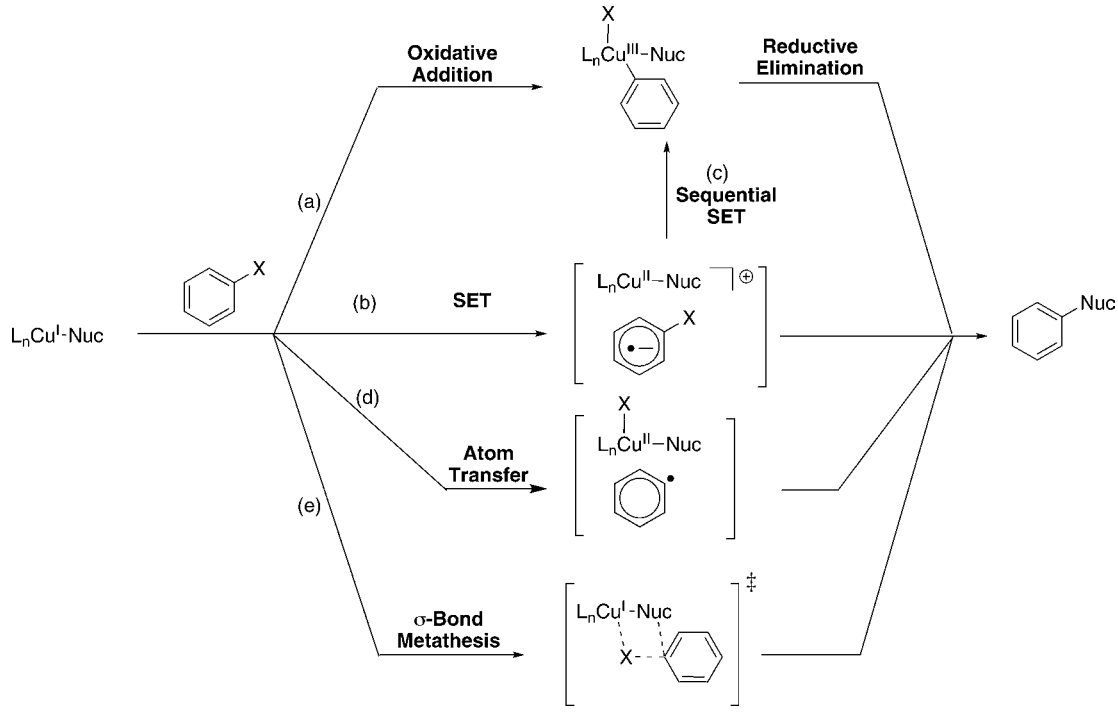
Scheme 3



There is less experimental evidence for mechanisms of aryl halide activation in Ullmann-type reactions involving *ligated* Cu^{I} complexes. Hida and co-workers[27] demonstrated that bromoanthraquinone radical anions could be detected by EPR spectroscopy in Ullmann-type reactions promoted by 2-aminoethanol, suggesting that the mechanism involves the oxidation of the Cu^{I} species to Cu^{II}. Whether a Cu^{III} complex was ever formed or the product was formed directly could not be ascertained from those investigations. Bethell and co-workers[28] observed that products consistent with the formation of a Cu^{III} intermediate are formed in related reactions of bromoanthraquinone with primary amines. Huffman and Stahl[29] demonstrated that N-arylation occurs via the coupling of Cu^{III}(aryl) species with nitrogen-based nucleophiles. This result could be explained by the initial formation of Cu^{III}(aryl)(nucleophile) intermediates that undergo reductive elimination to form C−N coupling products. These results suggest that reductive elimination from Cu^{III} intermediates can occur but do not rule out mechanisms involving formation of Cu^{I} or Cu^{II} intermediates prior to aryl activation.

Finally, Tye and co-workers[19] performed experimental investigations that appear to rule out the intermediacy of aryl free radicals and Cu^{II} intermediates in related reactions. On the basis of those experiments, the authors concluded that these reactions occur via mechanisms involving either concerted oxidative addition to form a Cu^{III} intermediate or inner-sphere electron transfer. In a notable series of experiments, ligated Cu^{I}(nucleophile) complexes were reacted with an aryl halide ortho-substituted with an allyloxy substituent that serves as a radical clock. Only products consistent with C−N coupling and reduction of the arylhalide were formed; cyclized products corresponding to the initial formation of an aryl radical and subsequent cyclization were not detected, suggesting that the reaction of the putative aryl radical with the Cu^{II}(nucleophile) complex must be faster than intramolecular cyclization. In fact, results provided in the present manuscript suggest that Cu^{II} intermediates are too short-lived to be detectable, consistent with those experiments. In another set of experiments, two aryl bromides and an aryl chloride with different reduction potentials but similar rates for halide dissociation from the aryl halide radical anion were reacted with Cu^{I}(nucleophile) complexes. While both aryl bromides reacted to form the C−N coupled product, no reaction was observed with the aryl chloride, even though it had a greater potential for reduction than the aryl bromides. On the basis of the differing results obtained with these aryl halides, this experiment could indicate that outer-sphere electron transfer leading to the formation of the radical anion does not occur. However, this experiment could also imply that aryl chlorides, even with greater potentials for reduction, are less likely to coordinate to copper than aryl bromides to facilitate electron transfer. In fact, few examples of the use of aryl chlorides in Cu-catalyzed Ullmann-type reactions are known. Such reactions typically require forcing conditions, the use of very electron-rich ligands, or the use of electron-poor aryl chlorides.[30−33] It has not been determined that the mechanisms for reactions involving aryl chlorides are identical to those involving aryl bromides and aryl iodides. Therefore, the fact that no reaction occurs in some examples involving aryl

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chlorides is not conclusive evidence that aryl halide radical anions are not formed during these types of reactions.

Previous computational investigations by Tye and co-workers[19] and by Guo and co-workers[20] on the mechanisms of Ullmann-type reactions have focused only on mechanisms involving oxidative addition; alternative mechanisms involving SET, atom transfer, and σ-bond metathesis were not explored.

The primary goal of the present study was the elucidation of the mechanism and source of ligand-directed N- versus O-selectivities in Ullmann-type arylation reactions. Computational studies using density functional theory (DFT) suggest that the observed selectivities arise from single-electron transfer or iodine atom transfer processes in which short-lived radical pairs are formed and then rapidly converted to products.

Computational Methodology

All of the calculations were carried out with the Gaussian03 suite of computational programs.[34] The B3LYP[35,36] and MPWB1K[37] DFT methods were used for geometry optimizations and single-point energy calculations, respectively.[38] The 6-31+G(d,p) basis set was employed for the C, H, N, and O atoms in the B3LYP calculations, and the MG3S[39] basis set was employed in the MPWB1K calculations. Both methods employed the LANL2DZ effective core potentials of Hay and Wadt with double-ζ basis sets for Cu, I, and Cs. These calculations were augmented by geometry optimizations with the CPCM solvation method[40] with UAKS cavities. Solvent parameters for acetonitrile (ε = 36.64) were employed, although DMF (ε = 36.71) was used in experiments involving the β-diketone ligand.[41] No parameters for the DMF solvent are available in Gaussian03. Calculations for reactions involving the 1,10-phenanthroline ligand involved the CPCM model for toluene. The Gibbs free energies presented in this article are MPWB1K electronic energies modified with zero-point-energy, thermal, and entropy corrections from B3LYP calculations and solvation-energy corrections from the CPCM method.

Results and Discussion

Computational models of the reagents used in the experiments were employed in an effort to reduce the computational cost associated with these calculations. Computational investigations were performed on separate reactions of iodobenzene with methanol and methylamine as models of the aminoalcohols used experimentally. The reactions involving Cu^I complexes **10** and **11** (Figure 1) were studied. All of the energies shown hereafter are referenced to energies for the reactions of methanol and methylamine with iodobenzene catalyzed by the ligated Cu^I-(iodide) complexes.

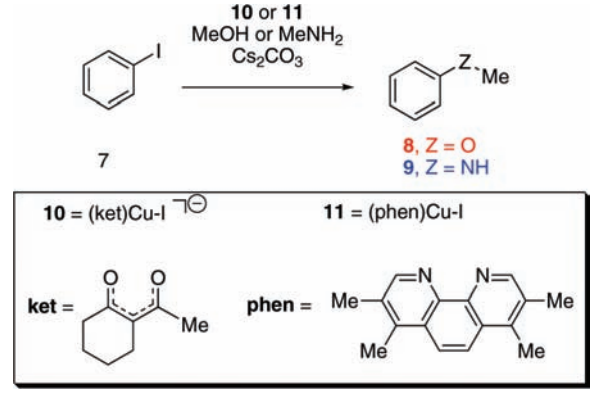

Figure 1. Computational models of reagents employed in N- and O-arylation reactions.

The formation of the ligated Cu^I(nucleophile) complexes was first considered (Figure 2). The formation of the Cu^I(methoxide) complex is preferred over the Cu^I(methylamido) complex with both ligands. With the β-diketone ligand, the reaction to form the Cu^I(methoxide) complex **12** is 12 kcal/mol more exergonic than the reaction to give the Cu^I(methylamido) complex **13**. With the phenanthroline ligand, the Cu^I(methoxide) complex is formed in a reaction that is 10 kcal/mol more exergonic than that of the Cu^I(methylamido) complex. These results suggest that the observed experimental selectivities most likely do not arise from the nature of the ligated Cu^I(nucleophile) complexes but occur in the aryl halide activation step of the reaction.

Computed free energies for key species in possible mechanisms for aryl halide activation of β-diketone- and phenanthroline-bound Cu^I complexes are shown in Table 1. The activation energies for oxidative addition of iodobenzene to the Cu^I(nucleophile) complexes are much larger than the energies computed for key complexes in the single-electron transfer (**SET**) and iodine atom transfer (**IAT**) mechanisms. The transition structure for oxidative addition to **12** has an energy of 65 kcal/mol. A similar transition state could not be found for oxidative addition of iodobenzene to **13**, but the barrier should be higher than the energy of the complex formed after oxidative addition (55 kcal/mol).

Similarly, the activation barriers for oxidative addition of iodobenzene to (phen)Cu^I(nucleophile) complexes are prohibitively large; 43 and 54 kcal/mol are required for oxidative addition of iodobenzene to the O-bound and N-bound complexes **14** and **15**, respectively. The oxidative addition steps involve the transformation of Cu^I complexes with closed-shell d^{10} electron configurations into Cu^{III} complexes with d^8 electron configurations with two unpaired electrons. The barriers for σ-bond metathesis are also unreasonably large and almost isoenergetic with the barriers for oxidative addition.

The barriers for the mechanisms involving **IAT** from iodobenzene to the Cu^I complexes and **SET** from the Cu^I complexes to iodobenzene were estimated from the energies of the completely separated Cu^{II}(nucleophile) complexes and the iodobenzene ionic radical or benzene radical formed by these processes. Transition states corresponding to **IAT** in these reactions could not be located after many attempts.

Activation free energies for **SET** mechanisms can also be estimated from the standard free energies of these reactions

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(41) The selectivities of reactions involving β-diketone-promoted Cu-catalyzed coupling of aminopentanol with aryl iodides in butyronitrile are similar to those in DMF.

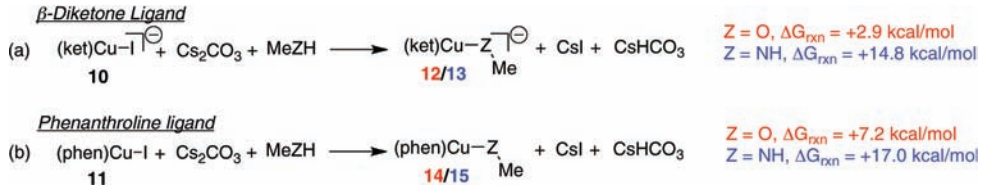
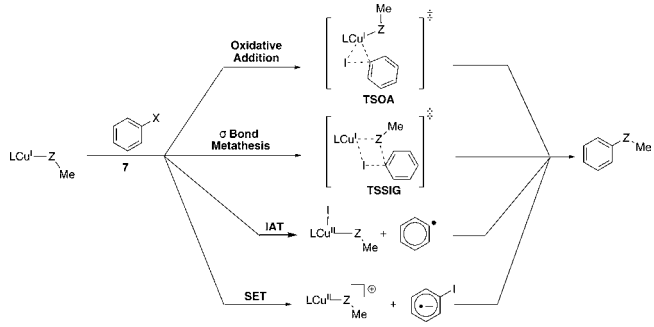


Figure 2. Reaction free energies (kcal/mol) in solution for Cu^{I}(nucleophile) formation from the reactions between Cu^{I}(iodide) complexes **10** and **11** and the methanol or methylamine nucleophiles. Energies are given in red and blue for reactions with methanol and methylamine, respectively.

Table 1. Free Energies (kcal/mol) for Key Stationary Points in the Mechanisms of Ligand-Promoted Ullmann-Type N- and O-Arylation Reactions (Z = O, NH)



	Cu(ZMe) formation	TSOA	TSSig	IAT	SET	product formation
			(ket)Cu Complexes			
MeO-bound (**12**)	2.9	64.6	57.1	32.9	27.2	−41.3
MeNH-bound (**13**)	14.8	55.0[a]	65.6	41.1	26.2	−48.0
			(phen)Cu Complexes			
MeO-bound (**14**)	7.2	43.2	43.4	34.0	43.6	−47.1
MeNH-bound (**15**)	17.0	53.7	50.9	39.6	35.1	−52.6

[a] Energy of the oxidative addition complex (see the text for details).

through Marcus−Hush theory and related formulations. The outer-sphere **SET** Marcus−Hush theory model is applicable when initial **SET** proceeds via the formation of an intermediate.[42,43] Activation energies due to **SET** involving electron transfer and accompanying cleavage of the aryl halide bond (i.e., concerted **SET**) can be derived from Savéant's model.[42,44] "Sticky" **SET** mechanisms are involved when concerted electron transfer results in the formation of a radical/ion pair in the solvent cage; Savéant's model can be extended to these cases. In the Supporting Information it is shown that the activation free energies for **SET** estimated using Marcus theory are only slightly larger than energies for the formation of the intermediates, as presented in Table 1.

The **IAT** and **SET** mechanisms require much lower activation energies than oxidative addition or σ-bond metathesis. The energies required for **IAT** to form O-bound and N-bound (ket)Cu^{II} complexes and the phenyl radical are 33 and 41 kcal/mol, respectively. **SET** from **12** and **13** to form the O-bound and N-bound (ket)Cu^{II} complexes and the iodobenzene radical anion requires only 27 and 26 kcal/mol, respectively (Table 1). These results suggest that the electron-rich β-diketone ligand promotes the **SET** mechanism, in which the electron is transferred from the Cu^{I}(nucleophile) complex. Although the N-bound Cu^{I}(nucleophile) complex is less stable than the O-bound Cu^{I}(nucleophile) complex, the N-bound pathway is favored in the **SET** mechanism because the amido substituent is a better electron donor than the methoxide substituent, which facilitates electron transfer. This is in agreement with the experimental observation of N-selective arylation in reactions promoted by the β-diketone ligand.

The β-diketone and phenanthroline ligands exhibit marked differences in selectivities for mechanisms involving **SET** and **IAT**. In contrast to the β-diketone ligand, the neutral, less electron-rich phenanthroline ligand increases the barriers for **SET** to 44 and 35 kcal/mol, respectively, for O-bound and N-bound (phen)Cu^{I} complexes. In contrast, the barriers for **IAT** are much less sensitive to the effects of ligands. The O-bound and N-bound (phen)Cu^{I} complexes require 34 and 40 kcal/mol for the **IAT** pathway, respectively, which are very similar to the barriers for the reactions involving the β-diketone complexes. Thus, when phenanthroline is used as the ligand, the **IAT** and **SET** mechanisms have similar barriers, and either may occur depending on the nucleophile. The Cu-catalyzed O-arylation

(42) (a) For a recent review of the estimation of activation free energies using Marcus theory, see: Houmam, A. *Chem. Rev.* **2008**, *108*, 2180–2237. (b) For a practical demonstration of the estimation of activation free energies using Marcus theory, see: Lin, C. Y.; Coote, M. L.; Gennaro, A.; Matyjaszewski, K. *J. Am. Chem. Soc.* **2008**, *130*, 12762–12774.

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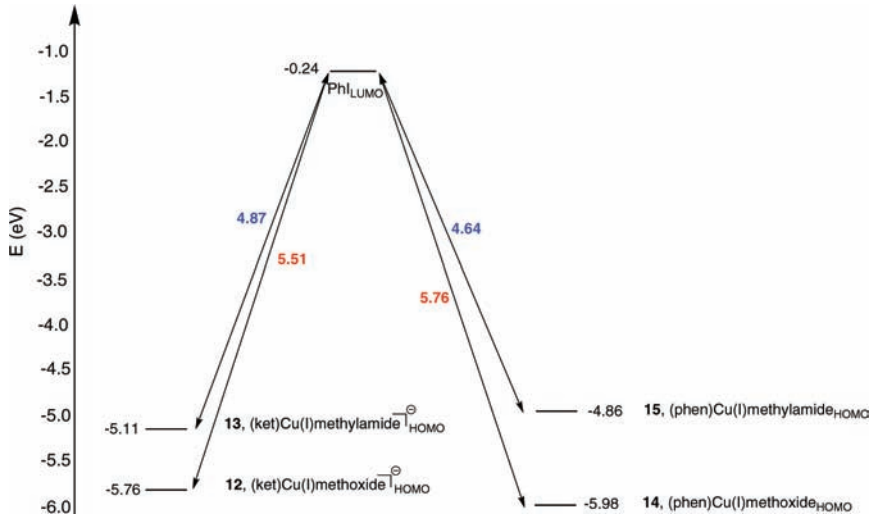


Figure 3. Interactions of HOMOs of **12, 13**, **14**, and **15** with the LUMO of iodobenzene.

reaction proceeds via **IAT**, while N-arylation proceeds via **SET**. This result is a notable departure from reactions involving Cu^{I} complexes ligated with the β-diketone ligand, in which **SET** processes are favored for reactions involving both types of nucleophiles. Overall, **IAT** from iodobenzene to the O-bound Cu^{I} complex **14** is more favorable ($\Delta G_{\mathbf{IAT}} = 34$ kcal/mol) than **SET** from the N-bound Cu^{I} complex **15** to iodobenzene ($\Delta G_{\mathbf{SET}} = 35$ kcal/mol).[45] This selectivity is in agreement with the experimentally favored O-selective reactions involving the phenanthroline ligand.[46] Finally, we note that the **SET** reactions involving the β-diketone ligand have comparatively lower barriers (26−27 kcal/mol) than those involving the phenanthroline ligand (34−35 kcal/mol). This is consistent with the fact that lower temperatures were required to promote reactions with the β-diketone ligand than those with the phenanthroline ligand (room temperature vs 90 °C).

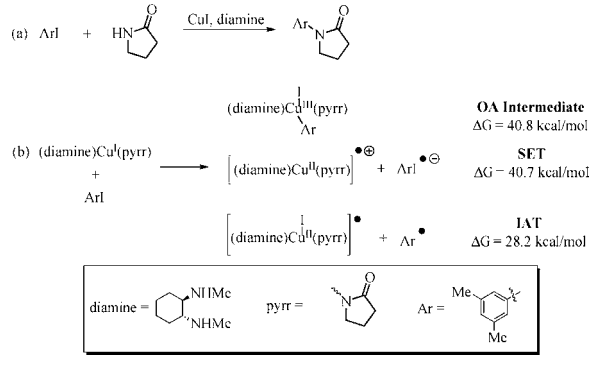
Frontier molecular orbital (FMO) analysis[47] of the interactions of the Cu^{I}(nucleophile) complexes with iodobenzene reveals that iodobenzene always interacts more favorably with the highest occupied molecular orbitals (HOMOs) of the N-bound Cu^{I}(nucleophile) complexes than those of the O-bound complexes. As shown in Figure 3, the Cu^{I}(methylamido) complexes **13** and **15** possess higher-lying HOMOs than the analogous Cu^{I}(methoxide) complexes **12** and **14**. Consequently, these Cu^{I}(methylamido) complexes interact more favorably with the lowest unoccupied molecular orbital (LUMO) of iodobenzene. This is consistent with the fact that amido compounds are generally more electron-rich than alkoxides and therefore possess higher-lying HOMOs that interact more favorably with electrophiles.[48]

Stronger FMO interactions between the N-bound complexes and electrophiles result in the selective formation of N-arylated products with the β-diketone ligand. However, O-arylation is promoted by the phenanthroline ligand. This preference is controlled by stronger Cu−O binding in the ligated Cu^{I}(nucleophile) complexes. The fact that both N-arylation and O-arylation products are formed despite the inherent >10 kcal/mol preference for the formation of O-bound intermediates suggests that the selectivities are caused by subtle differences in the electronic properties of the phenanthroline and β-diketone ligands in those intermediates that are manifested in the **SET** or **IAT** steps of these reactions.

Further analysis of the **IAT** and **SET** mechanisms reveals important insights into the nature of the intermediates on the potential energy surfaces of these reactions. Addition of the aryl radical to the metal center of the Cu^{II} complex formed by **IAT**

(45) The Marcus−Hush and Savéant theories were also used to estimate activation free energies for **SET** from reaction free energies for formation of the ligated Cu(II) intermediates and iodobenzene radical ions shown in Table 1 (see the Supporting Information for details). The estimated activation free energies for **SET** from (ket)Cu(methoxide) and (ket)Cu(methylamido) to iodobenzene are 28.1 and 26.6 kcal/mol, respectively; **SET** from (phen)Cu^{I}(methoxide) and (phen)Cu(methylamido) to iodobenzene requires energies of 38.0 and 35.6 kcal/mol, respectively. These barriers are similar to the reaction free energies presented in Table 1.

(46) For the purpose of comparison with the results presented in the main text, we computed the energies for **SET**, **IAT**, and oxidative addition (**OA**) complex formation in the reaction of 2-pyrrolidinone (pyrr) with 3,5-dimethyliodobenzene (ArI) catalyzed by CuI and *N*,*N*′-dimethylcyclohexane-1,2-diamine (diamine) [see (a) in the figure below; for further details, see refs 16 and 18]. As shown in (b) in the figure below, **SET** is isoenergetic with the formation of the **OA** intermediate ($\Delta G = 41$ kcal/mol). Significantly, **IAT** is more favorable than either **SET** or **OA** ($\Delta G = 28$ kcal/mol). This suggests that as a general trend, electron-rich β-diketones promote reactions via **SET**, while phenanthrolines, diamines, and other less electron-rich ligands promote reactions via **IAT**.



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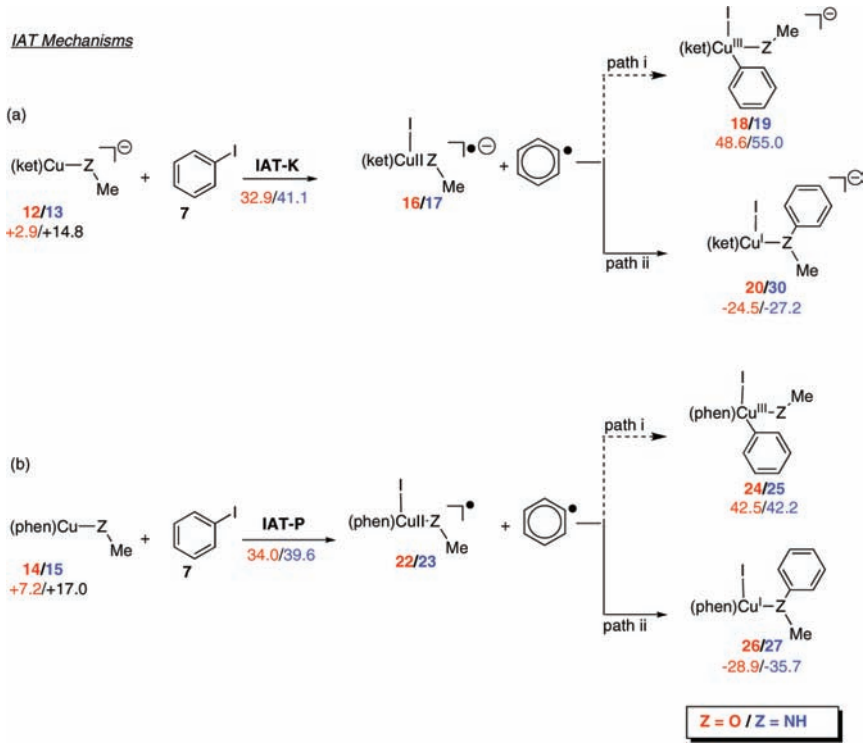

Figure 4. Free energies of intermediates in **IAT** mechanisms involving intermediates **12**, **13**, **14**, and **15**. Energies are given in red and blue for reactions with methanol and methylamine, respectively.

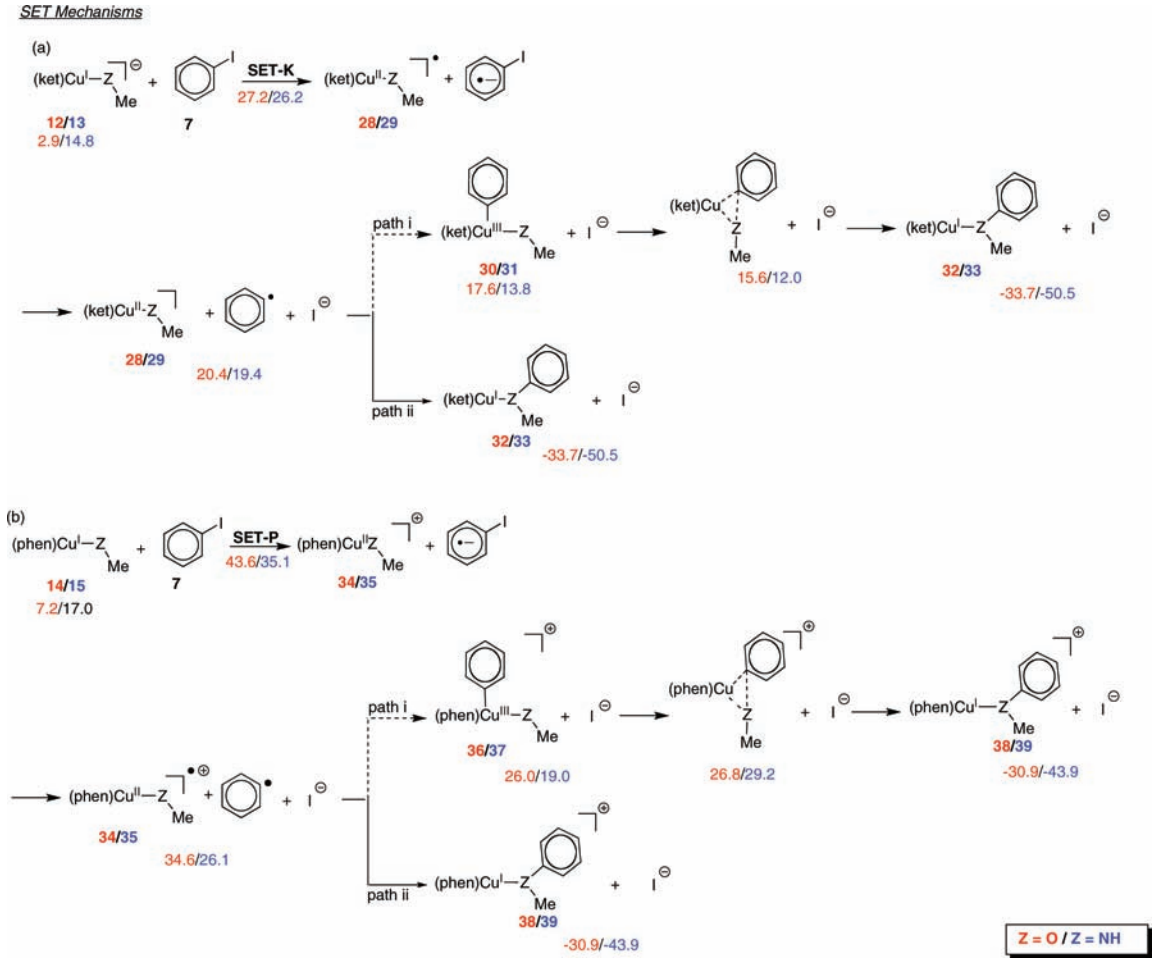

Figure 5. Free energies of intermediates in **SET** mechanisms involving intermediates (a) **12** and **13** and (b) **14** and **15**. Energies are given in red and blue for reactions with methanol and methylamine, respectively.

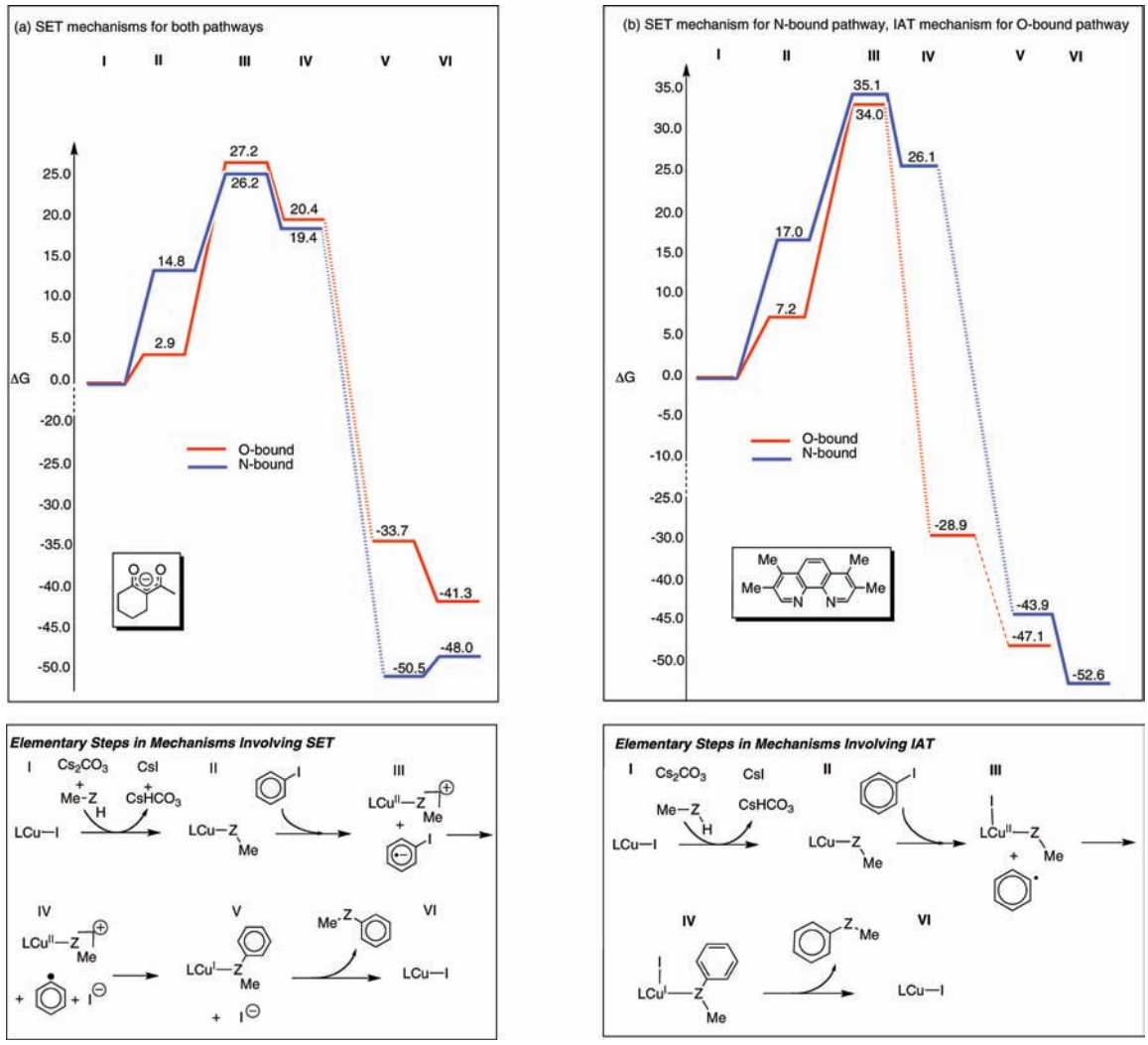

Figure 6. Free-energy profiles for (a) β-diketone- and (b) phenanthroline-promoted Cu^{I}-catalyzed reactions of methanol and methylamine with iodobenzene. Energies are given in red and blue for reactions with methanol and methylamine, respectively.

would lead to the formation of ligated Cu^{III}(iodide) complexes, which could then undergo reductive elimination to form product-ligated Cu^{I} complexes (Figure 4a,b, paths i). These pathways can be ruled out because of the high energies calculated for these Cu^{III} complexes in comparison with the radical intermediates. The alternative pathways involving addition of the phenyl radical to the heteroatom of the nucleophile moiety (Figure 4a-b, paths ii) are more likely. These reactions are highly exergonic because of the formation of the more stable Cu^{I} complexes in which the anisole and N-methylaniline complexes are bound to the metal center.

Two separate pathways are also possible in the **SET** mechanisms, as shown in Figure 5. The initially formed iodobenzene radical anion could fragment to form the iodide anion and the phenyl radical. The phenyl radical could then add to the metal centers of the ligated Cu^{II}(nucleophile) complexes **28**/**29** and **34**/**35** to form Cu^{III} complexes **30**/**31** and **36**/**37** from the β-diketone and phenanthroline ligands, respectively. Reductive elimination from these complexes would result in the formation of complexes **32**/**33** and **38**/**39** in which anisole and *N*-methylaniline are bound to the metal center. The more likely pathways are highly exothermic processes that involve direct formation of the more stable Cu^{I} complexes **32**/**33** and **38**/**39** by attachment of the phenyl radical to the oxygen or nitrogen atoms that are directly attached to the metal center. Mechanisms involving sequential electron transfers can usually be ruled out because of the high energies of the Cu^{III} intermediates relative to the Cu^{I} species. Then again, Cu^{III} intermediates such as **30**/**31** and **36**/**37** are similar to the Cu^{III} complexes proposed as intermediates in the work done by Huffman and Stahl.[29]

Finally, in Figure 6 we have provided detailed energetic profiles for the β-diketone- and phenanthroline-promoted reactions of methylamine and methanol with iodobenzene. These mechanisms, whether they proceed via **SET** or **IAT**, involve a Cu^{I}/Cu^{II} couple. Cu^{III} intermediates are predicted to be inaccessible because of their high energies. The large exothermicities of reactions involving the formation of Cu^{I}(product) complexes from the Cu^{II} intermediates suggest that Cu^{II} intermediates formed during **SET** or **IAT** are likely to be too short-lived to be detectable, in agreement with the observations of Hida and co-workers.[27] We postulate that these intermediates are generated not as free radicals but as caged radical pairs that are rapidly converted to products before adventitious reactions can occur. This proposal could rationalize the lack of experimental evidence for the presence of Cu^{II} intermediates as well as aryl radicals or aryl halide radical anions in related Cu^{I}-catalyzed reactions,[19,27] although we do not rule out the possibility that those reactions proceed via alternative mechanisms.

Overall, our results suggest that for phenanthroline- and β-diketone-promoted Cu^I-catalyzed Ullmann-type reactions of methanol and methylamine with iodobenzene, experimental selectivities arise in the aryl halide activation step of the reaction and not in the nucleophile formation step. Both ligands promote the formation of Cu^I(methoxide) intermediates in preference to Cu^I(methylamido) intermediates. The mechanism in the aryl halide activation step is determined by the electron-donating ability of the ligand and the nucleophile. The electron-rich β-diketone ligand promotes **SET** reactions involving both types of nucleophiles. The rate of **SET** is faster in reactions involving the Cu^I(methylamido) complexes than in reactions involving the Cu^I(methoxide) complexes, thereby leading to selective N-arylation; this selectivity is enough to overcome the inherent preference for the formation of the (ket)Cu^I(methoxide) complex. In contrast, the less electron-rich phenanthroline ligand promotes **SET** in the reaction involving the Cu^I(methylamido) complex but promotes **IAT** in the reaction involving the Cu^I(methoxide) complex. The combined rate for formation of the (phen)Cu^I(methoxide) complex and concomitant **IAT** is faster than the combined rate for formation of the (phen)Cu^I(methylamido) complex and **SET**, leading to the formation of O-arylated products.

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Supporting Information Available: Energies and Cartesian coordinates of stationary points from MPWB1K and B3LYP calculations and complete ref 34. This material is available free of charge via the Internet at http://pubs.acs.org.

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