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Theoretical Study on Copper(I)-Catalyzed Cross-Coupling between Aryl Halides and Amides

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The density functional theory method augmented with the CPCM solvation model was used to study the mechanism of Cu(I)-catalyzed aryl amidation. On the basis of the comparison of multiple reaction pathways, it was determined that diamine-ligated copper(I) amidate was the most reactive intermediate in the reaction mixture for the oxidative addition to aryl halide. Cationic diamine-ligated Cu(I) was calculated to have a lower free energy barrier for oxidative addition, but its concentration in the reaction mixture was too low to represent a useful catalyst. On the other hand, multiple ligation of the amide to Cu(I) at low diamine concentration led to the least reactive intermediate and, thereby, retarded the oxidative addition. Further calculations showed that oxidative addition was the rate-limiting step in Cu-catalyzed aryl amidation. Unlike the transformation from Pd(0) to Pd(II), the Cu(I) → Cu(III) oxidative addition product was pentacoordinated and, thereby, more sensitive to the steric hindrance. A major portion of the overall energy barrier in the oxidative addition to Cu(I) was contributed by the highly unfavorable formation of a $^2\eta$ complex between copper(I) amidate and aryl halide. Reductive elimination occurred through a square pyramidal structure from the pentacoordinated Cu(III) intermediate. Reductive elimination was a very facile step as compared to oxidative addition. Furthermore, our calculation indicated that *trans-N,N′*-dimethylcyclohexane-1,2-diamine was an excellent ligand for Cu-catalyzed aryl amidation, whereas TMEDA was almost completely inactive. These theoretical results were in good agreement with experimental observations, suggesting the possibility of using a combined theoretical and experimental approach to rationally improve Cu(I)-catalyzed cross-coupling reactions.

1. Introduction

Transition-metal-catalyzed amide arylation is a widely utilized reaction in both academic and industrial laboratories and, therefore, has been a focus of recent research interest. Significant improvements have been achieved in Pd-catalyzed amide arylation reactions,[2] but it often remains difficult to apply these reactions to large, industrial-scale syntheses due to the high cost of Pd and the difficulty in removing Pd residues from polar reaction products. An alternative method for amide arylation is the Cu-catalyzed Goldberg reaction.[3] This method is attractive from an economic standpoint because Cu is much less expensive than Pd. Despite this advantage, the Goldberg reaction is not considered as a popular reaction in traditional organic chemistry due to the necessity to use temperatures as high as 200 °C, highly polar aprotic solvents (e.g., DMSO), strong bases such as alkoxides and NaH, large amounts of the nucleophile, and often large amounts of Cu reagents.

An interesting recent finding is that the Goldberg amidation reaction can be considerably accelerated by some organic ligands.[4] Similar promotion effects have also been reported lately for many other Cu-catalyzed cross-coupling reactions.[5] These findings have given rise to a resurgence in interest in developing mild synthetic methods using Cu-based catalysts as an alternative to Pd catalysts for the formation of aryl−heteroatom bonds. Up to now, the ligands that have been found to promote the Cu-catalyzed Goldberg amidation reaction include diamines,[6] 2,2,6,6-tetramethyl-heptane-3,5-dione,[7] 1,10-phenanthroline,[8] *o*-hydroxybiphenyl,[9] neocuproine,[10] and amino acids.[11] These ligand-promoted processes display dramatically increased activ-

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[1] Reviews: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657.

[2] Recent examples: (a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (c) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Kalpars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (d) Xie, X.; Zhang, T. Y.; Zhang, Z. *J. Org. Chem.* **2006**, *71*, 6522. (e) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101. (f) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523.

[3] (a) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691. (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

[4] (a) Yamamoto, T.; Ehara, Y.; Kubota, M.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1299. (b) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459. (c) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. (d) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670. (e) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043. (f) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (g) Crawford, K. R.; Padwa, A. *Tetrahedron Lett.* **2002**, *43*, 7365. (h) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799.

[5] Reviews: (a) Deng, W.; Liu, L.; Guo, Q.-X. *Chin. J. Org. Chem.* **2004**, *24*, 150. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.

[6] Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684.

[7] Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623.

[8] (a) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973. (b) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151. (c) Moriwaki, K.; Satoh, K.; Takada, M.; Ishino, Y.; Ohno, T. *Tetrahedron Lett.* **2005**, *46*, 7559.

[9] Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269.

[10] Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315.

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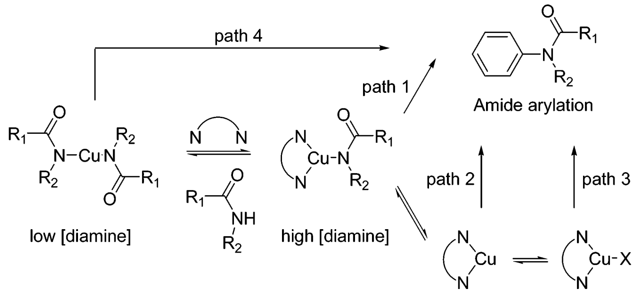
Scheme 1



Note: In each path, ArX oxidatively adds to each particular Cu complex as specified

ity and substrate scope relative to their unligated predecessors. Nonetheless, further development of improved catalysts is needed before these reactions can be more successfully applied to profit-driven synthesis. This hinges on our ability to accurately understand the catalytic events.

Unfortunately, up till now the mechanism of the Cu(I)-catalyzed carbon−heteroatom cross-coupling reactions has not been adequately studied. According to most authors, the mechanism of these reactions appears to involve a poorly characterized Cu(III) intermediate that is formed through oxidative addition onto the aryl−halide bond.[12] This theory vaguely indicates that the improved activity of Cu catalysts based on organic ligands such as 1,2-diamines is that they may reduce the oxidation potential of Cu(I), thus facilitating the activation of the aryl halide.[13] Nonetheless, alternative mechanisms for the Cu-catalyzed Goldberg reaction have also been proposed. One of them suggests that the transformation resembles the classical nucleophilic aromatic substitution due to the electronic activation of the aryl group by Cu(I) through a Cu−π interaction.[4b]

Kinetic analysis of the reaction under variable conditions provides a powerful approach to probe the reaction mechanism. Very recently, Buchwald and co-workers reported an interesting kinetic study on the Cu(I)-catalyzed, diamine-promoted amide arylation reaction using a calorimetric method.[14] It was found that, at low concentrations of diamine, the catalyst resides as a multiply ligated species, which required the dissociation of an amide through diamine coordination to generate the active Cu(I) amidate (Scheme 1). On the other hand, higher (and synthetically relevant) concentrations of the diamine ligand allowed the activation of the aryl iodide to become the rate-limiting step. Interestingly, the observed rate constant obeyed the following equation:

$$\text{rate} \approx k[\text{Cu}][\text{ArX}][\text{amide}] \qquad (1)$$

This equation strongly suggests a rate-limiting step where Cu(I), ArX, and amide must all be explicitly involved. On the basis of the kinetic data, Buchwald and co-workers proposed that the amide arylation product should be formed somehow from the copper(I) amidate intermediate (i.e., path 1 in Scheme 1). What remain unclear at the present time are (1) how the copper(I) amidate is transformed to the final product and (2) why the other possible pathways (i.e., paths 2−4) are not energetically favored.

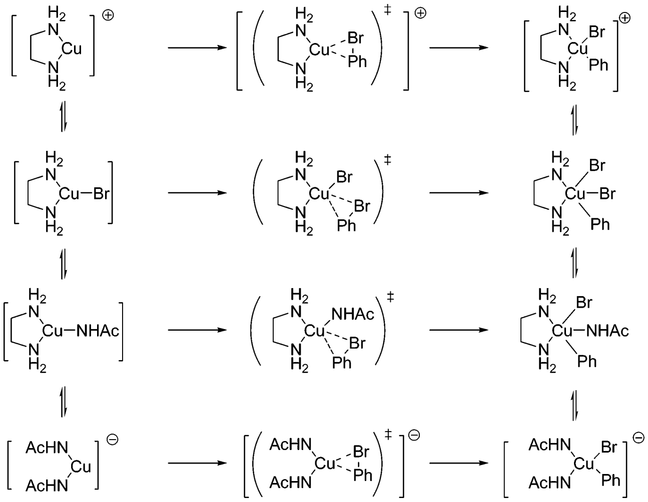


Figure 1. Possible oxidative additions to different copper complexes.

We consider that it will be difficult (if not impossible) to use any kinetic method to answer the above two interesting as well as important questions. As a consequence we seek to use the quantum chemistry approach to investigate the Cu(I)-catalyzed amide arylation reaction. As a complementary approach to the experiments, theoretical modeling allows us to visualize the details of the transformation and, in particular, to get some knowledge of the transition state. Furthermore, it allows us to investigate why some possible, but not experimentally observable transformation pathways are energetically ruled out. Up to now we have not been aware any previous theoretical study on the Cu(I)-catalyzed coupling reactions.[15] Thus, our study provides the first theoretical data in this particular area. Through the study it is found that all the theoretical results are fully consistent with Buchwald's copper amidate pathway. The mechanistic origin for the preference of this particular pathway over the other possible routes has been successfully identified. Furthermore, we have systematically compared the effects of different diamine ligands in the Cu(I)-catalyzed amidation reaction.

2. Oxidative Addition

2.1. Equilibrium between Different Copper Complexes. Buchwald and co-workers hinted that the oxidative addition might occur with the copper(I) amidate.[14] However, mechanistically there are four different modes of oxidative addition that can take place in the same reaction mixture (Figure 1). In the four modes, the first mode starts with a biscoordinated Cu(I) complex, and therefore, its oxidative addition resembles the classical oxidative addition of aryl halide to a palladium diphosphine complex. The second and third modes start with tricoordinated Cu(I) complexes that are presumably in rapid equilibrium with the biscoordinated Cu(I) complex. Compared to the biscoordinated Cu(I) complex, the tricoordinated ones are sterically more crowded and, therefore, may not be favorable in the oxidative addition. Finally, because Buchwald and co-

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[11] (a) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (b) Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2004**, *45*, 2311. (c) Lu, B.; Ma, D. *Org. Lett.* **2006**, *8*, 6115.

[12] (a) Cohen, T.; Cristea, I. *J. Am. Chem. Soc.* **1976**, *98*, 748. (b) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309.

[13] Rusonik, I.; Cohen, H.; Meyerstein, D. *J. Chem. Soc., Dalton Trans.* **2003**, 2024.

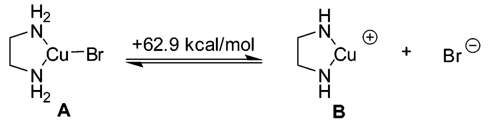
[14] Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120.

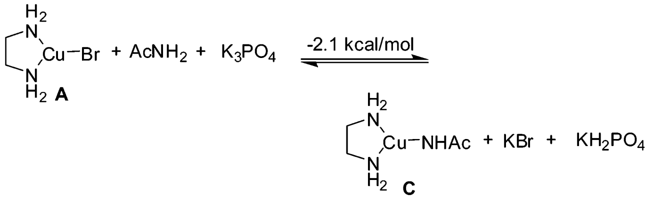
[15] Theoretical studies on some other Cu-catalyzed transformations have been conducted recently. For examples, see: (a) Brandt, P.; Soedergren, M. J.; Andersson, P. G.; Norrby, P.-O. *J. Am. Chem. Soc.* **2000**, *122*, 8013. (b) Fraile, J. m.; Garcia, J. I.; Martinez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616. (c) Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6278. (d) Fraile, J. M.; Garcia, J. I.; Gil, M. J.; Martinez-Merino, V.; Mayoral, J. A.; Salvatella, L. *Chem.—Eur. J.* **2004**, *10*, 758. (e) Suenobu, K.; Itagaki, M.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 7271.

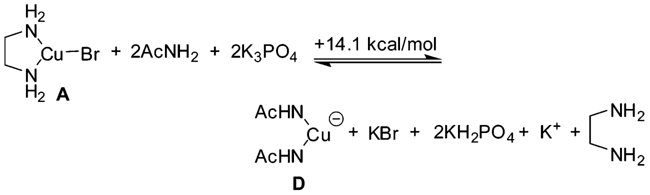
workers showed the existence of multiply amide-ligated Cu(I) complexes in their reaction mixture,[14] it is obligatory to investigate the possible oxidative addition of aryl halide to this type of Cu(I) compound. Noteworthy, the amidyl group does not have to be present in the oxidative addition step, because the product of the oxidative addition may also exchange its ligand before the subsequent reductive elimination (as shown by the right part in Figure 1).

Previously there has not been any rigorous theoretical analysis of the multiple possible oxidative addition pathways for the copper catalysis. Therefore, we have to make a few explicit assumptions before the calculation. (1) To simplify the calculation, we choose ethylenediamine to represent the diamine ligand (which by itself is a synthetically useful ligand in Cu catalysis[16]). We also use acetamide and bromobenzene to represent the amide and aryl halide. (2) We assume that the concentrations of PhBr and $AcNH_2$ in the reaction mixture are 1 mol/L (the solvent is toluene). We assume that the total concentration of CuBr and $NH_2CH_2CH_2NH_2$ in the reaction mixture is 0.1 mol/L (i.e., 10 mol % as compared to the substrates). (3) We choose K_3PO_4 as the base (and, therefore, KH_2PO_4 as the conjugate acid).

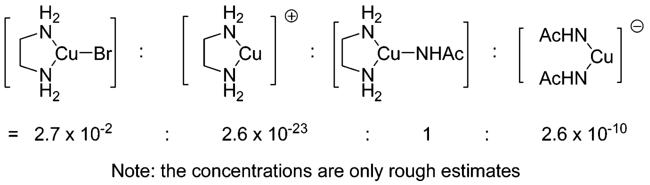
On the basis of the above assumptions and the following calculated equilibrium free energies, we can readily estimate the concentrations of the other copper species (we assume that K_3PO_4, KBr, and KH_2PO_4 stay as solids in the reaction).







Our calculations show that the ionization of the starting copper bromide **A** to cationic **B** and bromide anion is highly unfavorable in energy. On the other hand, due to the strong binding between Cu and amidate, the exchange from **A** to **C** is slightly favorable in the free energy. Finally, the formation of **D** is also a charge separation process and, therefore, not energetically favorable in the organic solvent. The calculation results indicate that **C** is the major copper species in the reaction mixture. On the basis of the calculated free energies, the relative ratio between the different copper complexes is estimated to be



Note: the concentrations are only rough estimates

2.2 Oxidative Additions to Different Copper Complexes. With the relative concentrations of the different copper species in hand, we next calculate their corresponding free energy barriers in oxidative addition. First, we start with complex **A**, where we successfully obtain a $^2\eta$ complex between **A** and bromobenzene (Figure 2). This complex is +24.5 kcal/mol higher in free energy than **A**, and it constitutes the direct precursor of the oxidative addition step. Subsequent migration of the copper from the top of the C═C double bond to the top of the C−Br bond provides the transition state of the oxidative addition (i.e., **TS-A**). This step costs a free energy of +7.1 kcal/mol calculated from the precursor $^2\eta$ complex. Finally, cleavage of the C−Br bond takes place, leading to a pentacoordinated Cu(III) complex as the product of oxidative addition.

As for complex **B**, the beginning Cu(I) species is found to be able to form a stable $^2\eta$ complex with PhBr (Figure 3). The free energy of this step is −6.0 kcal/mol. Migration of the copper from the top of the C═C double bond to the top of the C−Br bond provides the transition state of the oxidative addition (i.e., **TS-B**). This step costs a free energy of +9.0 kcal/mol calculated from the precursor $^2\eta$ complex. Finally, cleavage of the C−Br bond takes place, leading to a tetracoordinated Cu(III) complex as the product of oxidative addition.

As for complex **C**, the beginning tricoordinated copper(I) amidate can form a $^2\eta$ complex with PhBr (Figure 4). The free energy of this step is +24.9 kcal/mol, and therefore, the $^2\eta$ complex is highly unfavorable in free energy. Migration of the copper from the top of the C═C double bond to the top of the C−Br bond provides the transition state of the oxidative addition (i.e., **TS-C**). Significantly, this step only costs a free energy of +3.8 kcal/mol calculated from the precursor $^2\eta$ complex. Finally, cleavage of the C−Br bond takes place, leading to a pentacoordinated Cu(III) complex as the product of oxidative addition.

Finally, as for complex **D**, the beginning dicoordinated copper(I) amidate is found to have a linear N−Cu−N arrangement (Figure 5). This copper amidate can form a $^2\eta$ complex with PhBr, which costs +36.6 kcal/mol in free energy. Subsequent migration of the copper from the top of the C═C double bond to the top of the C−Br bond provides the transition state of the oxidative addition (i.e., **TS-D**). This step costs a free energy of +7.7 kcal/mol calculated from the precursor $^2\eta$ complex. Finally, cleavage of the C−Br bond takes place, leading to a tetracoordinated Cu(III) complex as the product of oxidative addition.

2.3. Comparing Different Copper Complexes. With all the detailed values in hand, we can systematically compare the activity of the several different copper complexes (Table 1). For the formation of the $^2\eta$ complex, it is found that complex **C** has the most favorable free energy presumably because it is a cationic species (and, thereby, highly electron deficient). Complexes **A** and **C** show similar free energies for the formation of $^2\eta$ complexes. Furthermore, complex **D** is the most reluctant to form the $^2\eta$ complex.

As for the free energy from the $^2\eta$ complex to the transition state, it is found that complex **B** exhibits the highest free energy. Compared to **B**, complex **A** has a lower free energy presumably because the coordinated bromide reduces the oxidation potential of Cu(I). A further decrease is seen for complex **C**, which should be related to the fact that amidate is much more basic than bromide. Nonetheless, it is interestingly to see that complex **D** gives a higher free energy than **C** although **D** is more electron rich than **C**. This is possibly due to the fact that in the oxidative addition to **D** the two negatively charged amidate ligands have to become closer to each other.

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(16) Kang, S.-K.; Kim, D.-H.; Park, J.-N. *Synlett* **2002**, 427.

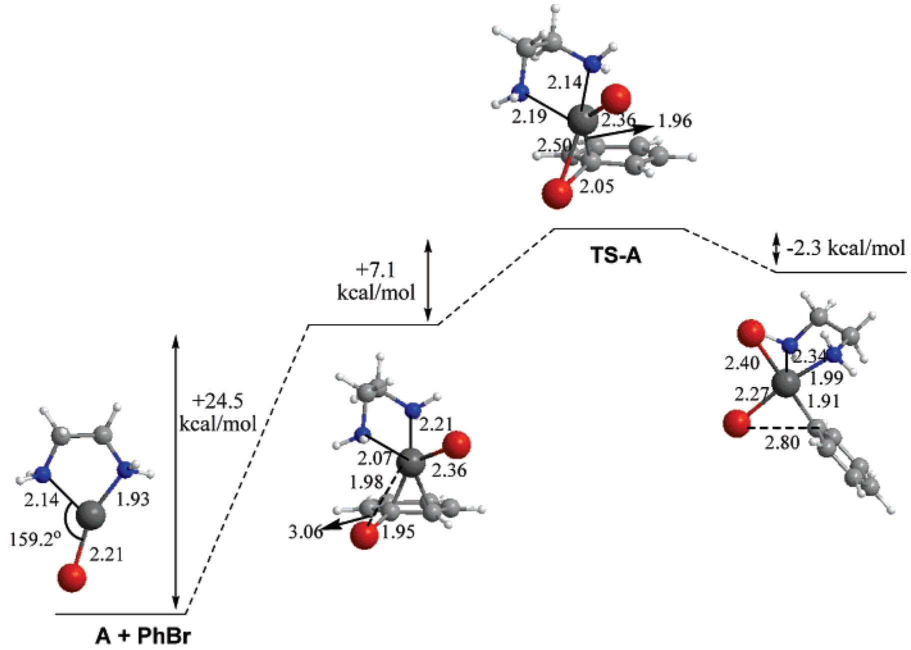

Figure 2. Oxidative addition to complex **A**.

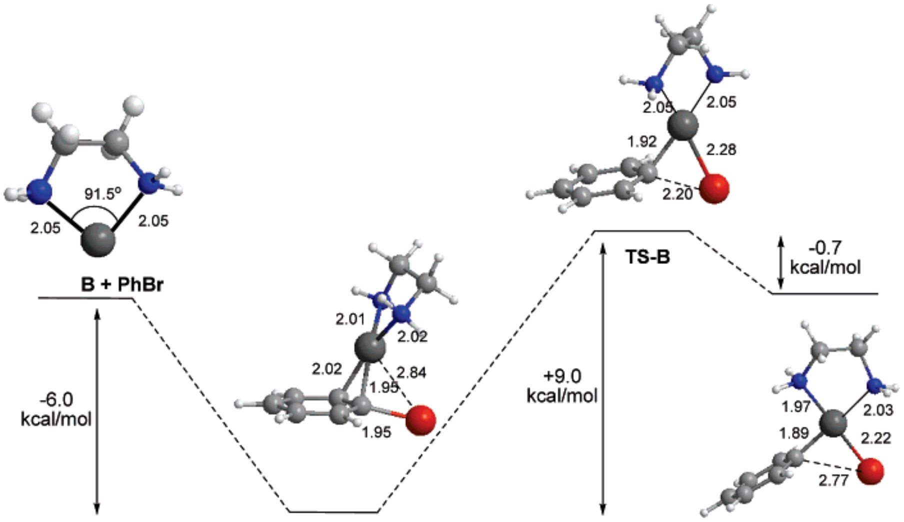

Figure 3. Oxidative addition to complex **B**.

The overall free energy barrier is defined as the free energy from the beginning Cu complex to the transition state (i.e., the sum of the free energy for the formation of the $^2\eta$ complex and the free energy from the $^2\eta$ complex to the transition state). As shown in Table 1, the overall free energy barrier decreases in the order **D** > **A** > **C** > **B**. The fact that **B** has the lowest barrier supports our original speculation that the dicoordinated Cu is energetically the most favorable for the oxidative addition due to its similarity to palladium diphosphines. Noteworthy, although **D** is also a dicoordinated Cu, it has the highest barrier presumably because **D** is a linear complex whose bending in the oxidative addition step is energetically unfavorable.

Nonetheless, it is important to note that the overall free energy barrier does not reflect the observed reactivity, because the copper complexes have dramatically different concentrations in the reaction solution. To solve this problem, we define the relative reactivity calculated by the following equation:

$$\text{relative reactivity} = \text{relative concentration} \times \exp\frac{-(\text{overall barrier})}{RT} \quad (2)$$

As shown in Table 1, the calculated relative reactivity decreases in the order **C** > **A** > **B** > **D**. Therefore, copper(I) amidate is the most important intermediate for the oxidative activation step. This result is in agreement with Buchwald's proposed mechanism on the basis of the experimental observations.[14]

Noteworthy, compared to that of complex **B**, the reactivity of complex **D** is extremely low. At low concentration of $NH_2CH_2CH_2NH_2$ we expect that complexes **A**, **B**, and **C** could not be formed because they all require the diamine ligand. This means that complex **D** should be the only copper species at low ligand concentration, where almost no oxidative addition can take place due to the low reactivity of **D**. As shown in Buchwald's experiment,[14] the arylation reactivity at zero diamine concentration was almost zero. Therefore, our theoretical result for complex **D** also agrees with the experimental observation.

3. Reductive Elimination

Having discussed the oxidative addition, we next complete the catalytic cycle by studying the reductive elimination. The major goal in this part is to examine whether our theory agrees

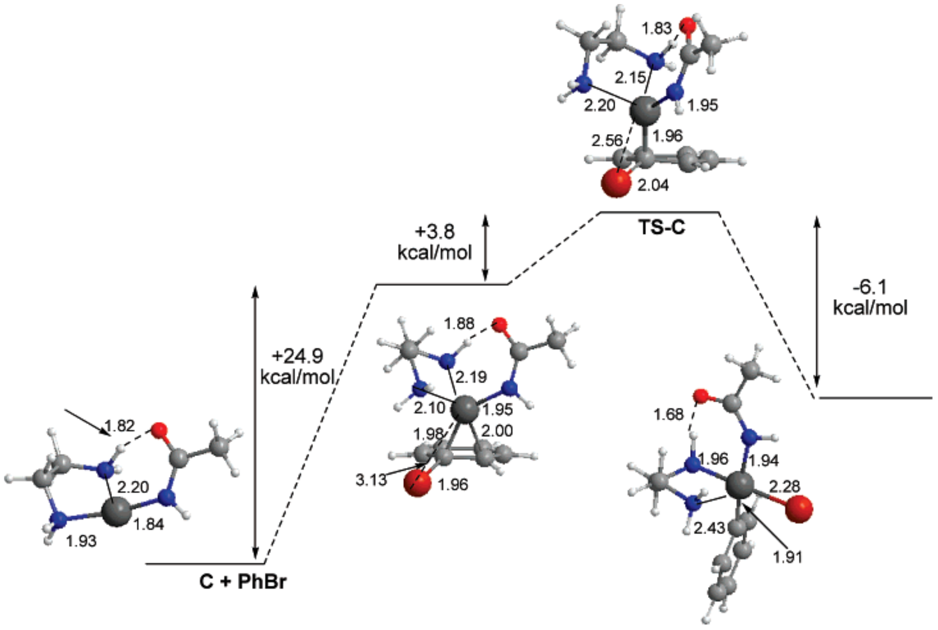

Figure 4. Oxidative addition to complex **C**.

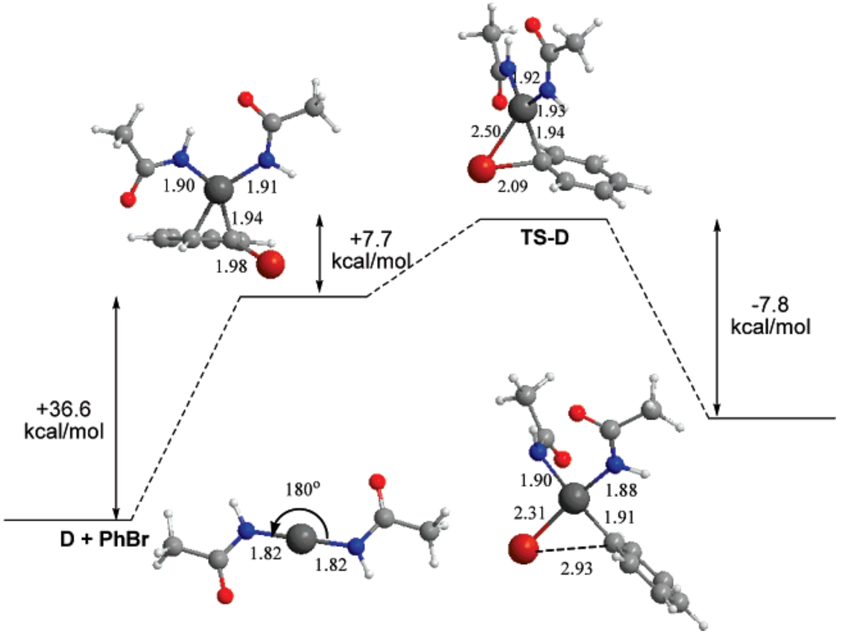

Figure 5. Oxidative addition to complex **D**.

with the experimental suggestion that oxidative addition is the rate-limiting step.[14] Furthermore, unlike the Pd-catalyzed cross-coupling reactions where the reductive elimination has been extensively studied both experimentally and theoretically,[17] very little has been known about the reductive elimination from a Cu(III) complex. Therefore, it is interesting to use theory to "visualize" the details of the reductive elimination of Cu(III).

As aforementioned, the starting intermediate for reductive elimination should be the product of the oxidative addition to complex **C**, i.e., a pentacoordinated Cu(III) carrying a diamine ligand, an amidate, a bromide, and a phenyl group. Note that in this Cu(III) complex the diamine nitrogens and bromide occupy the equatorial plane, whereas the amidyl and phenyl groups are in the axial positions and opposite each other. To achieve the reductive elimination, this Cu(III) complex has to undergo a pseudorotation so that the phenyl and amidyl groups become *cis* to each other (Figure 6). Our calculation suggests that two and only two possible Cu(III) intermediates can be formed through this pseudorotation as local minima on the potential energy surface. In one of the intermediates (i.e., the trigonal bipyramidal one), the diamine nitrogens and the phenyl group occupy the equatorial plane whereas the amidyl and bromide groups are in the axial positions. In the other intermediate (i.e., the square pyramidal one), the diamine

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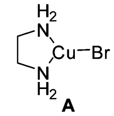
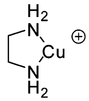
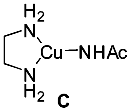
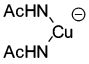
[17] Recent examples: (a) Yamashita, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5344. (b) Zuidema, E.; van Leeuwen, P. W. N. M.; Bo, C. *Organometallics* **2005**, *24*, 3703. (c) Popp, B. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 2804. (d) Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584. (e) Fujita, K.-i.; Yamashita, M.; Puschmann, F.; Alvarez-Falcon, M. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9044.

Table 1. Comparison of the Oxidative Additions to Different Cu Complexes

Cu complex	Relative concentration	Free energy for formation of ${}^2\eta$ complex	Free energy from ${}^2\eta$ complex to TS	Overall free energy barrier	Relative reactivity
 **A**	2.7×10^{-2}	+24.5 kcal/mol	+7.1 kcal/mol	+31.6 kcal/mol	2.1×10^{-4}
 **B**	2.6×10^{-23}	-6.0 kcal/mol	+9.0 kcal/mol	+3.0 kcal/mol	1.7×10^{-6}
 **C**	1	+24.9 kcal/mol	+3.8 kcal/mol	+28.7 kcal/mol	1.0
 **D**	2.6×10^{-10}	+36.6 kcal/mol	+7.7 kcal/mol	+44.3 kcal/mol	1.1×10^{-21}

nitrogens, the phenyl group, and the amidyl group occupy the same plane while the bromide is perpendicular to the plane.

Our calculation indicates that the triganol bipyramidal intermediate has a lower free energy as compared to the square pyramidal one by 2.5 kcal/mol. However, from the triganol bipyramidal intermediate to its subsequent reductive elimination transition state there is a free energy barrier of +5.9 kcal/mol, whereas from the square pyramidal intermediate to its subse-

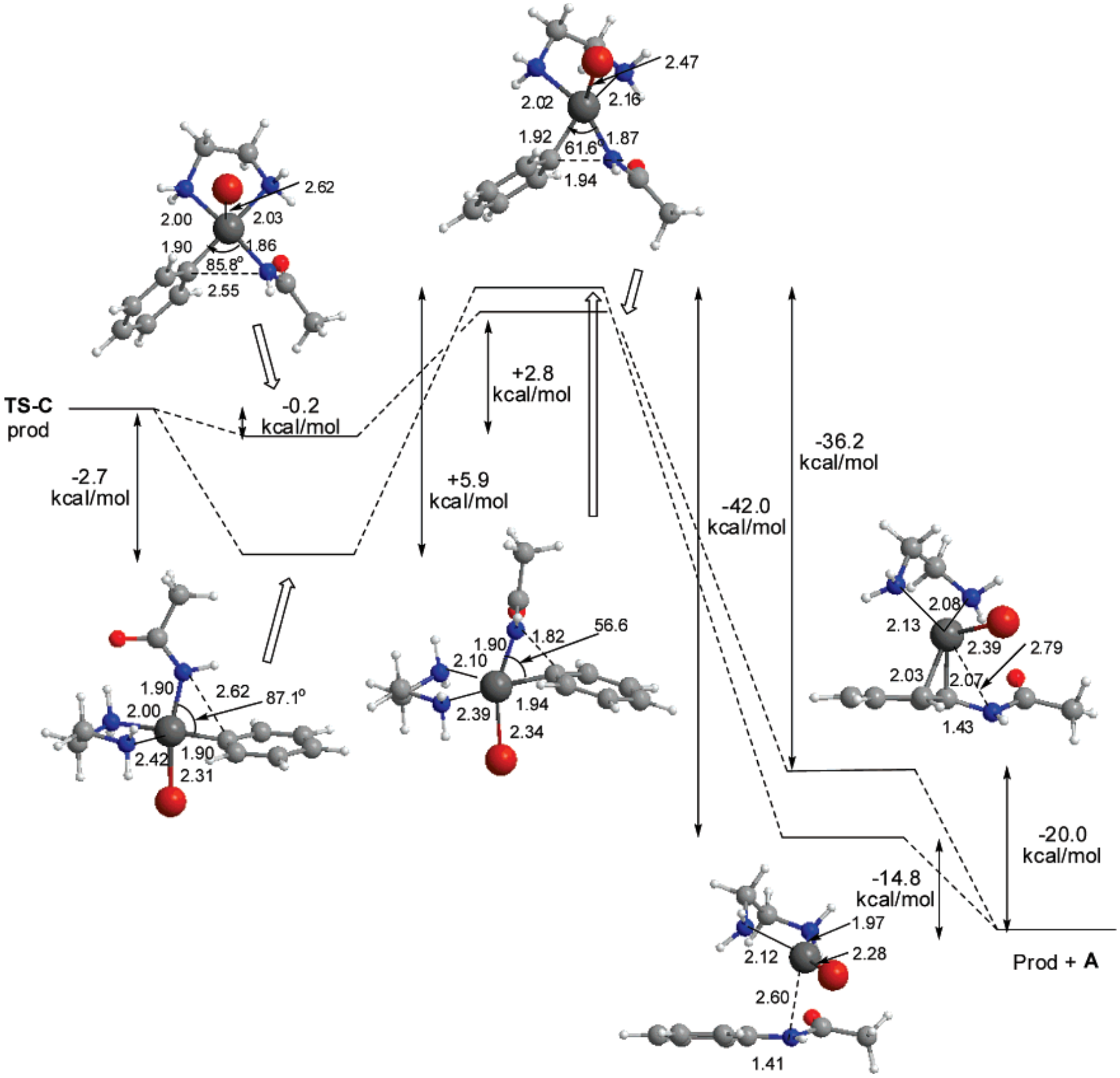


Figure 6. Reductive elimination from the Cu(III) complex in aryl amidation.

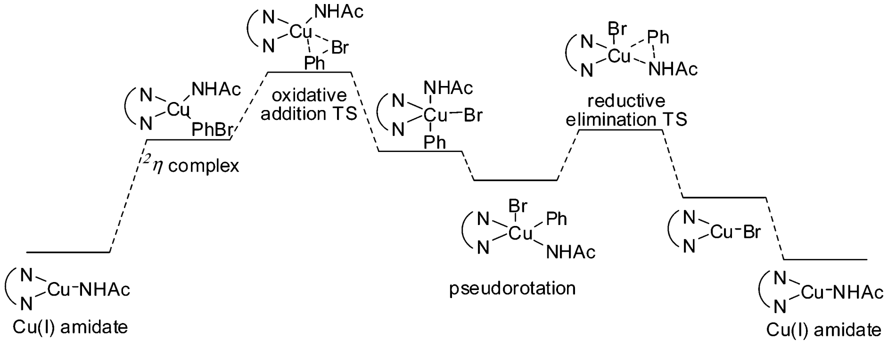


Figure 7. General mechanism for Cu-catalyzed aryl amidation.

quent reductive elimination transition state the free energy barrier is +2.8 kcal/mol. Combining the two energies, we conclude that the favored geometry for reductive elimination from pentacoordinated Cu(III) should have a square pyramidal conformation. The corresponding barrier is +2.6 kcal/mol as calculated from the immediate product of **TS-C**. Compared to oxidative addition whose transition state (i.e., **TS-C**) is +6.1 kcal/mol higher in free energy than the immediate product of **TS-C** (see Figure 4), the reductive elimination is evidently not the rate-limiting step in the overall catalytic cycle. Thus, it is concluded at this point that the rate-limiting step in Cu(I)-catalyzed aryl amidation reactions should be the oxidative addition of aryl halide to copper(I) amidate.

Due to the formation of a new C−N bond, the reductive elimination step has a highly negative reaction free energy. The immediate product of the reductive elimination is a $^2\eta$ Cu(I) complex with *N*-phenylacetamide. Subsequent dissociation of this $^2\eta$ complex ends up with CuBr ligated by the diamine (i.e., complex **A**) and free *N*-phenylacetamide. This is the end of a full catalytic cycle, where complex **A** can interact with acetamide to initiate a new catalytic cycle.

4. Effects of Different Diamine Ligands

The above results support the mechanism where the copper(I) amidate is the reactive intermediate and its oxidative addition to phenyl halide is the rate-limiting step (Figure 7). Because copper(I) amidate is found to have the lowest free energy in the catalytic cycle, the observed catalytic efficiency should be determined by the free energy change from Cu(I) to the oxidative addition transition state. Assuming that the concentration of the copper(I) amidate concentration is 0.1 mol/L ([PhBr] = [AcNH$_2$] = 1.0 mol/L as aforementioned), we can calculate the reaction rate as

$$v = 0.1\frac{k_\mathrm{B}T}{h}\exp\frac{-28.7}{RT} = 5.2 \times 10^{-2}\ \mathrm{mol/(L{\cdot}min)} \quad (3)$$

where $k_\mathbf{B}$ is the Boltzmann constant and h is Planck's constant (−28.7 kcal/mol is the overall free energy barrier). Remarkably, the magnitude of the estimated rate value is very close to that of Buchwald's experimental rates, which are about 0.01−0.02 M/min in the presence of 0.02 M Cu(I) and 0.1−0.3 M diamine ligand.[14]

To further test the validity of our theoretical mechanism, we compare the effects of several different diamine ligands in Cu-catalyzed aryl amidation reaction. Buchwald and co-workers reported in 2002 that, among the several diamines, the *N*,*N*′-dimethyldiamines were the most effective ligands.[18] They were followed by unsubstituted diamines, which were found less reactive. Furthermore, tetramethyldiamines such as TMEDA were demonstrated to be completely inactive ligands. On the basis of these observations, Buchwald and co-workers suggested that the role of a chelating diamine ligand could simply be to increase the stability constant of the catalytically active copper−amine complex.

Our calculation results are in agreement with Buchwald's proposition but with considerably more details. As shown in Table 2, it is found that the stability of the copper(I) amidate is greatly affected by the diamine ligand. *N*,*N*′-Dimethyldiamines provide the most stable copper(I) amidate, whereas the tetramethyldiamine leads to the most unstable copper(I) amidate. These observations can be explained by the balance between the electronic and steric effects of the methyl groups. Because the methyl group is electron donating, the electronic effect of the methyl substitution favors the formation of copper(I) amidate. On the other hand, excessive methyl substitution will resulti in a very crowded Cu complex which is not energetically favored.

The steric effect of the methyl substitution is also manifested by the stability of the $^2\eta$ complex between copper(I) amidate and phenyl bromide. As shown in Table 2, the $^2\eta$ complexes carrying unsubstituted diamine ligands have the lowest formation free energy, whereas the $^2\eta$ complex carrying TMEDA is the least stable. Furthermore, as for the free energy from the $^2\eta$ complex to the oxidative addition transition state, our calculation indicates that unsubstituted ethylenediamine gives the lowest free energy whereas TMEDA gives the highest free energy. This result can again be explained as a result of the balance between the electronic and steric effects of the methyl groups.

The overall free energy barrier is calculated as the sum of the free energies for the formation of copper(I) amidate, the formation of the $^2\eta$ complex, and the oxidative addition to the $^2\eta$ complexes. From the overall free energy barrier we can readily estimate the relative reactivity by using eq 2. As shown in Table 2, the highest reactivity is achieved by using *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine as the ligand, which is 35-fold more reactive than unsubstituted ethylenediamine. This is followed by *N*,*N*′-dimethylethylenediamine, which is about 8-fold more reactive than ethylenediamine. The relative reactivity of *trans*-cyclohexane-1,2-diamine is 0.22 as compared to the reactivity of ethylenediamine. Finally, the relative reactivity of TMEDA is as low as 1.1×10^{-5}.

Noteworthy, for the cross-coupling between 1-bromo-3,5-dimethylbenzene and pyrrolidin-2-one, Buchwald and co-workers reported yields of about 13%, 89%, 14%, 93%, and 0% for ethylenediamine, *N*,*N*′-dimethylethylenediamine, *trans*-cyclohexane-1,2-diamine, *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine, and TMEDA under the same reaction conditions.[18] Our calculation results are in good agreement with these observa-

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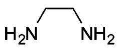
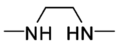
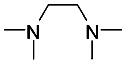
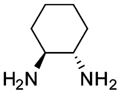
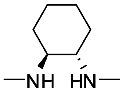
[18] Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

Table 2. Comparison of the Reactivities of Different Diamine Ligands[a]

Diamine	Free energy (kcal/mol)				Relative reactivity
	formation of Cu(I) amidate	formation of $^2\eta$ complex	from $^2\eta$ complex to oxidative addition TS	overall free energy barrier	
	-2.1	24.9	3.8	26.6	1.0
	-4.7	25.4	4.4	25.0	8.8
	+1.0	27.2	6.6	34.8	1.1×10^{-5}
	-1.9	24.0	5.6	27.7	0.22
	-6.6	26.2	4.4	24.0	36

[a] Note that (a) the free energy is calculated by using complex **A** as the reference compound (i.e., its free energy is fixed to be zero) and (b) the relative reactivity is calculated using eq 2.

tions, except that the calculated reactivity of *trans*-cyclohexane-1,2-diamine is predicted to be lower than that of ethylenediamine. This agreement between the predicted ligand effects and the experimental observations further supports the validity of the mechanism proposed in the present study.

5. Summary

Cu-catalyzed aryl amidation is a practical and efficient method for the construction of aryl C−N bonds in both academic and industrial laboratories. Although considerable synthetic as well as kinetic experimental studies have been conducted to optimize and to understand this transformation, no theoretical examination has been performed to examine any Cu-catalyzed cross-couplings. Here we utilize the density functional theory method augmented with the CPCM solvation model to study the Cu(I)-catalyzed cross-coupling between phenyl bromide and acetamide. The following conclusions can be made on the basis of our work.

(1) Diamine-ligated copper(I) amidate is the most reactive intermediate in the reaction mixture for the oxidative addition to aryl halide. Cationic diamine-ligated Cu(I) has a lower free energy barrier for oxidative addition, but its concentration in the reaction mixture is too low to represent a useful catalyst. On the other hand, multiple ligation of the amide to Cu(I) at low diamine concentration leads to the least reactive intermediate and, thereby, retards the oxidative addition.

(2) Oxidative addition is the rate-limiting step in Cu-catalyzed aryl amidation. Unlike the transformation from Pd(0) to Pd(II), the Cu(I) → Cu(III) oxidative addition yields a pentacoordinated complex which is, thereby, more sensitive to the steric hindrance. A major portion of the overall energy barrier in the oxidative addition to Cu(I) is contributed by the highly unfavorable formation of a $^2\eta$ complex between copper(I) amidate and aryl halide.

(3) Reductive elimination occurs through a square pyramidal structure from the pentacoordinated Cu(III) intermediate. Reductive elimination is a very facile step as compared to oxidative addition.

(4) Our calculation indicates that *trans-N,N′*-dimethylcyclohexane-1,2-diamine is an excellent ligand for Cu-catalyzed aryl amidation, whereas TMEDA is almost completely inactive.

These results are in good agreement with the experimental observations and, therefore, further support the validity of the proposed mechanism. They also indicate the possibility to use a combined experimental and theoretical approach to rationally improve Cu-catalyzed amidation and other types of cross-coupling reactions. We are now continuing the study in this direction.[19]

6. Computational Methodology

Ab initio calculations were performed with the Gaussian 03 suite of programs.[20] The density functional theory method with the B3LYP functional was used,[21−22] which has been demonstrated in many previous studies to be a reliable method for dealing with transition-metal complexes. All the geometries were fully optimized employing the standard 6-31G* basis set for all the atoms,[23] without any structural constraints. Harmonic force constants were computed

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(19) We recently found that amino acids had better performances than the diamine ligands in some Cu(I)-catalyzed cross-couplings between aryl halides and amides, sulfonamides, and thiols. See: (a) Deng, W.; Liu, L.; Zhang, C.; Liu, M.; Guo, Q.-X. *Tetrahedron Lett.* **2005**, *46*, 7295. (b) Deng, W.; Zou, Y.; Wang, Y.-F.; Liu, L.; Guo, Q.-X. *Synlett* **2004**, 1254.

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at the optimized geometries to characterize the stationary points as minima or saddle points. Transition states were optimized using the default Berny algorithm implemented in Gaussian 03 and further analyzed by IRC (intrinsic reaction coordinate) computations to verify that they connected the right reactants and products.

Single-point energy calculations were performed at the optimized geometries using the B3LYP/6-311+G(d,p) method. Zero-point vibrational corrections and thermal corrections to the Gibbs free energy were determined from the harmonic vibrational frequencies. To take the solvent effect into account, single-point solvent calculations were performed at the optimized gas-phase geometries for all of the intermediates and transition states using the CPCM solvation model,[24] which was an implementation of the conductor-like screening solvation model in Gaussian 03. Toluene, which is a frequently used solvent in copper-catalyzed amidation reactions, was chosen as the solvent. The UAHF (united atom Hartree−Fock) radii were used for all the atoms.

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Supporting Information Available: Detailed optimized geometries and free energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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