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Published in final edited form as:
J Am Chem Soc. 2010 May 5; 132(17): 6205–6213. doi:10.1021/ja100739h.

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 (DFT) calculations with 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- vs. 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 not derived from initial Cu(I)-nucleophile 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 ability of the ligand and nucleophile. Mechanisms involving either oxidative addition/reductive elimination or sigma-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 due to 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 are achieved when these ligands are used 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. β-Diketone **5** promoted the formation of N-arylated products in Cu^I-catalyzed reactions of 5-amino-1-pentanols with iodoarenes in DMF, but O-arylated products were formed in toluene by switching to the 1,10-phenanthroline ligand, **6**

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

(Scheme 1).[16] The β-diketone ligand **5** typically promoted N-arylation to 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 demonstrated that O-selective reactions are also formed with picolinic acid and N^1,N^2-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 influence whether the O-bound or N-bound nucleophiles are more acidic. The pKa 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 been studied experimentally recently; [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 only occurs after formation of the LCu^I(nucleophile) species at intermediate ligand concentrations.[18,19] Catalytic activity is diminished at higher ligand concentrations.

A computational study by Guo and coworkers showed the intermediacy of the LCu^I(nucleophile) complexes versus other potential copper species in the coupling of aryl halides with amides.[20] 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 barriers for reactions involving other complexes. Computational investigations by Tye *et al*. showed that the reaction of PhI with LCu^I(nucleophile) has a lower barrier for oxidative addition in comparison with other potential Cu^I complexes.[19]

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 single electron-transfer (Scheme 3c). An atom transfer mechanism has also been postulated, involving transfer of the halide atom from the aryl halide (Scheme 3d). A recent study has suggested that a four-centered sigma-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.

There is less experimental evidence for mechanisms of aryl halide activation in Ullmann-type reactions involving *ligated* Cu^{I}-complexes. Hida and coworkers have 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}.[27] Whether a Cu^{III} complex was ever formed, or the product was formed directly, could not be ascertained from these investigations. Bethell and coworkers observed that products consistent with the formation of a Cu^{III} intermediate are formed in related reactions of bromoanthraquinone with primary amines.[28] Huffman and Stahl have demonstrated that N-arylation occurs *via* the coupling of Cu^{III}(aryl) species with nitrogen-based nucleophiles.[29] This result could be accounted for by the initial formation of Cu^{III}(aryl)(nucleophile) intermediates which reductively eliminate 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 *et al*. performed experimental investigations which appear to rule out the intermediacy of aryl free radicals and Cu^{II} intermediates in related reactions.[19] Based on these 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 this manuscript suggest that Cu^{II} intermediates are too short-lived to be detectable, consistent with these 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. Based on 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 are known of the use of aryl chlorides in Cu-catalyzed Ullmann-type reactions. 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 chlorides is not conclusive evidence that aryl halide radical anions are not formed during these types of reactions.

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

The primary goal of this study was the elucidation of the mechanism and source of ligand-directed N- vs. O-selectivities in Ullmann-type arylation reactions. Computational studies

with density functional methods suggest that the observed selectivities arise from single electron transfer or iodine atom transfer processes in which short-lived radical pairs are formed before rapidly being converted to products.

Computational Methodology

All calculations were carried out with the Gaussian03[34] suite of computational programs. The B3LYP[35,36] and MPWB1K[37] density functional theory (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 for calculations involving B3LYP, and the MG3S[39] basis set was employed for calculations involving MPWB1K. 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[40] solvation method 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 are available in Gaussian03 for the DMF solvent. Calculations for reactions involving the 1,10-phenanthroline ligand involved the CPCM model for toluene. The Gibbs free energies presented in this article are derived from MPWB1K electronic energies, plus zero-point energy, thermal and entropy corrections from B3LYP calculations, plus solvation energy corrections from the CPCM method.

Results and Discussion

Computational models of reagents used in 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 or with methylamine, as models of the aminoalcohols used experimentally. The reactions involving Cu^{I} complexes, **10** and **11** (Figure 1) were studied. All energies shown hereafter are referenced to energies for the reactions of methanol and methylamine with iodobenzene catalyzed by the ligated Cu^{I}(iodide) complexes.

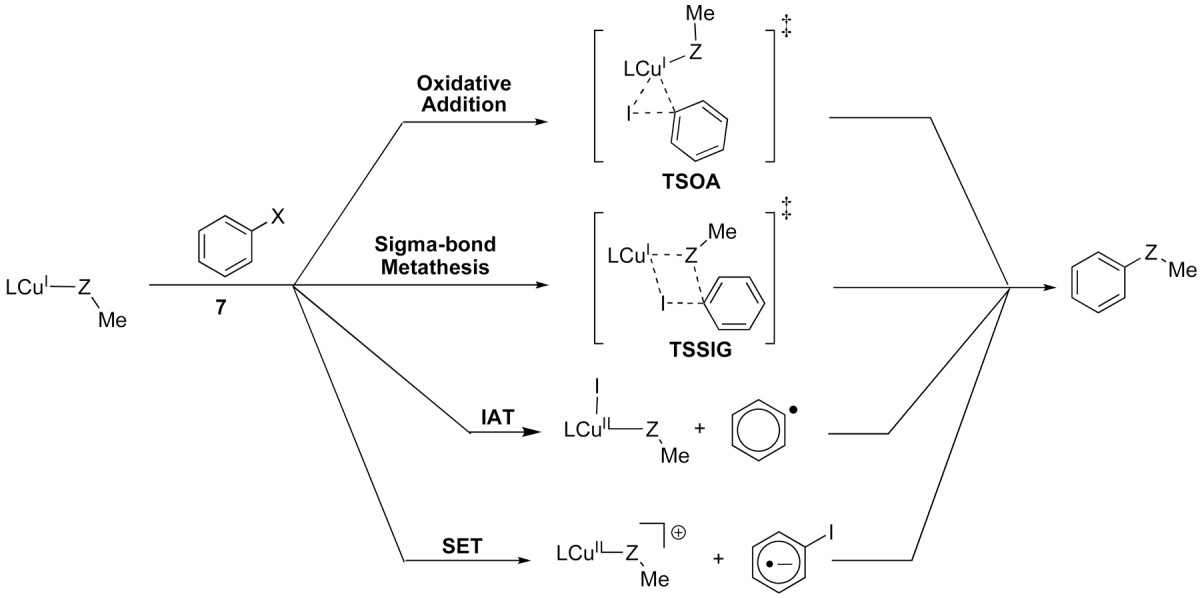
The formation of the ligated Cu^{I}(nucleophile) complexes was first considered (Figure 2). The formation of the Cu^{I}(methoxide) complex is preferred over the Cu^{I}(methylamido) complex with both ligands. With the β-diketone ligand, the reaction to form the Cu^{I}(methoxide) complex **12** is 12 kcal/mol 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 10 kcal/mol more exergonic reaction than that of the Cu^{I}(methylamido) complex. These results suggest that the observed experimental selectivities most likely do not arise due to 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 energies computed for key complexes in the SET or 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, which has an energy of 55 kcal/mol.

Similarly, activation barriers for the 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 sigma-bond metathesis are also unreasonably large, almost isoenergetic with barriers for oxidative addition.

Barriers for mechanisms involving the transfer of the iodine atom (**IAT**) from iodobenzene to the Cu^I complexes and for single-electron transfer (**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 iodine atom transfer 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 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. The supporting information that accompanies this article demonstrates that activation free energies for **SET** estimated by 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 sigma-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 since the amido substituent is a better electron-donor than the methoxide substituent, and facilitates electron transfer. This is in

agreement with experimentally observed 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 single-electron transfer and iodine atom transfer. 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, barriers for **IAT** are much less sensitive to the effects of ligands. O- and N-bound (phen)Cu^{I} complexes require 34 and 40 kcal/mol for the **IAT** pathway, respectively, very similar to reactions involving the β-diketone complexes. Thus, when phenanthroline is used as a ligand, **IAT** and **SET** mechanisms have similar barriers, and may both occur depending on the nucleophile. The Cu-catalyzed O-arylation 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 (ΔG_{IAT} = 34 kcal/mol) than **SET** from the N-bound Cu^{I} complex **15** to iodobenzene (ΔG_{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 energies (26–27 kcal/mol) than reactions 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 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 HOMOs (highest occupied molecular orbitals) 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 their analogous Cu^{I}(methoxide) complexes, **12** and **14**. Consequently, these Cu^{I}(methylamido) complexes interact more favorably with the LUMO (lowest unoccupied molecular orbital) 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 will interact more favorably with electrophiles.[48]

Stronger FMO interactions between the N-bound complexes and electrophiles results 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 which 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** can lead to the formation of ligated Cu^{III}(iodide) complexes, which can then reductively eliminate and form product-ligated Cu^{I} complexes (Figure 4 a-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 4 a–b, paths ii) are more likely. These are

highly exergonic reactions due to 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 **SET** mechanisms as shown in Figure 5. The initially formed iodobenzene radical anion fragments to form the iodide anion and the phenyl radical. The phenyl radical could add to the metal center of the ligated Cu^{II}(nucleophile) in 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 results 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 process, and 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 compared 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 work done by Huffman and Stahl.[29]

In closing, we have provided the detailed energetic profiles for the β-diketone and phenanthroline-promoted reactions of methylamine and methanol with iodobenzene (Figure 7). These mechanisms, whether they involve **SET** or **IAT**, involve a Cu^{I}/Cu^{II} couple. Cu^{III} intermediates are predicted to be inaccessible owing to 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 coworkers.[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 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. By 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 due to the formation of the (phen)Cu^{I}(methoxide) and concomitant **IAT** is faster than the combined rate due to formation of (phen)Cu^{I}(methylamido) and **SET** leading to the formation of O-arylated products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the National Institute of General Medical Sciences (NIGMS), National Institutes of Health (NIH) for financial support (Grants GM-58160 to SLB and GM-36700 to KNH), and to the National Science Foundation *via* the National Center for Supercomputing Applications (NCSA) for supercomputing resources.

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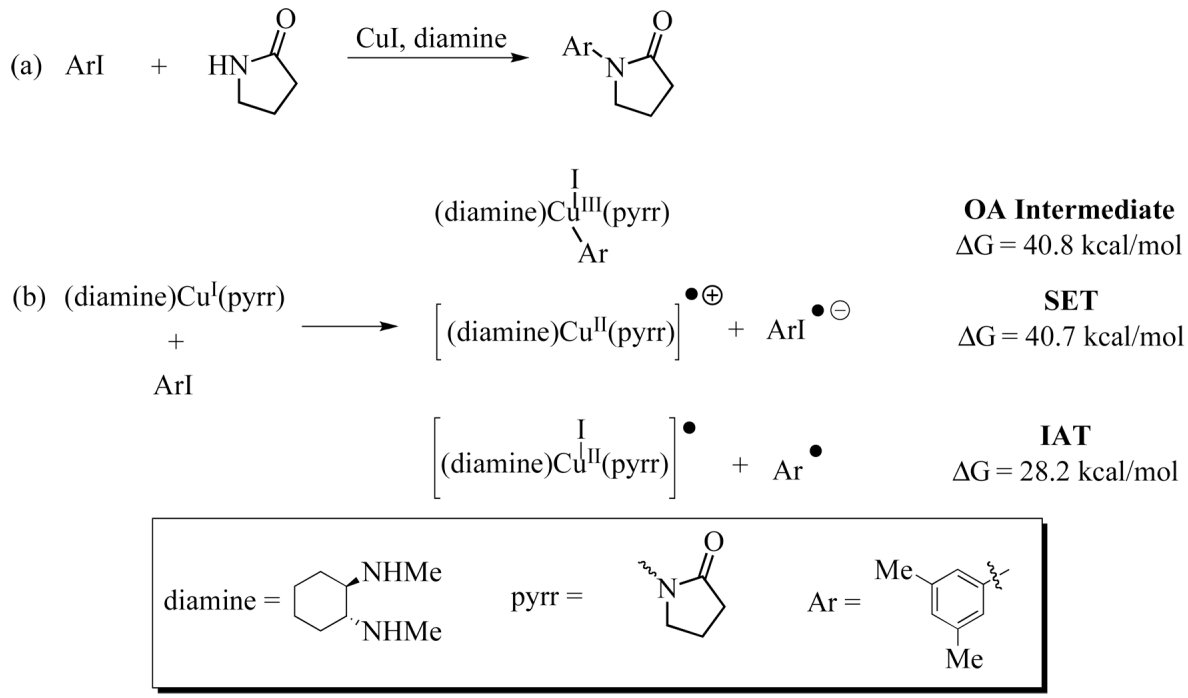
45. Marcus-Hush and Savéant theories were also used to estimate activation free energies for SET from reaction free energies for formation of the ligated Cu(II) intermediates and iodobenzene radical ions shown in Table 1 (see supporting information for details). The estimated activation free energies 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 require 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 article, we have computed the energies for **SET, IAT** and OA-complex formation in the reaction of 2-pyrrolidinone (pyrr) with 3,5-dimethyliodobenzene (ArI) catalyzed by CuI and N^{1},N^{2}-dimethylcyclohexane-1,2-diamine (diamine) (see figure (a) below; for further details see references 16 and 18). As shown below in

figure (b), **SET** is isoenergetic with the formation of the OA intermediate (ΔG = 41 kcal/mol). Significantly, **IAT** is more favorable than either **SET** or **OA** (ΔG = 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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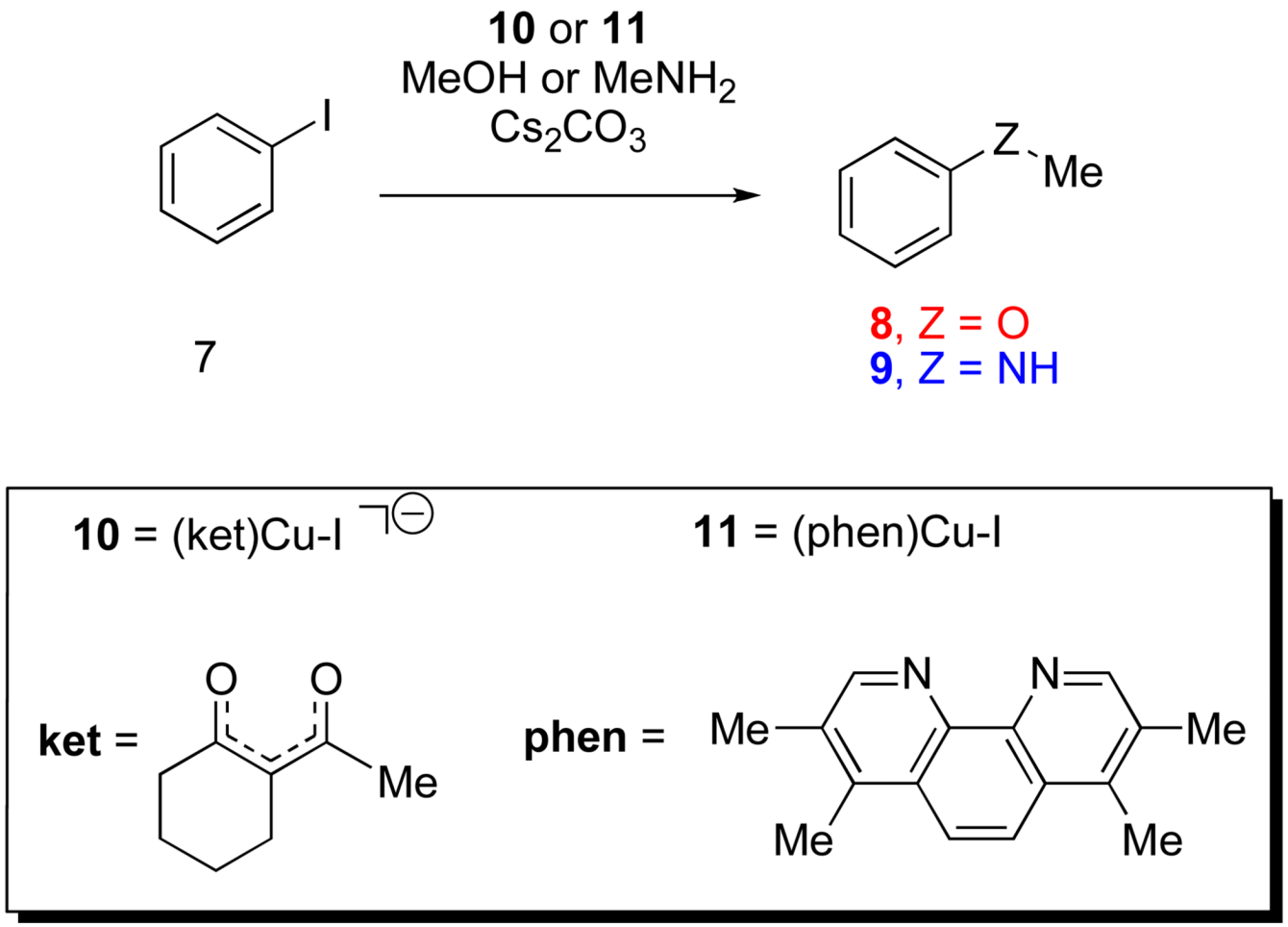


Figure 1.
Computational models of reagents studied in N- and O-arylation reactions.

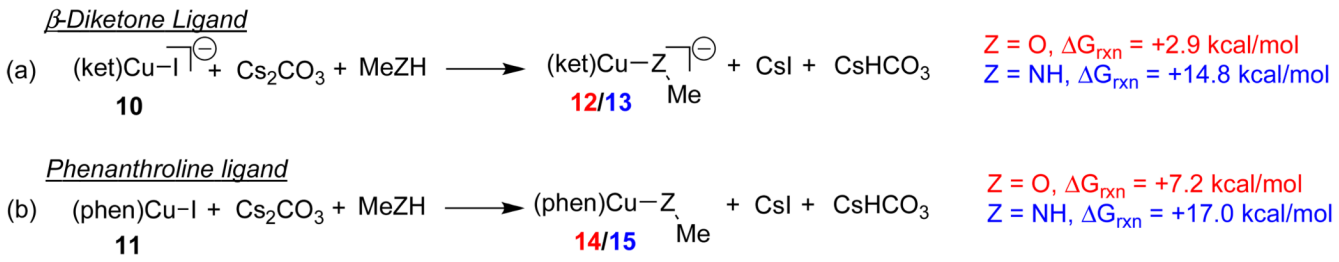


Figure 2.

Reaction free energies in 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 for reactions with methanol and methylamine, respectively.

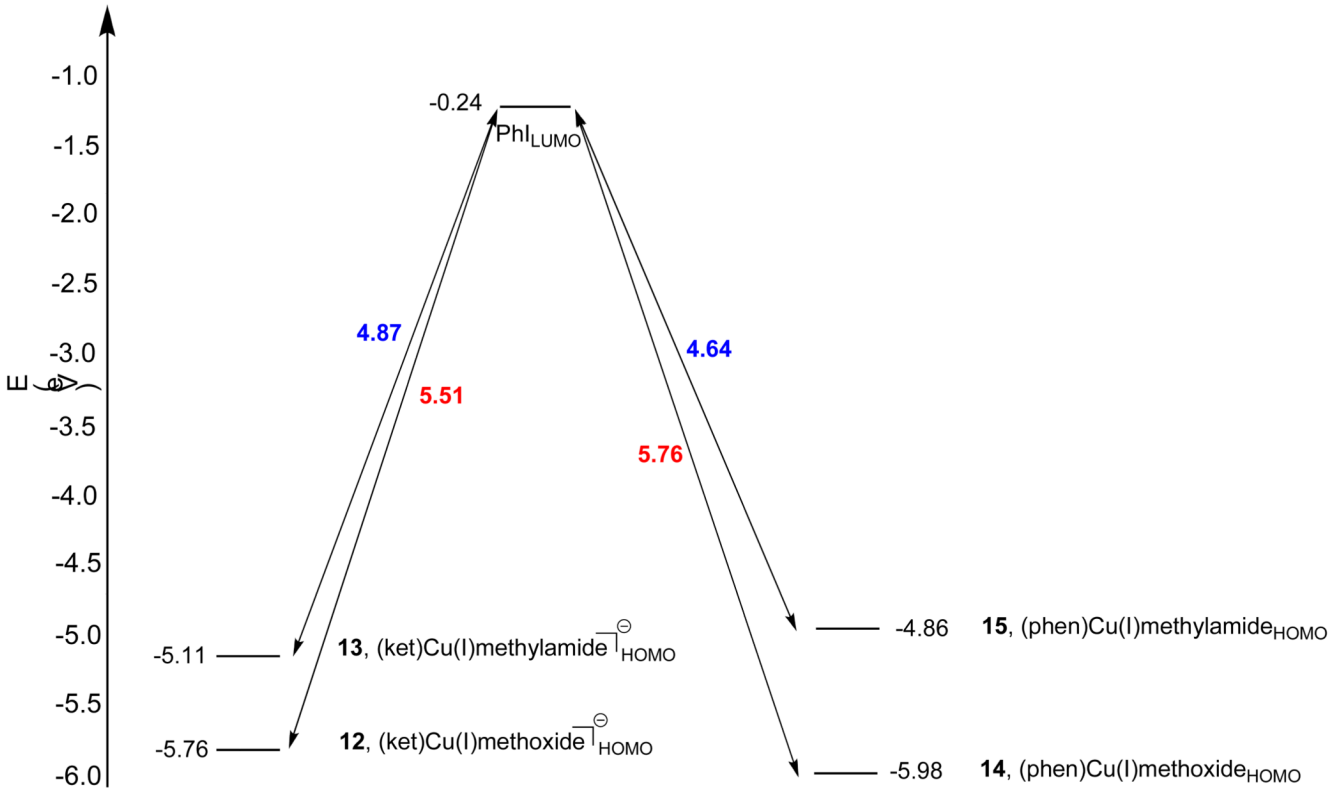


Figure 3.
Interactions of frontier molecular orbitals of **12, 13, 14** and **15** with the LUMO of iodobenzene.

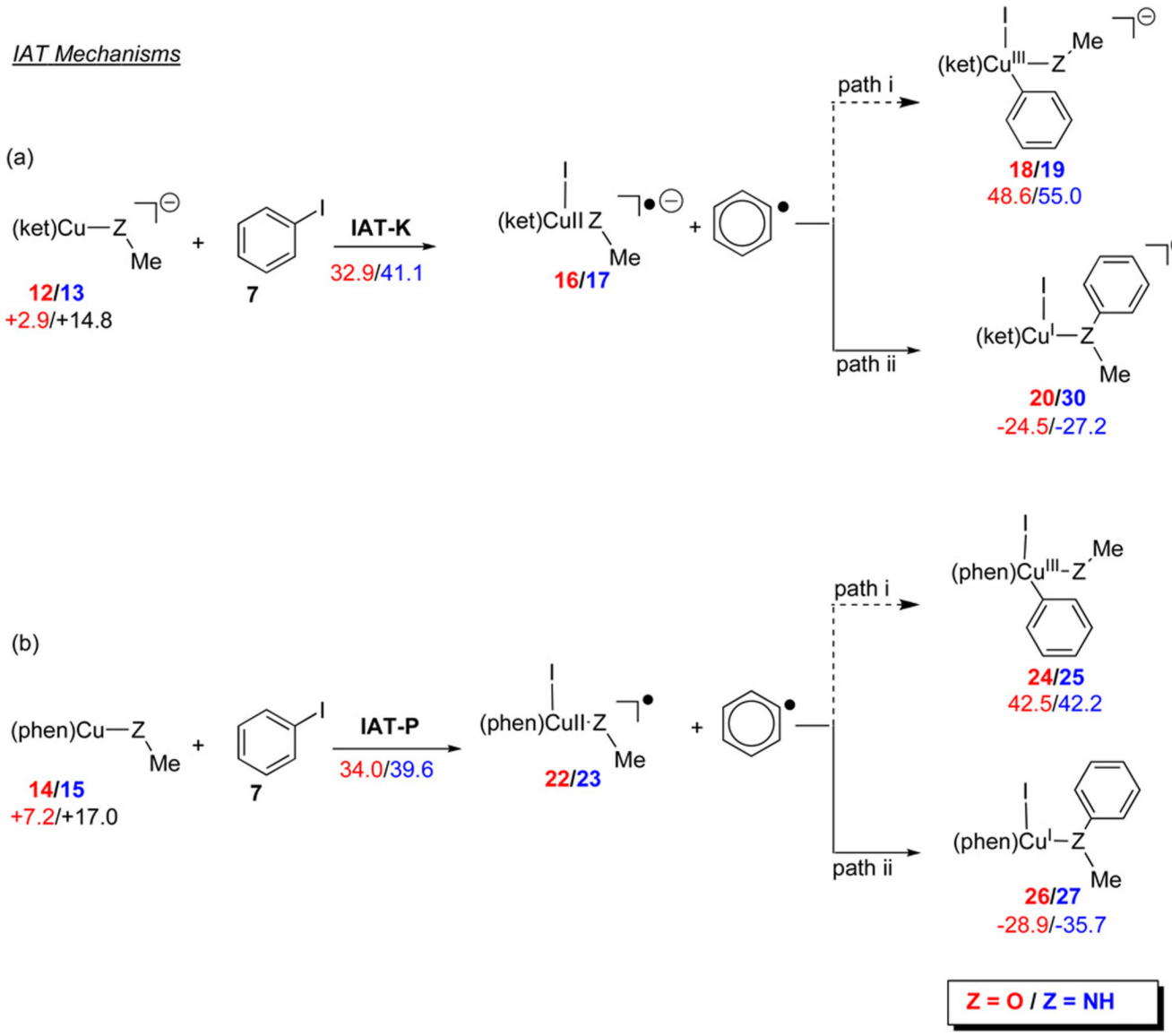


Figure 4.

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

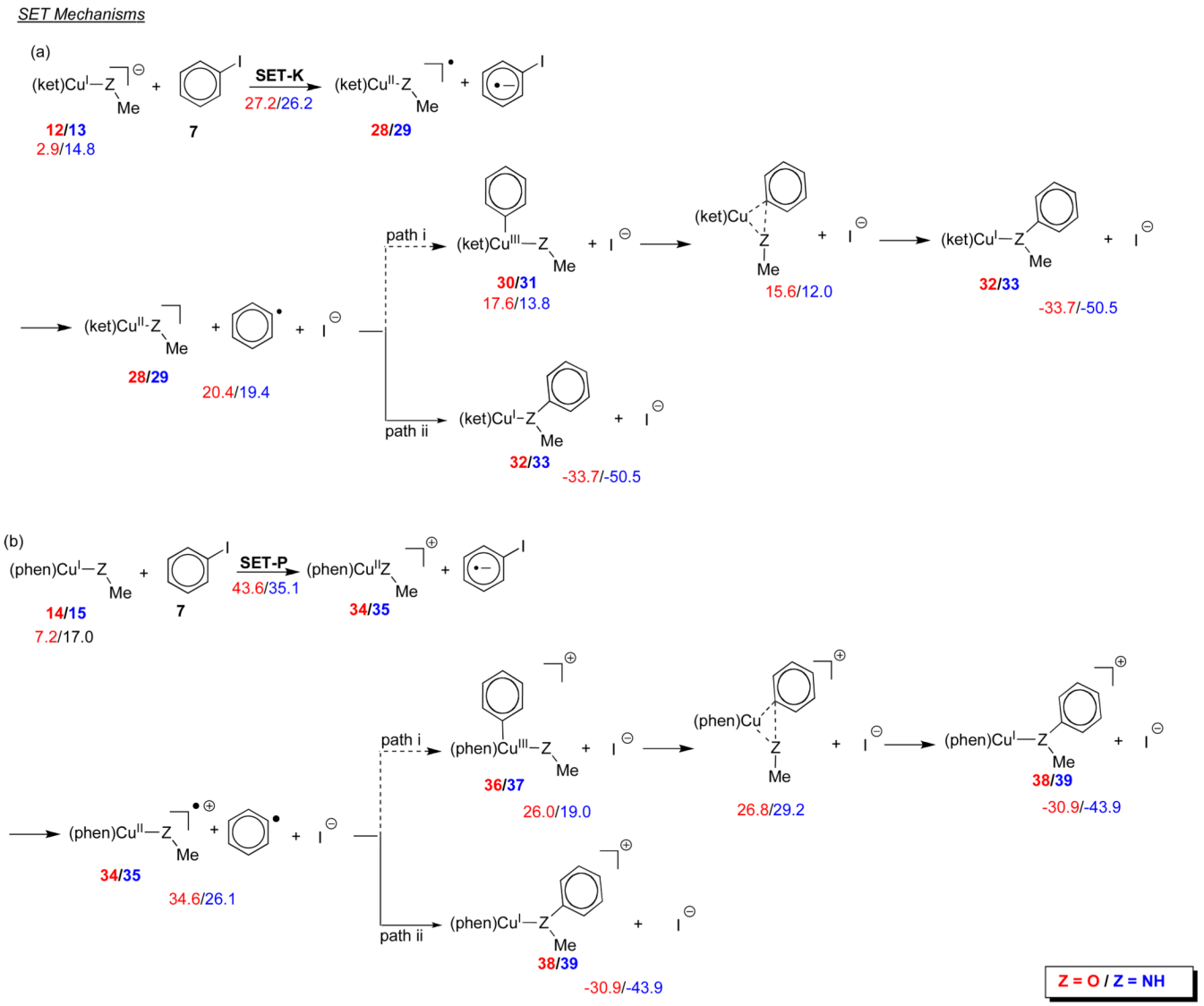


Figure 5.

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

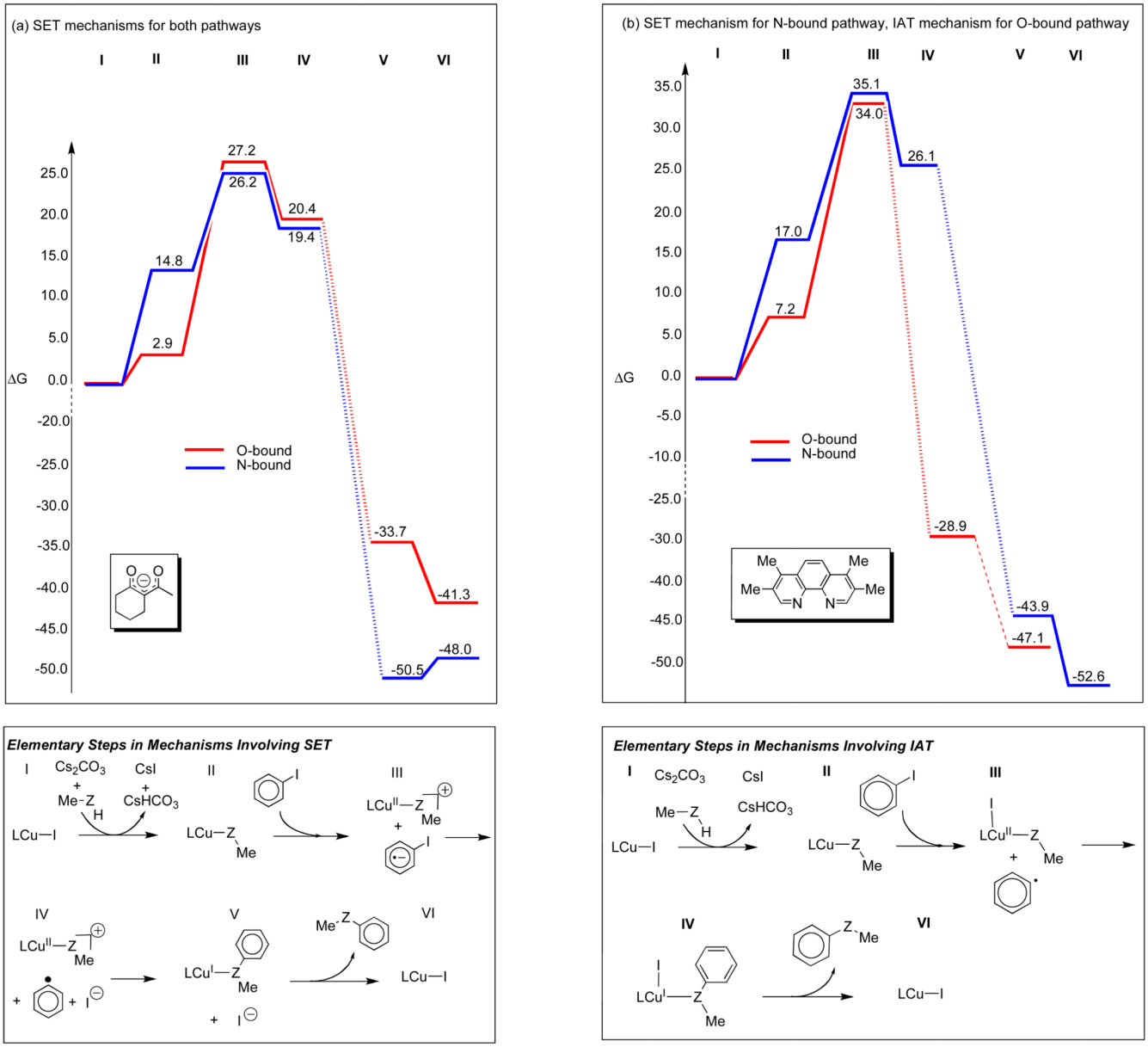
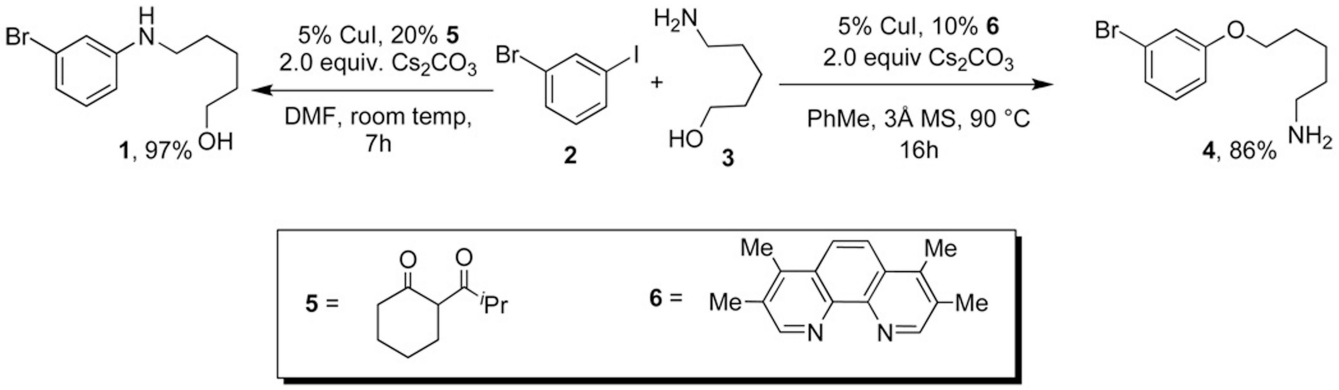
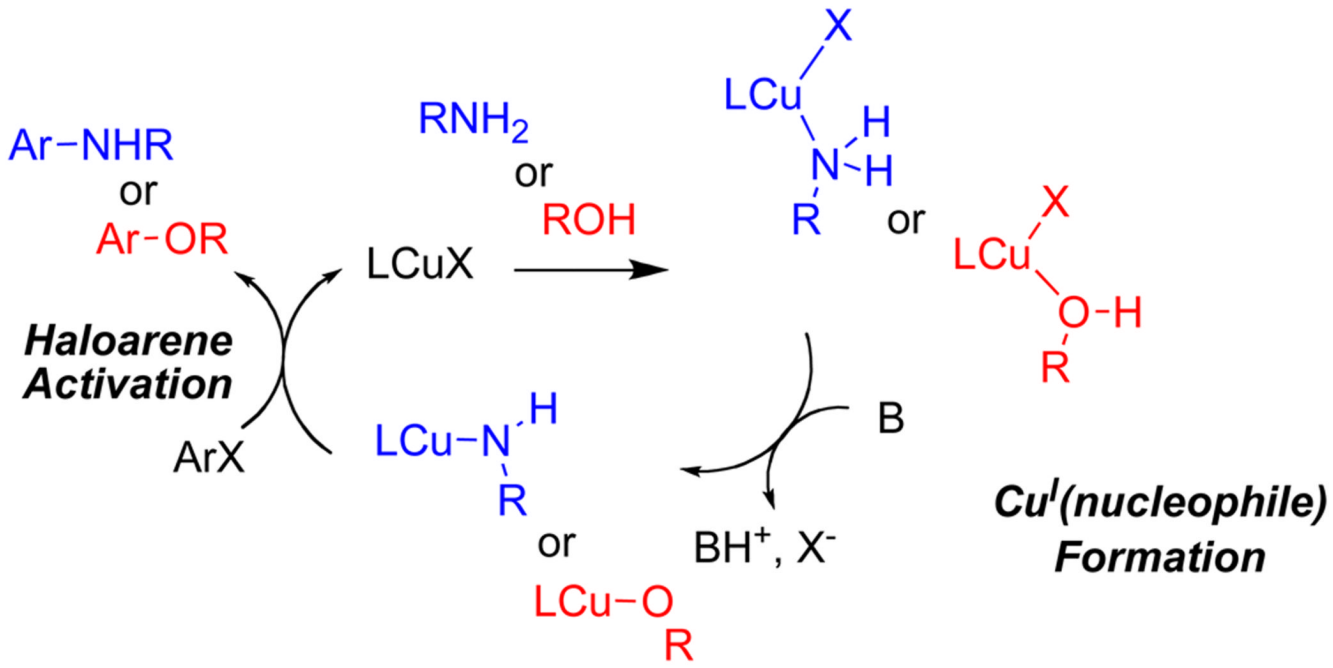


Figure 7.

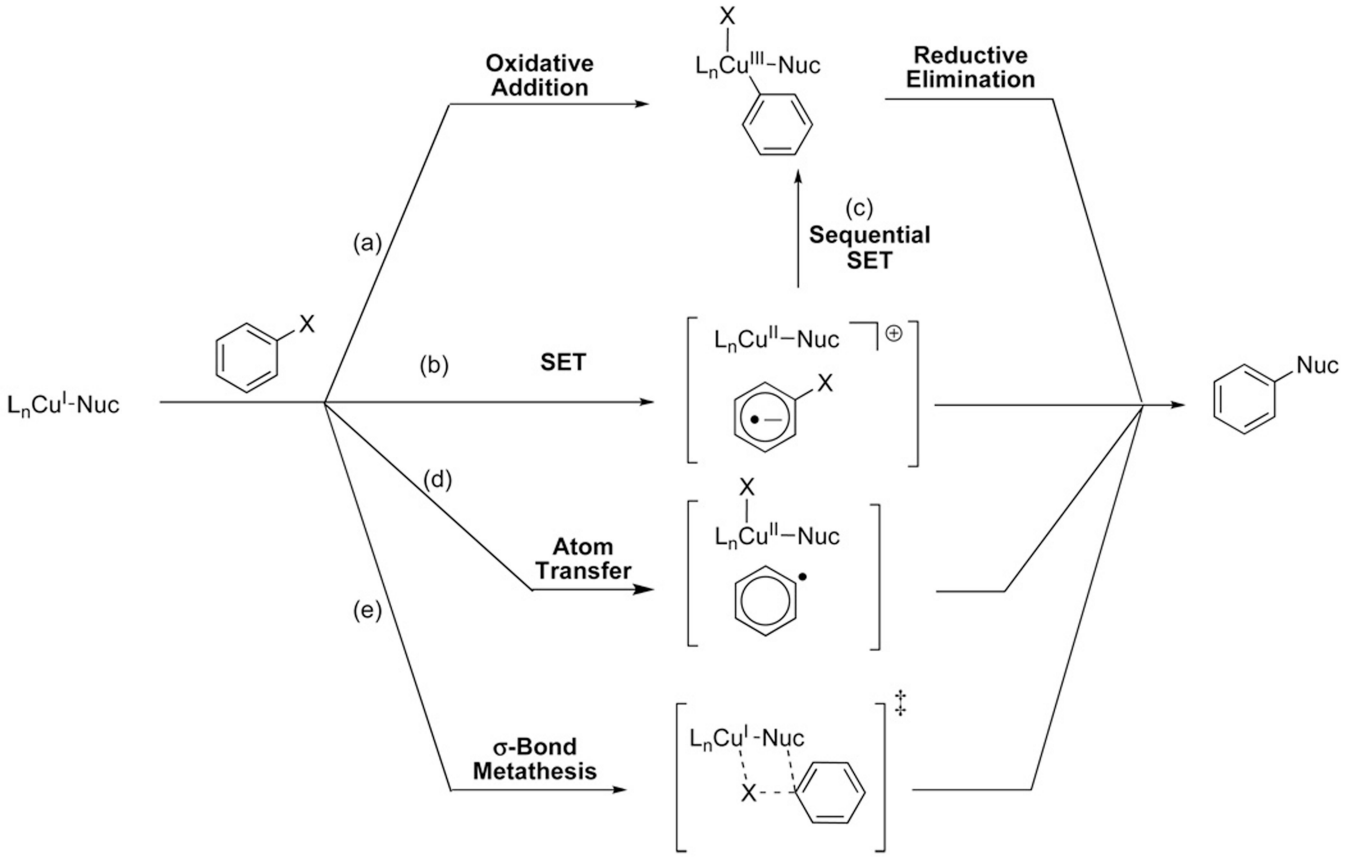
Free energy profiles for (a) β-diketone and (b) phenanthroline-promoted Cu^{I}-catalyzed reactions of methanol and methylamine with iodobenzene. Energies are given for reactions with methanol and methylamine, respectively.



Scheme 1.



Scheme 2.



Scheme 3.

Table 1

Free energies in kcal/mol for key stationary points in 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 text for details.