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Alternative Mechanistic Explanation for Ligand-Dependent Selectivities in Copper-Catalyzed *N*- and *O*-Arylation Reactions

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Abstract: The ligand-dependent selectivities in Ullmann-type reactions of amino alcohols with iodobenzene by β-diketone- and 1,10-phenanthroline-ligated Cu^{I} complexes were recently explained by the single-electron transfer and iodine atom transfer mechanisms (Jones, G. O.; Liu, P.; Houk, K. N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 6205.). The present study shows that an alternative, oxidative addition/reductive elimination mechanism may also explain the selectivities. Calculations indicate that a Cu^{I} complex with a negatively charged β-diketone ligand is electronically neutral, so that oxidative addition of ArI to a β-diketone-ligated Cu^{I} prefers to occur (and occur readily) in the absence of the amino alcohol. Thus, coordination of the amino alcohol in its neutral form can only occur at the Cu^{III} stage where *N*-coordination is favored over *O*-coordination. The coordination step is the rate-limiting step and the outcome is that *N*-arylation is favored with the β-diketone ligand. On the other hand, a Cu^{I} complex with a neutral 1,10-phenanthroline ligand is positively charged, so that oxidative addition of ArI to a 1,10-phenanthroline-ligated Cu^{I} has to get assistance from a deprotonated amino alcohol substrate. This causes oxidative addition to become the rate-limiting step in the 1,10-phenanthroline-mediated reaction. The immediate product of the oxidative addition step is found to undergo facile reductive elimination to provide the arylation product. Because *O*-coordination of a deprotonated amino alcohol is favored over *N*-coordination in the oxidative addition transition state, *O*-arylation is favored with the 1,10-phenanthroline ligand.

1. Introduction

The Cu-catalyzed carbon-heteroatom cross-couplings have been shown to be highly useful in modern synthetic chemistry for the preparation of medicinally active compounds and agrochemicals.[1] These reactions originally required fairly harsh conditions such as high temperatures, use of high-boiling solvents, and stoichiometric quantities of copper.[2] Recently, by the use of chelating ligands such as β-diketones,[3] diamines,[4,5] amino acids,[6] and others,[7−9] many carbon-heteroatom coupling reactions can now be conducted under mild conditions with Cu as the catalyst. However, most of the reported Cu-catalyzed coupling reactions proceed well only when relatively simple reactants are used, whereas their application to the synthesis of complex molecules remains challenging.[10,11] An important, yet relatively less examined, subject in the field of Cu-catalyzed cross-couplings is how to control the reaction selectivity for the substrates carrying multiple nucleophilic groups.[12−14]

In this context, Buchwald et al. recently reported Cu-catalyzed cross-couplings in which selective *N*- or *O*-arylation can be achieved when different ligands are used (Scheme 1).[14] The β-diketone ligand (**L1**) causes selective formation of the *N*-arylated product in DMF at room temperature, whereas the 1,10-

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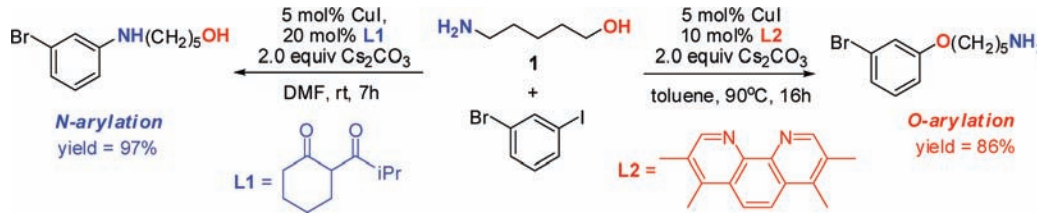
Scheme 1



phenanthroline type ligand (**L2**) promotes selective *O*-arylation in toluene at 90 °C. To explain the intriguing ligand-directed selectivities, a computational study was recently conducted on the simplified model reactions of iodobenzene with MeOH and $MeNH_2$ promoted by β-diketone- and 1,10-phenanthroline-ligated Cu^I complexes.[15] The experimental selectivities were proposed to originate from the steps involving aryl halide activation. The calculations indicated that the β-diketone ligand promoted *N*-arylation via the single-electron transfer (SET) mechanism, whereas the phenanthroline ligand promoted *O*-arylation via the iodine atom transfer (IAT) mechanism.[16−18] The mechanisms involving either oxidative addition/reductive elimination[19] or σ-bond metathesis[20] were suggested to be disfavored.

In our study on the same *N*- versus *O*-selectivity problem in Cu catalysis, $NH_2(CH_2)_5OH$ was used as the model compound to describe the experiments. Our calculations surprisingly provided some different results that support the oxidative addition/reductive elimination mechanism instead of the SET and IAT mechanisms. It was found that the oxidative addition/reductive elimination mechanism may also explain the selectivities observed experimentally. In this explanation, the experimental selectivities originate not from the steps involving aryl halide activation, but from the steps involving nucleophile coordination and oxidative addition. Thus, the goal of the present study was to report how an alternative mechanistic proposal may explain the fascinating *N*- and *O*-selectivities in Cu catalysis.

2. Methods

All calculations were performed using Gaussian03 suite of programs.[21] Density functional theory method B3LYP was used,[22] because this method has been shown to be a good method for studying Cu-mediated organic transformations.[23,24] Geometry optimizations were conducted without any constraint using standard Pople all-electron basis set 6-31G(d) for all the atoms except I and Cs atoms, which were described by the effective core potentials (ECPs) of Hay and Wadt with a double-valence basis set (Lanl2DZ).[25] The polarization functions were added for Cu (ξ(f) = 3.525) and I (ξ(d) = 0.334).[26] For compounds that had multiple conformations, efforts were made to find the lowest-energy conformation by comparing the structures optimized from different starting geometries.

Frequency calculations at the same level of theory were performed to verify the stationary points to be real minima (zero

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imaginary frequency) or transition states (one imaginary frequency) and to provide free energies at 298.15 K. Transition states were located using the Berny algorithm. Intrinsic reaction coordinates (IRC)[27] were calculated for the transition states to confirm that the saddle point connected the correct reactant and product on the potential energy surface. Single-point energy calculations were performed on the stationary points by using a larger basis set, that is, LANL2DZ for I and Cs, 6-311+G(d,p) for C, H, O, N, Cl, and Br atoms, and 6-31G(d) for Cu.

Solvent effect was calculated by using self-consistent reaction field method with CPCM solvation model[28] and Bondi radii.[29] The solvent parameters for MeCN ($\epsilon = 36.64$) was used for reactions with **L1** ligand because no parameters are available in Gaussian03 for DMF ($\epsilon = 36.7$).[30] Toluene ($\epsilon = 2.37$) was used as solvent for reactions with **L2** ligand. Note that in the present study we carried out solution-phase calculations on the gas-phase geometries, because the solution-phase optimization failed to converge for many structures in our work. A similar treatment (i.e., solution-phase energy calculations on gas-phase geometries) was also used in many other recent computational studies.[31]

Single-point energies corrected by Gibbs free energy corrections and solvation corrections to free energies were used to describe the reaction energetics throughout the study. All the solution-phase free energies reported in the paper correspond to the reference state of 1 mol/L, 298 K.

3. Results and Discussion

3.1. Model Reaction. An oxidative addition/reductive elimination pathway that involves a Cu^{I}/Cu^{III} catalytic cycle has been proposed in many previous studies.[32−38] Here, the cross-coupling between 5-amino-1-pentanol (**1**) and iodobenzene was chosen as the model reaction (eqs 1 and 2). The 1,10-phenanthroline ligand (**L2′**) was used to replace 3,4,7,8-tetramethyl-1,10-phenanthroline to reduce the computational cost.

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Functional	**L1**-mediated reaction*		**L2**-mediated reaction*	
	L1-Int3a'	**L1-Int3c**	**L2-TS1a**	**L2-TS4b**
B3LYP	+18.2	+22.0	+26.5	+30.2
B3P86	+13.5	+20.0	+19.0	+20.8
B3PW91	+16.3	+21.3	+23.0	+28.3
MPWLYP1W	+12.3	+15.3	+23.9	+24.5
BLYP	+12.7	+17.4	+25.6	+27.1
BP86	+9.7	+13.8	+19.8	+21.4
MPWPW91	+6.5	+12.8	+19.4	+21.1

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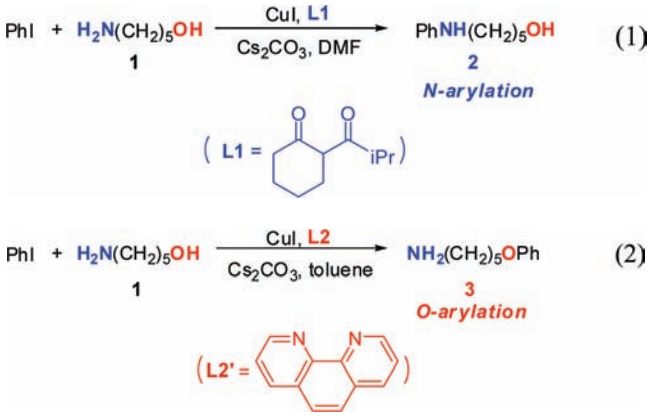
(35) The Cu^{I}/Cu^{III} catalytic cycle was explicitly suggested in recent experimental studies: (a) Tye, J. W.; Weng, Z.; Johns, A. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 9971. (b) Tye, J. W.; Weng, Z.; Giri, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 2185.

(36) Theoretical studies supporting the Cu^{I}/Cu^{III} cycle through oxidative addition/reductive elimination: (a) Zhang, S.-L.; Liu, L.; Fu, Y.; Guo, Q.-X. *Organometallics* **2007**, *26*, 4546. (b) Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350.

(37) Cu^{III} was suggested to be formed during the coupling of aryl halides with amides/amines, see: Bethell, D.; Jenkins, I. L.; Quan, P. M. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1789.

(38) Some Cu^{III} complexes have been characterized recently: (a) Bertz, S. H.; Cope, S.; Dorton, D.; Murphy, M.; Ogle, C. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7082. (b) Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A.; Taylor, B. J. *J. Am. Chem. Soc.* **2007**, *129*, 7208. (c) Gärtner, T.; Henze, W.; Gschwind, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 11362. (d) Bartholomew, E. R.; Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A. *J. Am. Chem. Soc.* **2008**, *130*, 11244. (e) 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. (f) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196.



3.2. Selective N-Arylation in eq 1.

3.2.1. Equilibrium between Different Cu^I Complexes. Before oxidative addition, a number of Cu^I complexes may exist in equilibrium through ligand exchange in the reaction solution.[32−36] A similar treatment was reported in our previous study on Cu-catalyzed amidation reactions.[36a]

As shown in Scheme 2, we name the **L1**-ligated Cu^I complex with I^- as **L1-Int1a** (Note: **Int** denotes intermediate). This complex can exchange I^- with the amino group of the substrate to form **L1-Int1b**. The amino-coordinated complex **L1-Int1b** can isomerize to the alcohol-coordinated complex **L1-Int1c**. Both **L1-Int1b** and **L1-Int1c** can be deprotonated to generate **L1-Int1e** and **L1-Int1f**. Finally, **L1-Int1a** can also exchange I^- with iodobenzene to produce an η^2 complex **L1-Int1d**. Our calculations indicate that the most stable species in these Cu^I complexes is **L1-Int1b**. As shown later, although **L1-Int1b** is not the direct starting material for oxidative addition, the fact that **L1-Int1b** has the lowest energy still determines how the energy barrier should be calculated.

Figure 1 shows the optimized structures for the Cu^I complexes involved in Scheme 2. It is found that all the three-coordinated Cu^I complexes adopt the distorted T-shape structure, except for **L1-Int1a** that adopts the Y-shape geometry. Note that we have also tried to locate the four-coordinated complex in which both the amino and alcohol groups of the amino alcohol substrate coordinate to the Cu center (Scheme 3). However, the four-coordinated complex does not correspond to a local minimum, because the alcohol group dissociates automatically from Cu during the optimization.

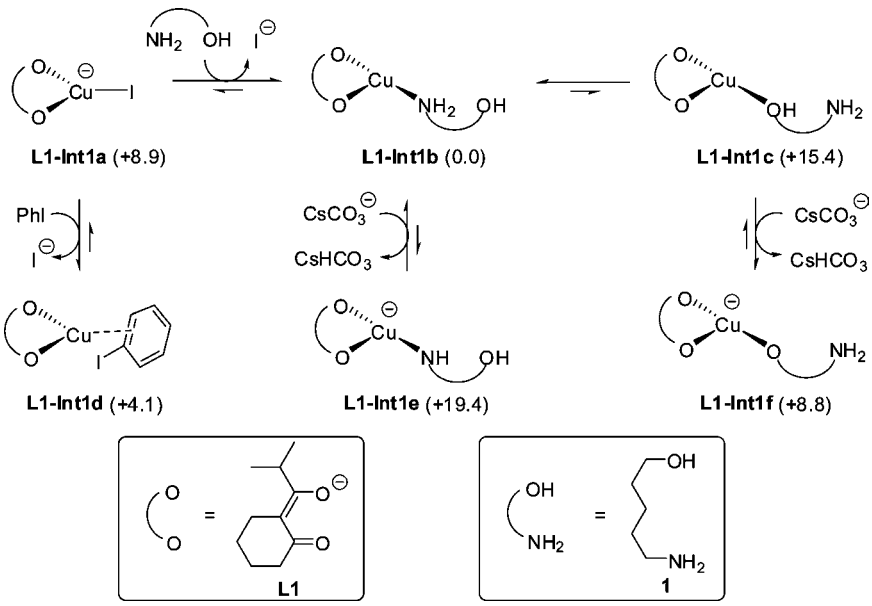
3.2.2. Oxidative Addition. All the Cu^I complexes in Scheme 2 can react with iodobenzene to start the oxidative addition step. It is necessary to examine all these possible oxidative addition processes, because a more stable starting material (intermediate) may not lead to a more favorable transition state (Curtin-Hammett Principle).

To save space we use **L1-Int1b** as an example to explain how the transition state for the oxidative addition process is located. This particular Cu^I complex can form different η^2-coordinated intermediates with iodobenzene depending on the orientation of the phenyl ring relative to the **L1** ligand (Scheme 4). Subsequently, two isomeric transition state structures (**L1-TS1a**, **L1-TS1a′**) can be identified for oxidative addition (Figure 2). Our calculations indicate that the free energies of the two isomeric transition states are close to each other. Nonetheless, because **L1-TS1a′** has a lower free energy, this transition state is selected for all the remaining parts of the study.

Note that in Scheme 4, the formation of the η^2 intermediate with iodobenzene (for instance, **L1-Int2a′**) is a highly unfavorable step with a free energy change of +17.5 kcal/mol. By comparison, the free energy change from the η^2 intermediate **L1-Int2a′** to the oxidative addition transition state **L1-TS1a′** is only +7.9 kcal/mol. This phenomenon indicates that the concerted oxidative addition from the η^2-coordinated intermediate is energetically feasible. Therefore, we identified the transition state from **L1-Int1d** (Scheme 5 and Figure 3), in which the amino alcohol nucleophile is temporarily removed from the Cu^I center during oxidative addition. Although **L1-Int1d** is less stable than **L1-Int1b** by 4.1 kcal/mol, **L1-TS1b** has a free energy of only +13.8 kcal/mol. Thus, compared to **L1-TS1a′** (+25.4 kcal/mol), oxidative addition through **L1-TS1b** is much more favorable.

The above results show that an energetically more stable starting material (intermediate) may not lead to a more favorable

Scheme 2[a]



[a] Values in parentheses are free energies in kcal/mol.

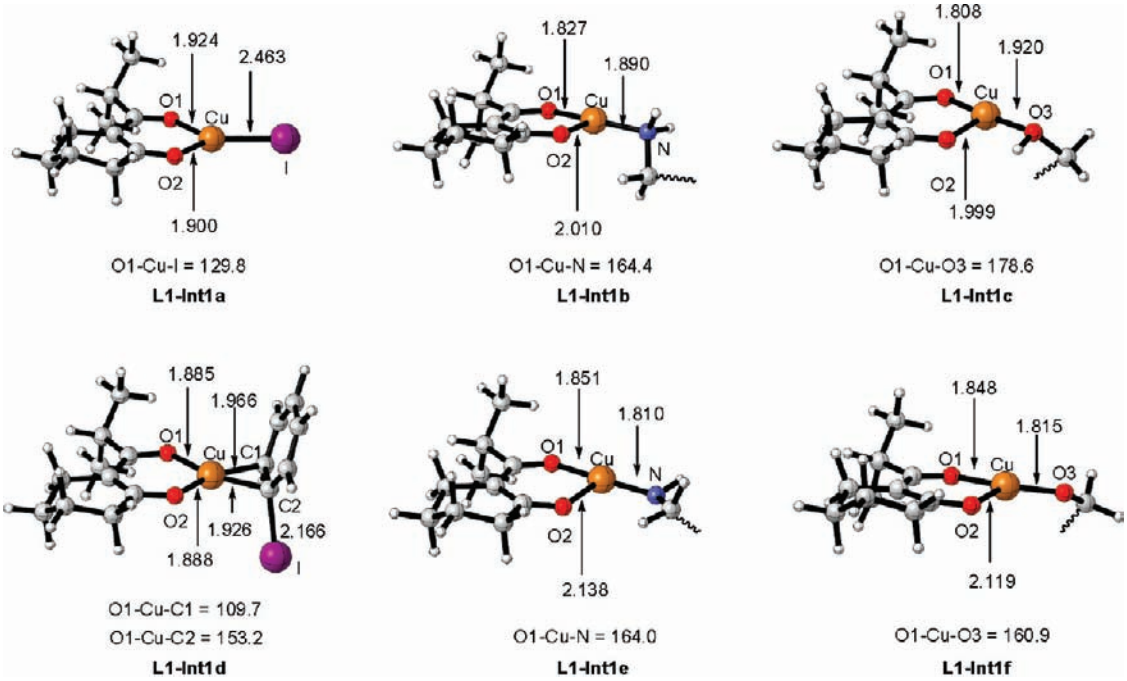
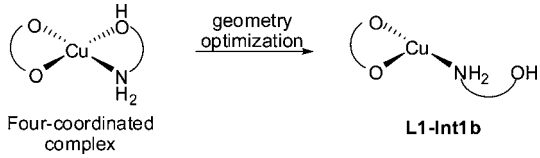


Figure 1. Optimized structures for the Cu^{I} complexes. Note that for clarity reasons, only the coordinating amino or alcohol group is shown, whereas the remaining atoms of the amino alcohol substrate are not shown in this and the following figures.

Scheme 3

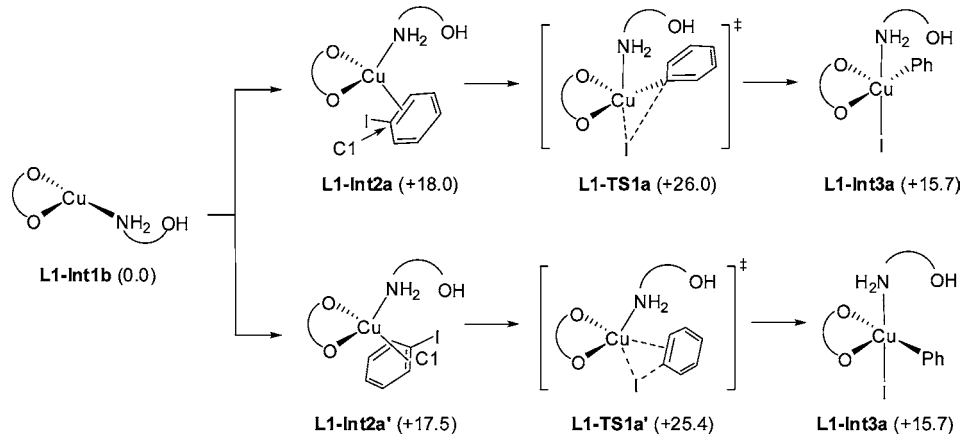


transition state in the reaction path. To derive a more accurate mechanism, it is important to examine all the possible intermediates and transition states for the transformation in eq 1 (Figure 4). Comparing the energy profiles for different oxidative addition processes, we find that the formation of other η^2 intermediates **L1-Int2b**, **L1-Int2c**, **L1-Int2d**, and **L1-Int2e** is considerably more unfavorable than that for **L1-Int2a′**. Their subsequent oxidative addition transition states (**L1-TS1c**, **L1-TS1d**, **L1-TS1e**, and **L1-TS1f**) also have very high free energies. It is therefore concluded that the most favorable transition state for oxidative addition is **L1-TS1b** that does not involve the amino alcohol nucleophile. Note that some previous experimental studies also proposed that arylhalide activation may occur before nucleophile coordination in Ullmann-type reactions.[39,40]

3.2.3. Removal of HI and Reductive Elimination. Oxidative addition through **L1-TS1b** produces a four-coordinated Cu^{III} intermediate **L1-Int3b** (Figure 4). This intermediate must be coordinated by the amino alcohol nucleophile to produce a five-coordinated Cu^{III} complex before it can generate the final *N*- or *O*-arylation product (Figure 5). Our calculations show that this coordination step is a highly endergonic process and the major contribution to the free energy comes from the entropy changes.[41] The formation of the amine-coordinated intermediate (**L1-Int3a′**) is more favorable than the formation of the alcohol-coordinated intermediate (**L1-Int3c**) by 3.8 kcal/mol.

Note that an alternative pathway for the nucleophile coordination is that one of the ligand, either one of the oxygens from **L1** or the I^- anion, is removed to leave a vacant position. However, this alternative pathway is calculated to be even more

Scheme 4[a]



[a] Values in the parentheses are free energies in kcal/mol.

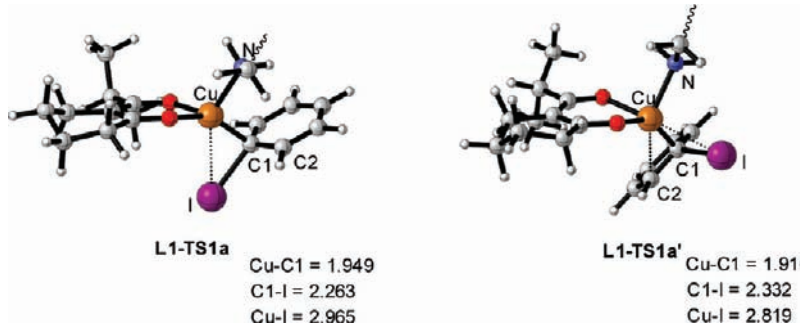
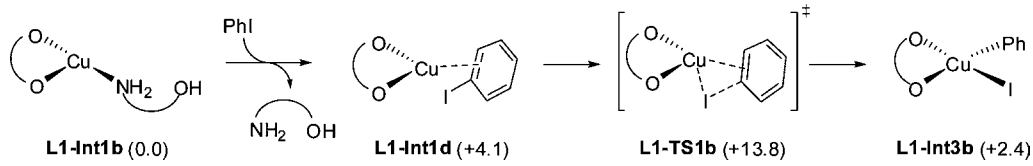


Figure 2. Optimized structures of the two isomeric transition states.

Scheme 5[a]



[a] Values in the parentheses are free energies in kcal/mol.

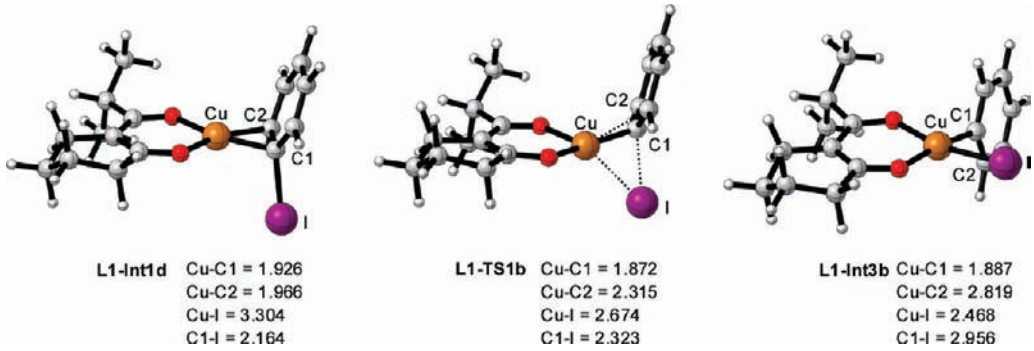


Figure 3. Optimized structures for **L1-Int1d**, **L1-TS1b**, and **L1-Int3b**.

unfavorable (For more details see Supporting Information). Also note that in the above coordination step we only consider a neutral nucleophile, because the base (e.g., Cs_2CO_3) used in the transformation is not strong enough to deprotonate the amino or alcohol group in a free amino alcohol substrate.[42] Thus, removal of H^+ from the amino alcohol coordinated to Cu^{III} must take place before reductive elimination.

Note that the solubility of Cs_2CO_3 in DMSO is low. Therefore, the energy levels of **L1-Int3a′** and **L1-Int3c** are estimated values. The possible pathway for the proton exchange step is as follows (Figure 4): First, the I^- anion on **L1-Int3a′** or **L1-Int3c** is exchanged with a basic anion $CsCO_3^-$ (the energy change of −5.3 kcal/mol is slightly overestimated due to the low solubility of the Cs_2CO_3). Second, the resulting intermediate **L1-Int4a** and **L1-Int4b** undergo an intramolecular proton transfer reaction through **L1-TS2a** and **L1-TS2b** with relatively low energy barriers. Finally, dissociation of $CsHCO_3$ from the Cu^{III} center produces four-coordinated intermediates **L1-Int6a** and **L1-Int6b**.[43]

Intermediates **L1-Int6a** and **L1-Int6b** are ready for reductive elimination to produce the final *N*- and *O*-arylation products and a Cu^I species that re-enters the catalytic cycle. Our calculations (Figure 4) show that the reductive elimination from either **L1-Int6a** or **L1-Int6b** is a very facile step with a fairly low free energy barrier (+3.9 or +11.9 kcal/mol, respectively).

3.2.5. Comparison of N- and O-Arylations Mediated by the Ligand L1. Comparing the energy profiles for the *N*- and *O*-arylation pathways in Figure 4, we can draw the following conclusions:

(39) (a) Ouali, A.; Spindler, J.-F.; Jutand, A.; Taillefer, M. *Adv. Synth. Catal.* **2007**, *349*, 1906. (b) Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2005**, *11*, 2483. (c) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607. (d) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276.

(40) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. *Chem. Sci.* **2010**, *1*, 326.

(41) During the transformations of **L1-Int3b→L1-Int3a'** and **L1-Int3b→L1-Int3c**, the major contribution to the free energy comes from the entropy.

	ΔG(kcal/mol)	ΔH(kcal/mol)	ΔS(J/mol/K)
L1-Int3b→L1-Int3a'	15.8	1.0	-241.9
L1-Int3b→L1-Int3c	19.6	4.4	-246.6

(42) The deprotonation of the free amino alcohol substrate by Cs_2CO_3 is calculated to be highly endergonic, that is, +13.6 and +34.0 kcal/mol for the alcohol and amine groups, respectively.

(43) Energy profiles for dissociation of HI via the $CsCO_3^-$ substitution/nucleophile coordination pathway together with direct reductive elimination on **L1-Int5a**/**L1-Int5b** are provided in Supporting Information.

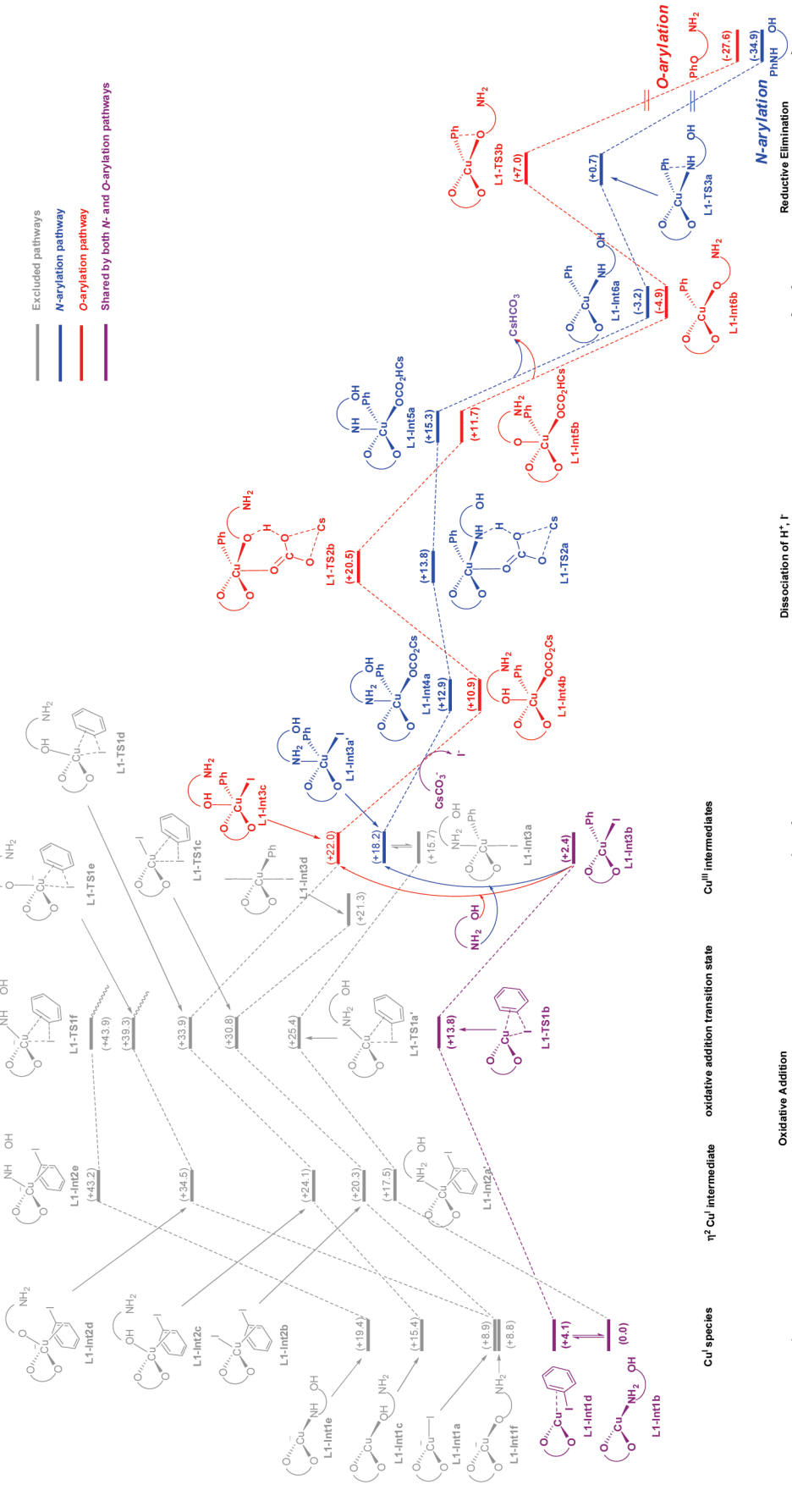


Figure 4. Energy profiles for the transformation in eq 1 (values in the parentheses are free energies in kcal/mol).

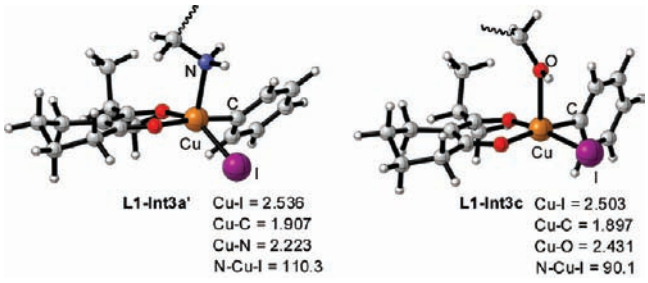


Figure 5. Optimized structures for **L1-Int3a′** and **L1-Int3c**.

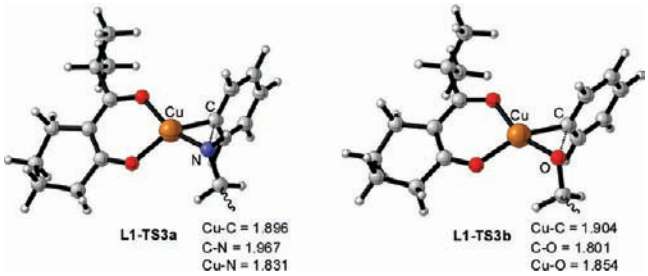


Figure 6. Optimized structures for reductive elimination transition states.

(1) Oxidative addition is not the rate-limiting step for iodobenzene in **L1**-mediated arylation reactions. The optimal oxidative addition transition state is **L1-TS1b** that does not involve the amino alcohol nucleophile. The free energy barrier for oxidative addition is only +13.8 kcal/mol as calculated from the most stable Cu^{I} complex.

(2) Reductive elimination is a very facile step (in particular, reductive elimination of an *N*-arylation precursor has an energy barrier of only +3.9 kcal/mol), so that any isomerization reaction between different reductive elimination precursors (e.g., the isomerization from **L1-Int6a** to **L1-Int6b** through proton transfer and coordinate atom exchange) will be disfavored. In other words, once an *N*-arylation precursor (such as **L1-Int3a′**) is produced, its fate can only be the formation of the *N*-arylation product.

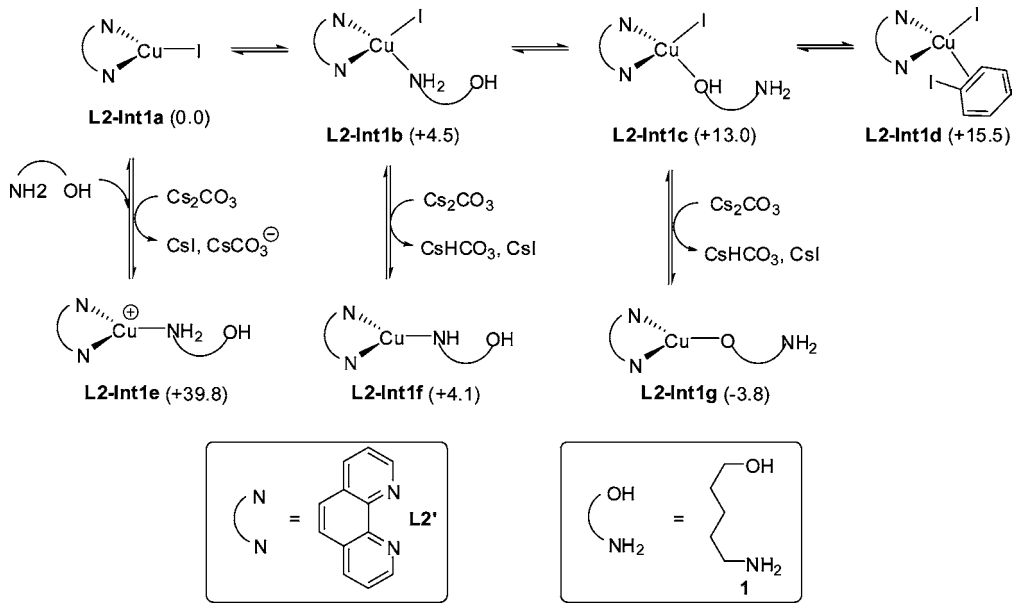
(3) The highest-energy species in the **L1**-mediated catalytic cycle is the five-coordinated Cu^{III} complex (i.e., **L1-Int3a′** or **L1-Int3c**). The nontrivial energetic difference between the amine-coordinated one **L1-Int3a′** and the alcohol-coordinated one **L1-Int3c** of 3.8 kcal/mol can be used to explain why *N*-arylation is more favorable than *O*-arylation in the presence of **L1** ligand. It is expected that the stronger binding of the amine correlates with the selectivity with the anionic ligand, and provides a means to rationalize the selectivity. However, the details of how these binding energies translate to the selectivity cannot be exactly calculated at the present time due to the difficulty of modeling insoluble Cs_2CO_3 bases in organic solvents.

Note that when examining the selectivity problem, we should study the transition state instead of the intermediate. Unfortunately, after many failed attempts we cannot locate the transition state for the coordination step from **L1-Int3b** to **L1-Int3a′** or **L1-Int3c**. Nonetheless, the coordinate step is expected to have a very late transition state, so that the transition state should resemble **L1-Int3a′** or **L1-Int3c** *in both structure and free energy*. Similarly, the transition state of the substitution processe of (**L1-Int3a′→ L1-Int4a**) or (**L1-Int3c → L1-Int4b**) was also expected to be resemble **L1-Int3a′** or **L1-Int3c** structurally and energetically. In other words, it is reasonable to use **L1-Int3a′** and **L1-Int3c** to imitate the transition states in the *N*- and *O*-arylation pathways.

3.3. Selective O-Arylation for eq 2.

3.3.1. Equilibrium between different Cu^{I} complexes. The equilibrium between different Cu^{I} complexes with the **L2** ligand has also been examined for the transformation in eq 2 (Scheme 6). Our calculations indicate that any ionic species (such as **L2-Int1e**) is highly unstable in toluene. Four-coordinated complexes (i.e., **L2-Int1b**, **L2-Int1c**, and **L2-Int1d**) are less stable than the three-coordinated complexes (i.e., **L2-Int1a**, **L2-Int1f**, and **L2-Int1g**). Moreover, due to the stronger acidity of the OH group than the NH_2 group, **L2-Int1g** is considerably more stable than **L2-Int1f** by 7.9 kcal/mol. Note that **L2-Int1g** is also found to be the most stable complex in the equilibrium.

Scheme 6[a]



[a] Values in the parentheses are free energies in kcal/mol.

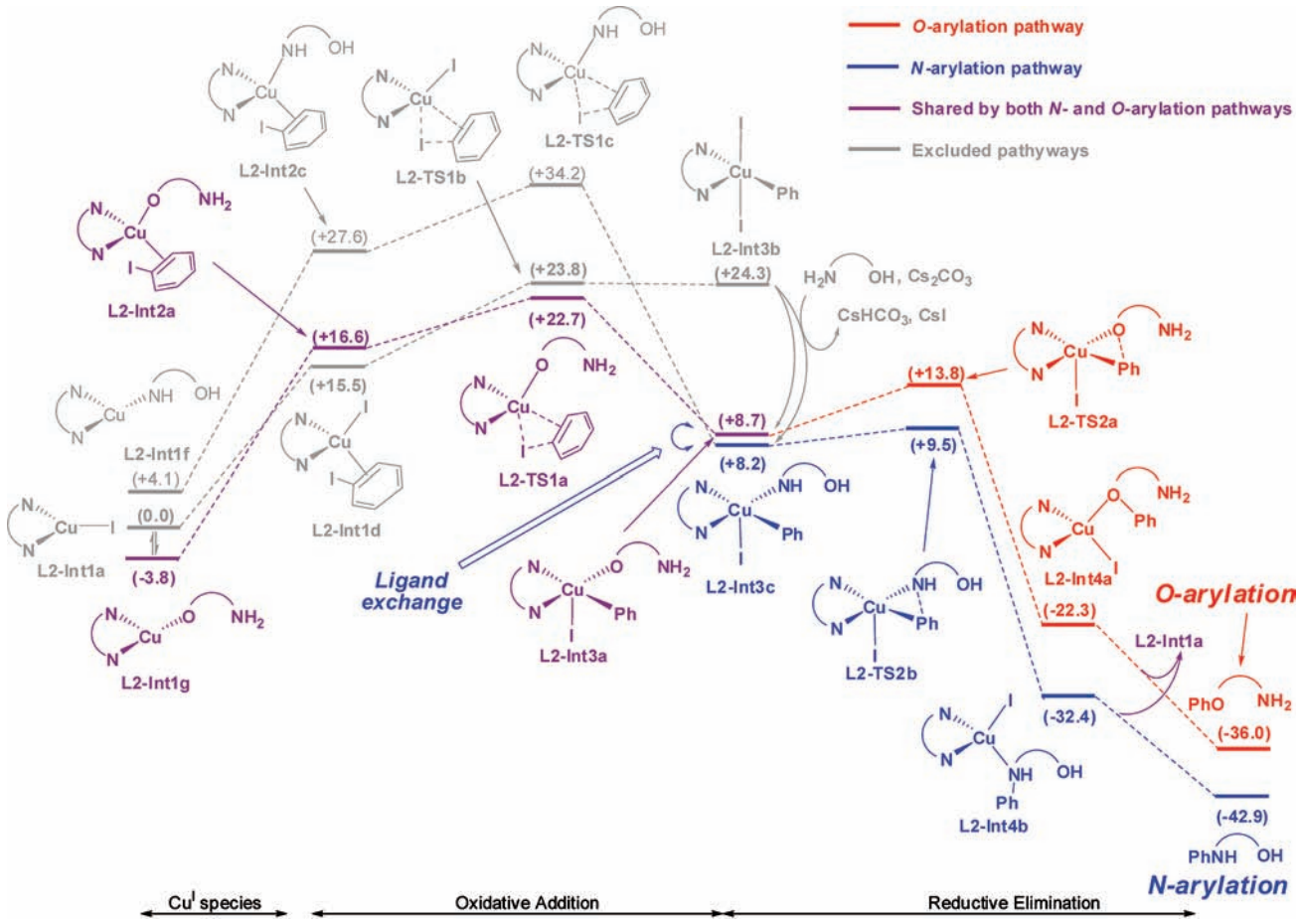


Figure 7. Energy profiles for the transformation in eq 2 (values in the parentheses are free energies in kcal/mol).

3.3.2. Oxidative Addition. In principle, all the Cu^{I} complexes in Scheme 6 can react with PhI to start the oxidative addition process. However, it is important to point out that the experimental transformation was carried out in toluene with a very low dielectric constant. As a consequence, the involvement of any charged species is strongly disfavored. Due to this reason, in the following discussion we focus on the neutral species for the **L2**-mediated cross-coupling (Figure 7).

As to oxidative addition, our calculations indicate that the four-coordinated Cu^{I} complexes in Scheme 6 (i.e., **L2-Int1b**, **L2-Int1c**, and **L2-Int1d**) cannot form η^2 complexes with PhI. On the other hand, η^2 complexes **L2-Int1d**, **L2-Int2a** and **L2-Int2c** can be readily located for the three-coordinated Cu^{I} species (i.e., **L2-Int1a**, **L2-Int1f**, and **L2-Int1g**). From the η^2 complexes we next obtain the transition states for oxidative addition (Figure 7). Interestingly, **L2-TS1a** with an anionic oxygen ligand and **L2-TS1b** with an anionic I^- are found to have relatively low free energies, whereas **L2-TS1c** with an anionic amide ligand is found to considerably less stable (Figure 8).

Note that **L2-TS1a** and **L2-TS1c** are isomers of each other. The energy difference between **L2-TS1a** and **L2-TS1c** can be explained again by the stronger acidity of the RO-*H* group than the RNH-*H* group, which is not fully compensated by the binding with the Cu center. A similar behavior is observed for the Cu^{I} complexes **L2-Int2a** (*O*-coordination, more stable) and **L2-Int2c** (*N*-coordination, less stable). Interestingly, after oxidative addition the Cu^{III} complex **L2-Int3a** (*O*-coordination) is found to be slightly less stable than its *N*-coordination isomer **L2-Int3c**. These observations indicate that the oxidative addition transition state is an early transition state, in which the Cu center is electronically similar to Cu^{I} instead of Cu^{III}.

3.3.3. Generation of the N-Arylation Precursor. The above oxidative addition process generates Cu^{III} complexes (i.e., **L2-Int3a**, **L2-Int3b**, and **L2-Int3c**) that can undergo reductive elimination to afford the *O*-arylation product, iodobenzene starting material, and *N*-arylation product, respectively. As shown in Figure 7, direct generation of the *N*-arylation precursor **L2-Int3c** through oxidative addition to **L2-Int2c** is an excluded pathway because of its very high energy barrier. This poses a question as to how the *N*-arylation product can be generated in the **L2**-mediated process?

Our proposition is that the *N*-arylation precursor **L2-Int3c** can be generated through the ligand exchange reaction of **L2-Int3a** or **L2-Int3b**. As an example, Figure 9 shows the isomerization from **L2-Int3a** to **L2-Int3c** (The isomerization from **L2-Int3b** to **L2-Int3c** is shown in the Supporting Information). It is found that the isomerization has to proceed through a necessary step involving protonation (of the Cu-bound alkoxy anion) and deprotonation (of the neutral amino group) of the Cu^{III}-bound nucleophile. This step must be assisted by a base and we assume that the base promotes the protonation/deprotonation in an intramolecular fashion. The energy barrier for the isomerization from **L2-Int3a** to **L2-Int3c** is calculated to be +17.7 kcal/mol. This barrier is much higher than the barrier for reductive elimination (+5.1 kcal/mol, see below),

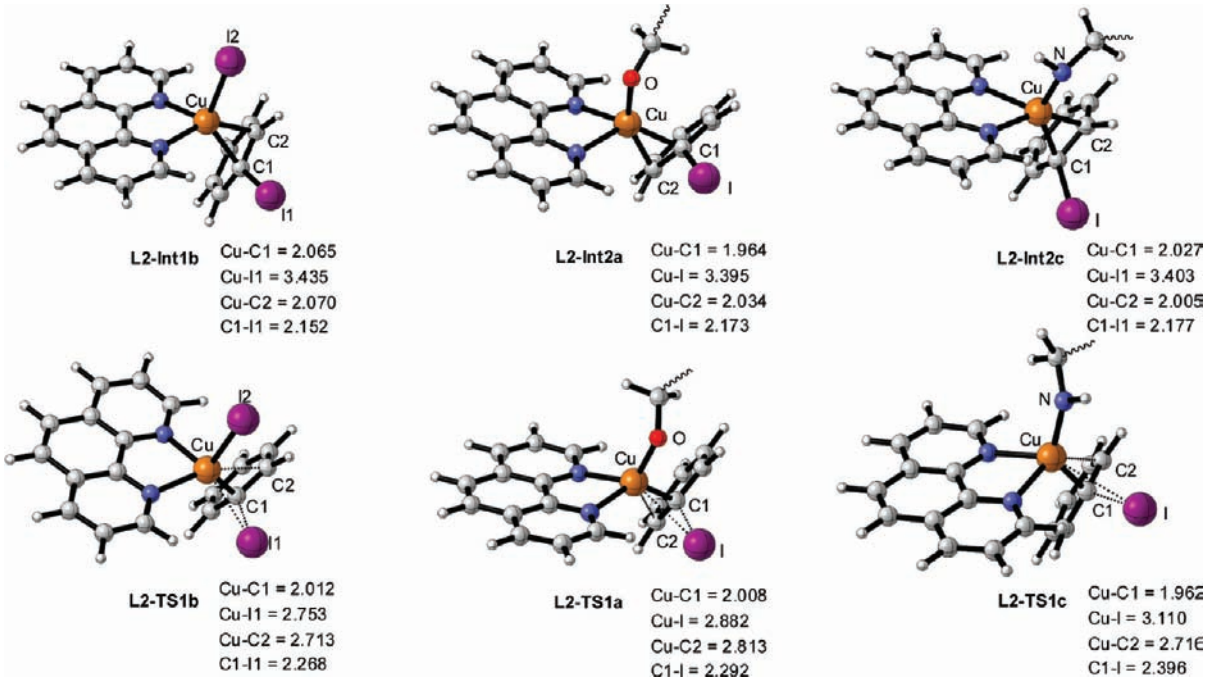


Figure 8. Optimized structures for oxidative addition precursors and transition states.

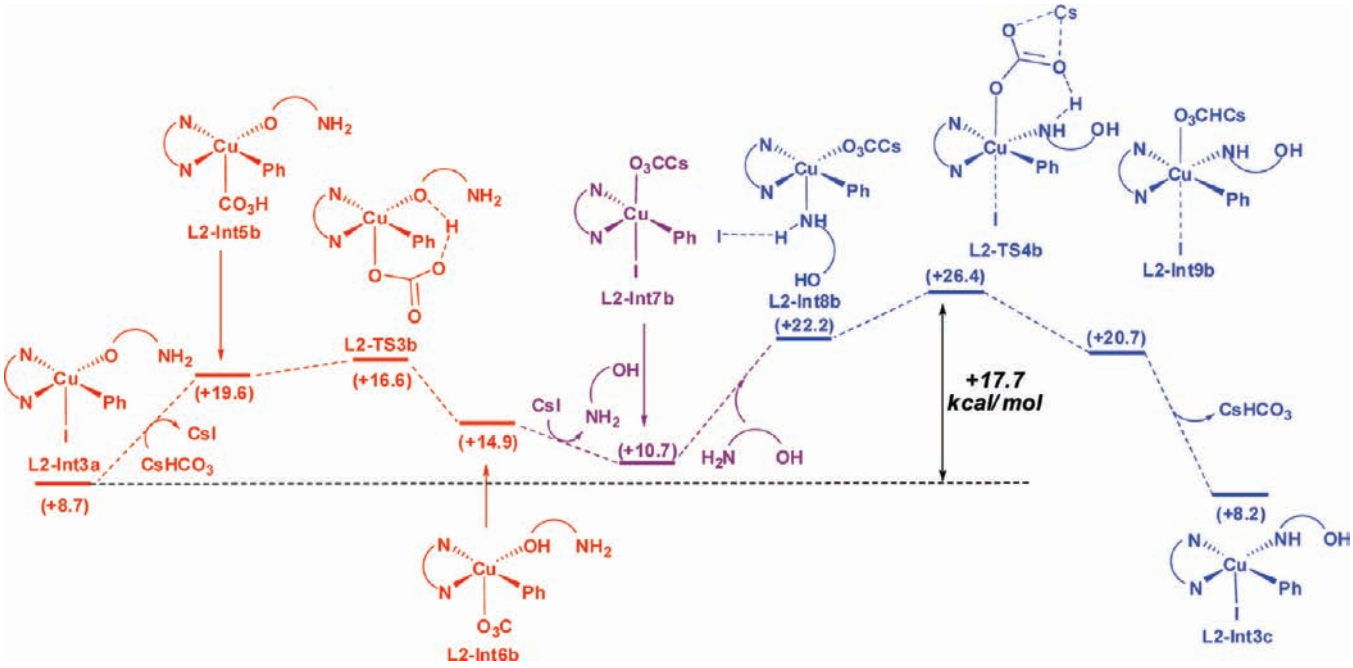


Figure 9. Energy profile for isomerization from **L2-Int3a** to **L2-Int3c** (values in the parentheses are free energies in kcal/mol).

so that the *O*-arylation product is generated faster before the *O*-arylation precursor isomerizes to the *N*-arylation precursor.

3.3.4. Reductive Elimination. Intermediates **L2-Int3a** and **L2-Int3c** can undergo reductive elimination to produce the final *O*- and *N*-arylation products and a Cu^{I} species that re-enters the catalytic cycle. Our calculations (Figures 7 and 10) show that the reductive elimination from either **L2-Int3a** or **L2-Int3c** is a very facile step with a fairly low free energy barrier (+5.1 or +1.3 kcal/mol, respectively).

3.3.5. Comparison of N- and O-Arylations Mediated by the Ligand L2. Comparing the energy profiles for the *N*- and *O*-arylation pathways in Figure 7, we can draw the following conclusions:

(1) Oxidative addition is the rate-limiting step for reaction of iodobenzene with the amino alcohol substrate in **L2**-mediated arylation reactions. The optimal oxidative addition transition state is **L2-TS1a** that is *O*-coordinated with the deprotonated amino alcohol substrate.

(2) On the other hand, the *N*-coordinated oxidative addition transition state **L2-TS1c** has a very high free energy. Thus, direct formation of the *N*-arylation precursor **L2-Int3c** through oxidative addition is excluded. Instead, it is proposed that **L2-Int3c** can be produced through the isomerization reaction of the *O*-arylation precursor **L2-Int3a**.

(3) Reductive elimination is a very facile step and its free energy barrier is even lower than that of the isomerization

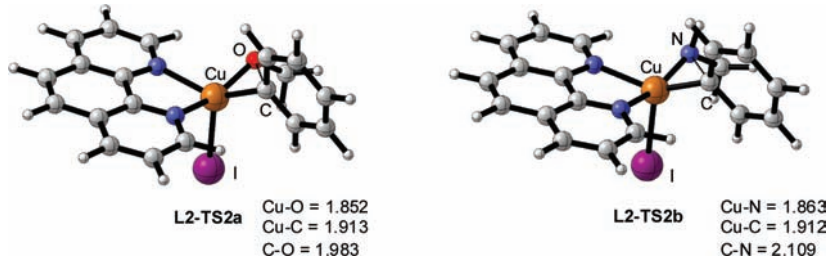


Figure 10. Optimized structures for reductive elimination transition states.

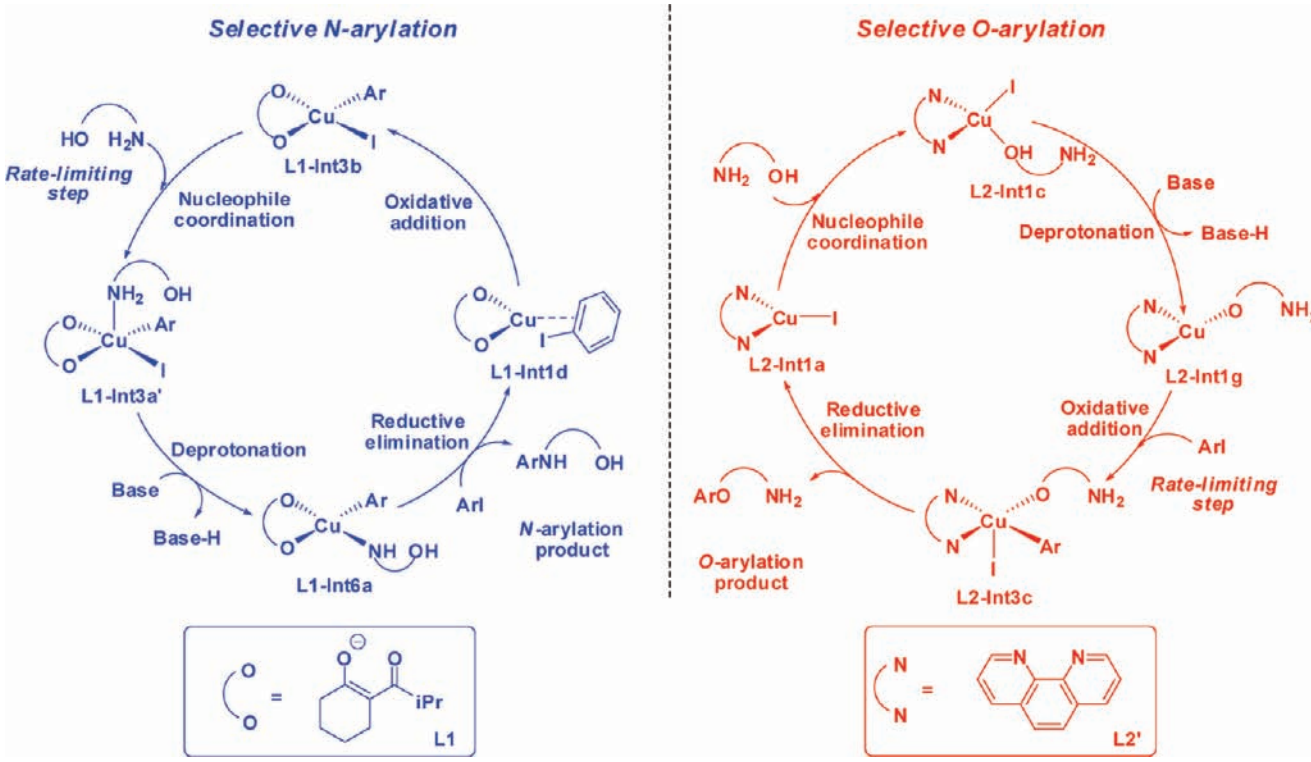


Figure 11. Comparison of the *N*- and *O*-selective arylation reactions.

reaction. As a result, most of the *O*-arylation precursor should undergo reductive elimination to generate the *O*-arylation product. This explains the experimental *O*-selectivity in the **L2**-mediated cross-coupling.

3.4. Mechanistic Origin of the *N*- and *O*-Selectivities. The calculation results through the above complicated analysis are in good agreement with the selectivities observed experimentally (Figure 11).[14] Here we summarize the fundamental reasons for the selectivities.

First, a Cu^{I} complex with a negatively charged **L1** is already electronically neutral. Oxidative addition of ArI to a **L1**-ligated Cu^{I} prefers to occur (and occur readily) without the assistance by the amino alcohol substrate. Thus, coordination of the amino alcohol (in its neutral form) can only occur at the Cu^{III} stage, where *N*-coordination is favored over *O*-coordination. This coordination step is fairly difficult and becomes a rate-limiting step. Deprotonation and reductive elimination then takes place rapidly, so that once the *N*-coordination occurs the *N*-arylation product will be generated. This is the fundamental reason why *N*-arylation is favored with **L1**.

Second, a Cu^{I} complex with a neutral **L2** is still positively charged and therefore, oxidative addition is unfavorable. Oxidative addition of ArI to a **L2**-ligated Cu^{I} occurs with a lower barrier from an alkoxide complex formed by a deprotonated amino alcohol substrate, causing the oxidative addition transition state to be much more crowded than that in the **L1**-case. Thus, oxidative addition becomes the rate-limiting step, in which the deprotonated amino alcohol prefers *O*-coordination than *N*-coordination. Subsequent reductive elimination is a very facile step, so that once the *O*-coordinated precursor is produced it will generate the *O*-arylation product. This is proposed to be the fundamental reason why *O*-arylation is favored with **L2**.

4. Discussion

4.1. Problems with the SET and IAT Pathways. In a recent mechanistic study on the coupling reactions of iodobenzene with MeOH and $MeNH_2$ promoted by β-diketone- and 1,10-phenanthroline-ligated Cu^{I} complexes, it was proposed that the arylation should occur via the SET pathway for *N*-arylation, and via the IAT pathway for *O*-arylation (Figure 12).[15] Our re-examination of the SET and IAT mechanisms using different model reactions (namely, eqs 1−2) as the nucleophile provides some different results.

First, as to the SET mechanism, the previous study estimated the energy barrier (using the combined MPWB1K[38] and B3LYP density functionals) by examining the energy difference between **L1′**-Cu^{I}−I and **L1′**-Cu^{II}−NHMe (Figure 12).[15] In our study it

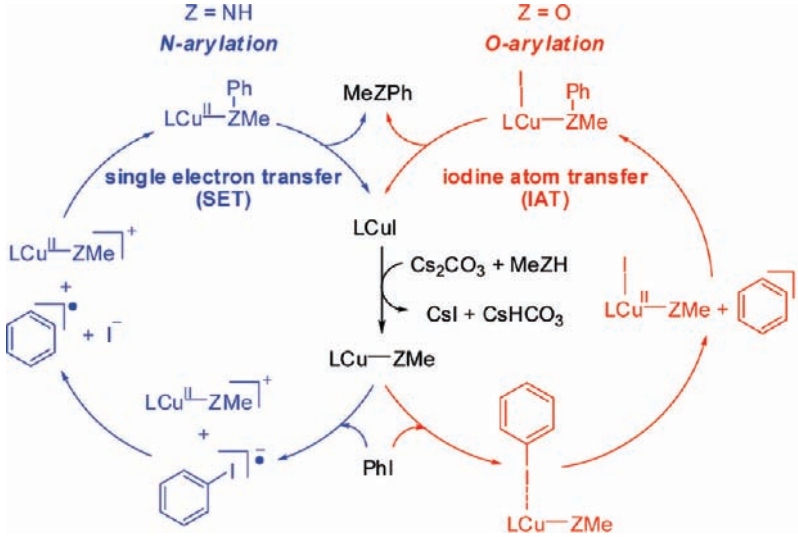


Figure 12. Previously proposed SET and IAT mechanisms.

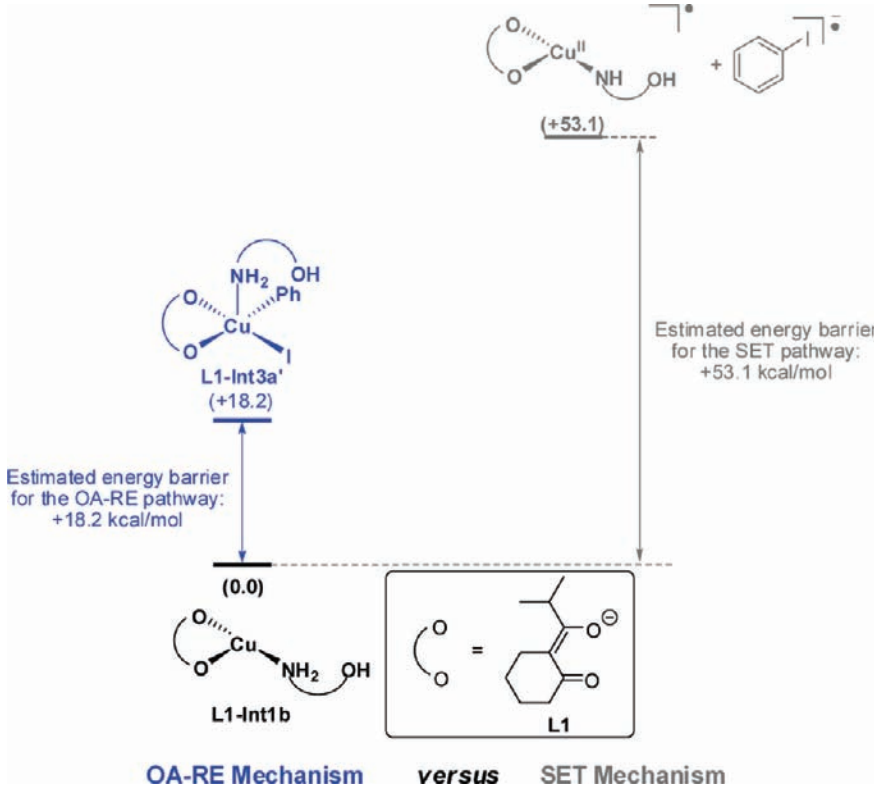


Figure 13. Comparison of the oxidative addition/reductive elimination mechanism and the SET mechanism in eq 1.

is found that **L1**-Cu^{I}−I (i.e., **L1-Int1a**) is not the most stable species among all the possible Cu^{I} complexes. Because the Cu^{I} complexes are assumed to equilibrate with each other in the reaction mixture, a more rigorous estimation of the energy barrier should use the energy difference between **L1**-Cu^{II}−NHR and the most stable species, that is, **L1-Int1b**. In our calculation, the energy difference between **L1**-Cu^{II}−NHR and **L1-Int1b** is as large as +53.1 kcal/mol (Figure 13). This large energy difference may suggest that the SET mechanism should be disfavored.

Second, as to the IAT mechanism, the previous study estimated the energy barrier of the reaction by using the energy difference between **L2**-Cu^{I}−I and **L2**-Cu^{II}−I(OMe) (Figure 12).[15] In our study **L2**-Cu^{I}−I (i.e., **L2-Int1a**) is not the most stable species among all the Cu^{I} complexes. Moreover, we doubt the reliability of using the energy of the IAT product (i.e., **L2**-Cu^{II}−I(OR) and phenyl radical) to estimate the IAT energy barrier. To solve these problems, we have identified more favorable formed Cu^{I} species, i.e. **L2-Int1g** and **L2′**-Cu-(OR)(I-Ph) (Figures 12 and 14). We have also tried to estimate the energy of the IAT transition state by scanning the energy of the **L2′**-Cu-(OR)(I-Ph) complex at different Ph-I bond distances (see Figure 15. Note: All the attempts to optimize the IAT transition state have failed). According to our analysis, the energy difference between the most stable Cu^{I} complex (i.e., **L2-Int1g**) and the IAT transition state should be larger than

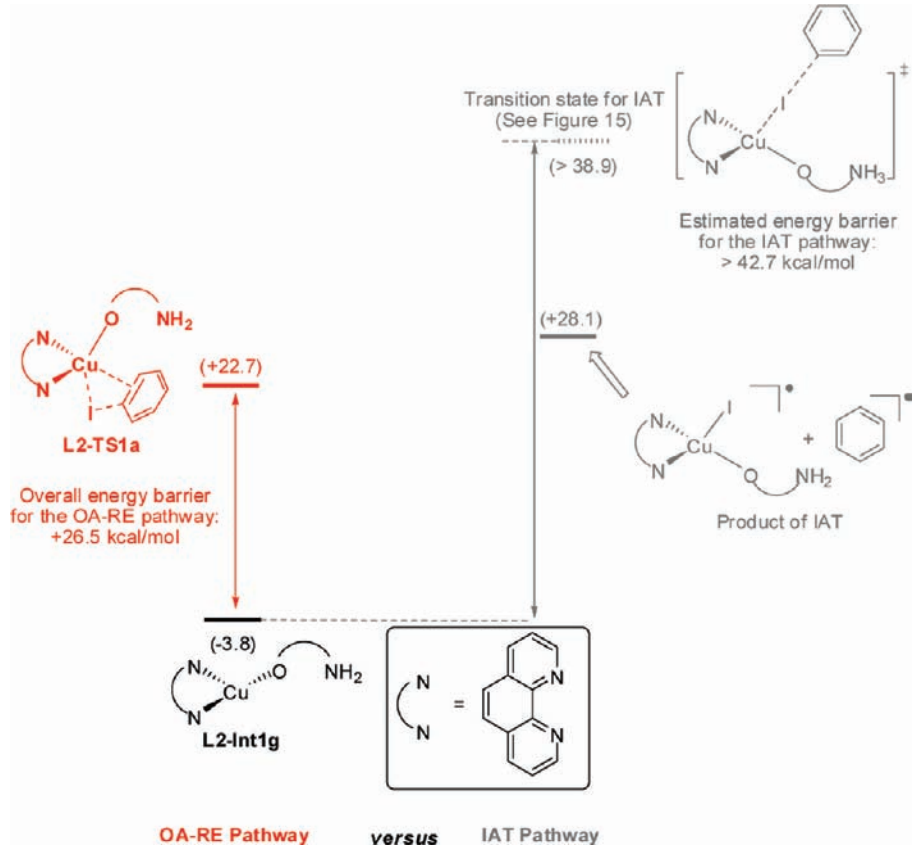


Figure 14. Comparison of the oxidative addition/reductive elimination mechanism and the IAT mechanism in eq 2.

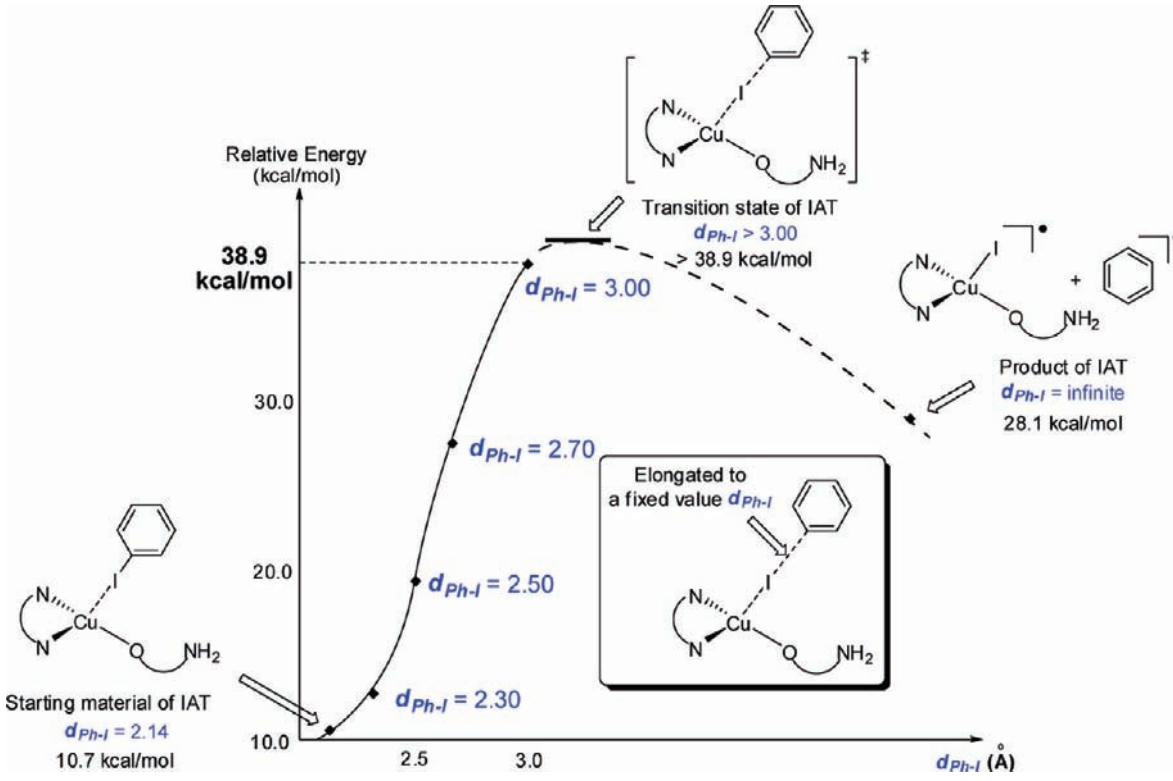


Figure 15. Estimation of the energy barrier of the IAT mechanism. To accomplish this goal the Ph-I distance of the L2′-Cu-(OR)(Ph-I) complex is fixed at several values and the remaining geometry parameters are fully optimized.

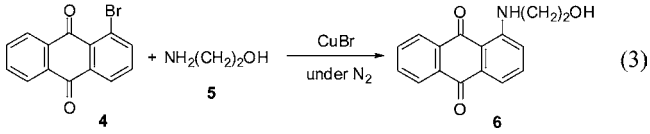
+42.7 kcal/mol. This energy barrier may suggest that the IAT mechanism should also be disfavored.

Finally, as to the oxidative addition/reductive elimination mechanism, the previous study identified some transition states

for oxidative addition with fairly high energies (>+43.2 kcal/mol). In the present study we have located the transition states that are calculated to have much lower free energies. For instance, with the optimal transition state, the free energy barrier for **L1**-mediated oxidative addition is only +13.8 kcal/mol, whereas the free energy barrier for **L2**-mediated oxidative addition is only +26.5 kcal/mol. These energy barriers are considerably lower than the barriers for the SET (+53.1 kcal/mol) and IAT (>+42.7 kcal/mol) mechanisms calculated in the present study. As a result, our results favor the oxidative addition/reductive elimination mechanism for the titled cross-coupling reaction.

Finally, we have also examined the possible σ-bond metathesis pathway from **L2-Int1g**. The transition state of σ-bond metathesis is calculated to have a very high energy barrier of +41.5 kcal/mol. As a result, we exclude the σ-bond metathesis pathway.

4.2. Concerning the Experiments Related to the SET or IAT Mechanism. First, it is important to know that there have been experimental evidence supporting the SET or IAT mechanism in some Cu-mediated coupling reactions.[16−18,44] However, these experiments were usually carried out with more active reactants (such as diacyl peroxides and diazoniums) that can readily cause the formation of organic radicals.[16−18] Also, Hida et al. once showed the involvement of Cu(II) species and 1-bromoanthraquinone radical in CuBr-mediated coupling between compounds **4** and **5** (eq 3).[44] For this particular case, our calculations indicate that the C−Br bond dissociation energy (BDE) of compound **4** is +71.7 kcal/mol, which is value about 6 kcal/mol lower than the C−Br BDE of bromobenzene (+77.6 kcal/mol). This means that substrate **4** is not a common bromobenzene derivative.



(3)

Second, there have also been experimental data disfavoring the SET or IAT mechanism in some Cu-promoted coupling reactions.[19,45,46] For instance, the recent experiments of the Hartwig group showed that the use of a radical clock (e.g., *ortho*-allyloxy substituted aryl halide) as reactant did not lead to the formation of any cyclized products corresponding to the initial formation of an aryl radical and subsequent cyclization.[35] Some early experiments reported by Cohen et al. also showed that the product distribution in the homocoupling of *o*-bromonitrobenzene is insensitive to the presence of tetrahydronfunan (which is an efficient trap for aryl radicals).[19a] Furthermore, it is difficult to explain the reactivity order ArI > ArBr ≫ ArCl by using the SET and IAT mechanisms. On the other hand, the oxidative addition/reductive elimination mechanism is more consistent with the observed reactivities. For example, for the **L2′**-mediated coupling, our calculations show that the oxidative addition barriers for PhI, PhBr, and PhCl are +26.5, +28.3, and +32.6 kcal/mol. According to the standard transition state theory, the large energy jump from PhBr to PhCl by +4.3 kcal/mol means that PhCl should be about 10^3-fold less active than PhBr.

To summarize this part, the SET or IAT mechanisms may be involved in some Cu-mediated processes that involve more active substrates. However, for common aryl iodides and bromides, it is more likely that the reaction proceeds through the oxidative addition/reductive elimination pathway.

5. Conclusion

The recent discovery of ligand-dependent *N*- or *O*-selective arylation reactions by the Buchwald group is fundamentally important to the field of Cu-catalyzed cross-couplings. Mechanistic understanding of these intriguing selectivities may provide important insights into the development of more powerful Cu catalysts to solve other selectivity problems in complex target synthesis. In a recent computational study the single-electron transfer (SET) and iodine atom transfer (IAT) mechanisms were proposed to explain the experimental selectivities. We propose in the present study a different mechanistic explanation that involves oxidative addition/reductive elimination pathway. In this explanation, the experimental selectivities originate not from the steps involving aryl halide activation, but from the steps involving nucleophile coordination and oxidative addition.

It is important to point out that the results in both the present work and the previous mechanistic study[15] are obtained through computation. These studies show how different mechanisms may explain the intriguing experimental observations. Further experimental investigations are needed to clarify the mechanism.

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Supporting Information Available: Detailed optimized geometries, free energies, thermal corrections. Full citation of Gaussian 03 program in ref 21. This material is available free of charge via the Internet at http://pubs.acs.org.

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