J|A|C|S ARTICLES

Published on Web 06/08/2009

Mechanism of Ni-Catalyzed Selective C−O Bond Activation in Cross-Coupling of Aryl Esters

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Abstract: Ni-catalyzed selective C−O bond activation opens a door for the cross-coupling of aryl esters. The present study reports a thorough theoretical analysis of Ni-catalyzed cross-coupling between aryl esters and arylboronic acids, with an emphasis on explaining the cause for the surprising selectivity in C−O activation. The overall catalytic cycle is found to include three basic steps: oxidative addition, transmetalation, and reductive elimination. Oxidative addition of Ar−OAc to Ni(0) in the presence of PCy_3 ligand proceeds through the monophosphine pathway (instead of the alternative two-phosphine pathway) with a relatively low barrier of +22.9 kcal/mol. Transmetalation proceeds *via* a base-assisted mechanism with a barrier of +31.2 kcal/mol. Reductive elimination is the most facile step in the whole catalytic cycle. Comparatively, oxidative addition of ArO−Ac to Ni(0) is a more facile process (barrier = +14.2 kcal/mol) than oxidative addition of Ar−OAc to Ni(0). However, the former process is associated with a fairly low reverse barrier, and its product does not transmetalate easily (barrier = +33.1 kcal/mol). By comparison, the latter process is an irreversible reaction, and its product transmetalates more readily. These results explain why only the cross-coupling products from the Ar−OAc activation (but not from the ArO−Ac activation) were observed in experiments.

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1. Introduction

Transition metal catalyzed C−C and C−heteroatom cross-couplings present important tools in modern synthesis.[1] These reactions have fundamentally affected the logic of chemical synthesis and provided robust, practical solutions for the synthesis of organic intermediates, pharmaceuticals, and fine chemicals even on the industrial scale.[2] Well-established cross-couplings include the Kumada−Corriu coupling, Heck olefination, Suzuki coupling, Stille coupling, Negishi coupling, Sonogashira coupling, Tsuji−Trost reaction, and Buchwald−Hartwig amination.[3] They are usually conducted with Pd or Ni catalysts, where aryl (or alkenyl) iodides and bromides are common substrates.

A recent advance has been the attempt to use less expensive substrates in the cross-couplings. Extensive efforts have been made toward the use of aryl chlorides[4] and aryl ethers.[5−8] However, not all the aryl chlorides or ethers are readily available, and they may not be the best starting materials for certain transformations. Comparatively, direct use of aryl esters in the cross-coupling may provide a more appealing synthetic method because of the following reasons: (1) aryl esters can be readily synthesized and are much less expensive than aryl halides or sulfonates; (2) the avoidance of using halides causes less environmental problems in large scale productions; (3) aryl esters may also offer orthogonal groups to aryl halides on a molecule that can be selectively functionalized.

Nonetheless, the use of aryl esters in the cross-couplings presents several challenges. The most significant challenge is to selectively activate the relatively strong Ar−O bond in the presence of a much more reactive carbonyl C−O bond (Figure 1). To overcome this problem Shi[9] and Garg[10] recently discovered that $Ni(PCy_3)_2Cl_2$ can selectively catalyze the cross-coupling of aryl carboxylates with aryl boroxines (or aryl boronic acids) to make biaryls. This finding not only offers a novel synthetic tool for the synthesis of biaryls from aryl esters

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[‡] University of Science and Technology of China.

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(3) For a compilation of accounts on cross-coupling reactions, authored by some pioneers in the field, see: *J. Organomet. Chem.* **2002**, *653*, 1−303.

(4) Representatively examples: (a) Böhm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1602. (b) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (d) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (e) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373.

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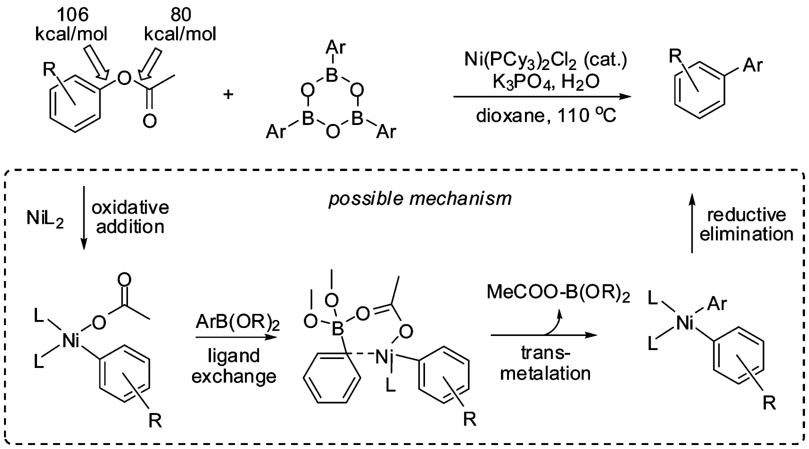
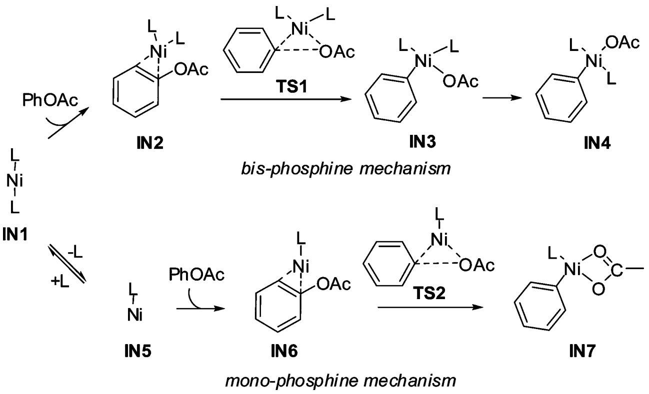


Figure 1. Ni(PCy$_3$)$_2$Cl$_2$-catalyzed cross-coupling between aryl acetates and aryl boroxines. “106” and “80” are bond dissociation energies of the two C−O bonds.

but also shows the intriguing power of transition metal mediated catalysis to manipulate traditionally “inert” chemical bonds.

The remarkable selectivity in the Ni-catalyzed activation of the C−O bond of aryl esters poses an interesting question as to the mechanism of this novel transformation. Although a plausible mechanistic pathway was proposed (Figure 1),[9,10] many details have not been examined. These include the following: (1) How does each of the catalytic steps take place? (2) Which step is rate determining in the catalytic cycle? (3) Why does oxidative addition occur selectively to activate the stronger Ar−O bond? (4) Why is Pd unable to compete with Ni in this chemistry? Answers to these questions not only improve understanding of transition metal catalyzed C−O bond activation but also may shed light on how to design more powerful catalysts to handle more “inert” chemical bonds.

Scheme 1



2. Full Catalytic Cycle

Recently the mechanism of Pd-catalyzed Suzuki coupling has been extensively studied, in particular by the Sakaki, Thiel, and Maseras groups.[11−13] We examined the mechanism of Ni-catalyzed Heck reactions.[14] Lin and Phillips studied Ni-catalyzed Negishi coupling.[15] Nakamura et al. studied the ligand exchange and oxidative addition steps in the Ni-catalyzed Kumada−Tamao−Corrie reaction.[16,17] On the basis of these studies we propose that Ni-catalyzed cross-coupling between aryl acetates and aryl boroxines should proceed through a catalytic cycle involving three basic steps: (1) oxidative addition of C−O bond to Ni(0); (2) transmetalation from boron to Ni; and (3) reductive elimination with regeneration of the Ni(0) catalyst. In the following we will examine this three-step mechanism in detail with the standard B3PW91 method (Scheme 1), where the solvent effect is handled by the IEF-PCM method.[18] The advantages of using the B3PW91 functional to study Ni chemistry were demonstrated in a number of recent studies.[19]

2.1. Oxidative addition. In the experiments the catalyst precursor was Ni(PCy$_3$)$_2$Cl$_2$, and it was proposed to be reduced in the presence of arylboroxines to produce the active catalytic species Ni(0).[9,10] This poses a question of whether the two phosphine ligands stay attached to the Ni center throughout the

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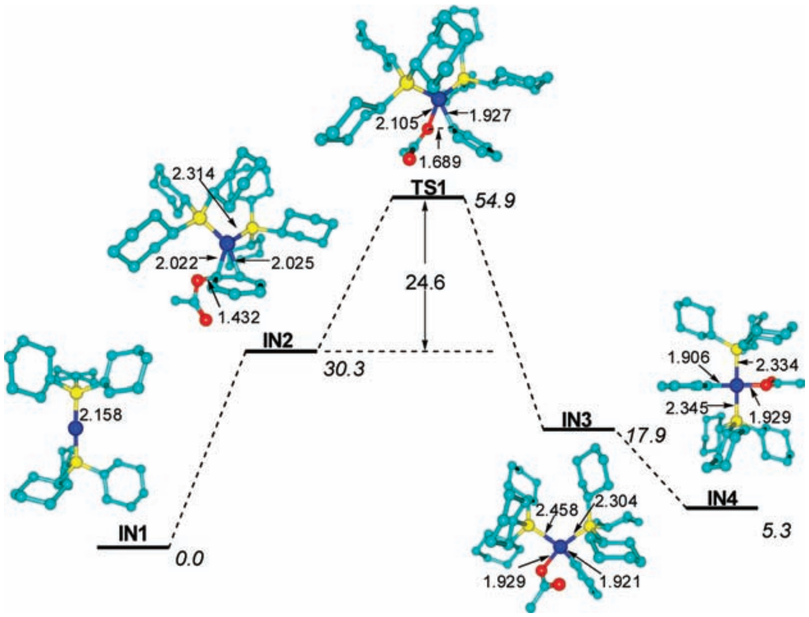

Figure 2. Energy profile for the bis-phosphine mechanism (Unit: kcal/mol). Green balls denote C, yellow balls denote P, blue balls denote Ni, and red balls denote O.

catalytic cycle (Scheme 1). Previous experimental[20] and theoretical[21] studies suggested that, in Pd(0)-catalyzed cross-coupling, monoligated Pd(0) should be catalytically more active. Less has been known in cases of Ni chemistry.

2.1.1. Bis-phosphine Mechanism. This mechanism starts with a bis-ligated Ni(0) intermediate **IN1**. The approach of PhOAc toward **IN1** leads to the formation of an η^2 complex **IN2** (Figure 2). From **IN2** a three-membered-ring transition state **TS1** is indentified for the oxidative addition. The overall barrier from **IN1** to **TS1** is +54.9 kcal/mol. The immediate product of oxidative addition is a four-coordinated *cis*-Ni(II) complex **IN3**. This complex can isomerize to the more stable, square planar *trans*-Ni(II) intermediate **IN4**. Maseras et al. previously studied the possible mechanism of the *cis*−*trans* isomerization for related Pd(II) species.[11e] It was concluded that such isomerization might occur easily through either phosphine dissociation or association of an external ligand. It is safe to assume that the energy barrier for the isomerization is fairly low in the overall cross-coupling process.

2.1.2. Monophosphine Mechanism. To directly compare with the bis-phosphine mechanism, the free energy profile for the monophosphine mechanism is also calculated relatively to $Ni(0)(PCy_3)_2$. As shown in Figure 3, removal of one PCy_3 ligand from **IN1** gives a monoligated Ni(0) species **IN5** with a positive energy of +10.5 kcal/mol. Coordination of **IN5** with PhOAc generates an η^2 complex **IN6**. In **IN6** the distance between Ni and one of the carboxyl oxygens is 2.143 Å, indicating the presence of a weak coordination interaction. The free energy of **IN6** is 0.8 kcal/mol higher than that of **IN1**. From **IN6** a three-membered-ring transition state **TS2** is indentified for the oxidative addition. The overall barrier from **IN1** to **TS2** is +22.9 kcal/mol. This free energy barrier is much lower than that for the bis-phosphine mechanism (+54.9 kcal/mol). Therefore, oxidative addition of PhOAc to $Ni(0)(PCy_3)_2$ prefers the monophosphine mechanism. Similar observations have been reported for Pd-catalyzed couplings.[20,21]

The immediate product of the oxidative addition is a Ni(II) complex **IN7**, where both of the carboxyl oxygens are coordinated to the Ni center. **IN7** is more stable than **IN1** by −30.3 kcal/mol. **IN7** is also more stable than **IN4** by 35.6 kcal/mol. Note that **IN7** and **IN4** can readily transform into each other through phosphine association or dissociation and, therefore, they both may enter the ensuing transmetalation step.

2.2. Transmetalation. In Pd-catalyzed couplings many studies have shown that the starting point for transmetalation should be a Pd(II)monophosphine complex.[22] For the present Ni-catalyzed reaction our results support this mechanism. In careful searches starting from various geometries, we cannot find any reaction pathway for the addition of phenylboronic acid to a coordinatively saturated Ni(II)diphosphine compound, such as **IN4**. In contrast, we can readily find several possible reaction channels for the transmetalation of Ni(II)monophoshpine complex **IN7**.

2.2.1. Base-Free Transmetalation. Base-free transmetalation takes place in two steps (Scheme 2). In the first step phenylboronic acid coordinates to **IN7** to form intermediate **IN8** through an η^2 coordination mode. Interaction between one of the carboxyl oxygens and boron is also observed in **IN8**. The second step corresponds to the transmetalation itself, with the acetate migrating from Ni to B centers and the phenyl group becoming exclusively bonded to Ni. Two possible transition states (**TS3a** and **TS3b**) are located. Their energies relative to **IN7** are +59.0 kcal/mol for **TS3a** and +54.7 kcal/mol for **TS3b**. Evidently, transmetalation is too energy demanding in the absence of base.

2.2.2. Base-Assisted Transmetalation. In the presence of an appropriate base and water, organoboronic acid exists in equilibrium

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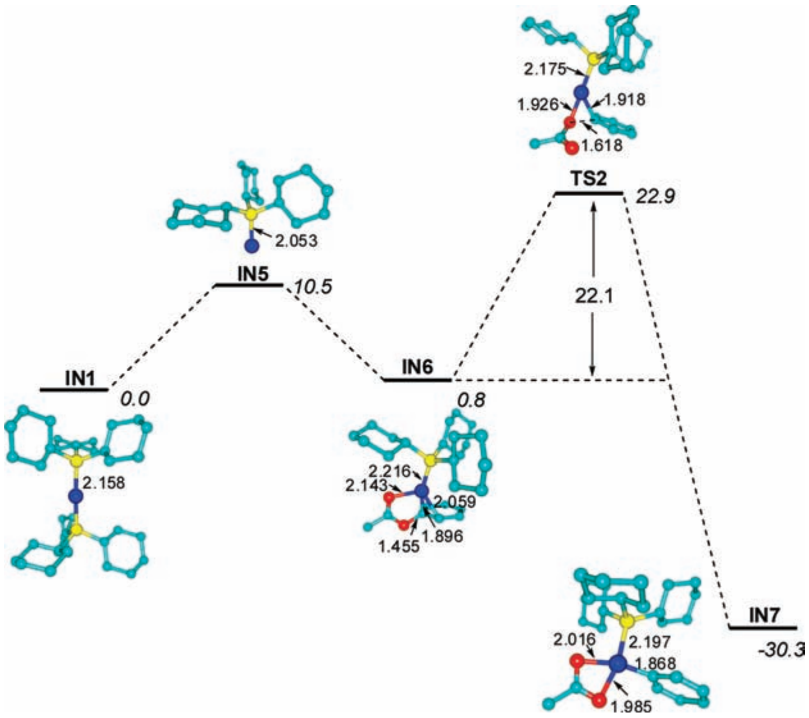
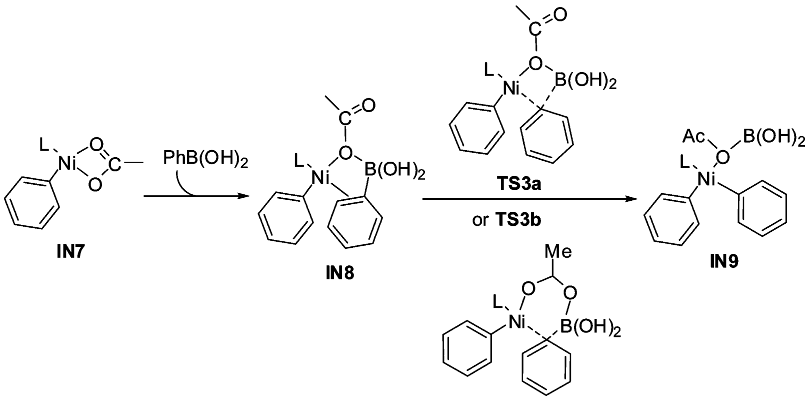


Figure 3. Energy profile for the monophosphine mechanism (Unit: kcal/mol). Green balls denote C, yellow balls denote P, blue balls denote Ni, and red balls denote O.

Scheme 2



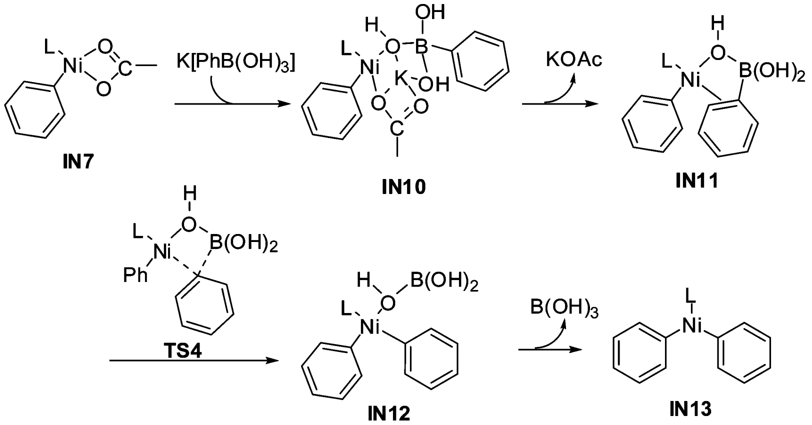
with the ArB(OH)$_3^-$ anion. It has been proposed in a number of theoretical studies that ArB(OH)$_3^-$ is the actual species entering transmetalation of Pd-catalyzed cross-couplings.[11] Here we use the same assumption for the Ni-catalyzed reaction with a slight modification. That is, to avoid charged species in organic solvent we use K[PhB(OH)$_3$] instead of PhB(OH)$_3^-$. The reason for this change is twofold: (1) a free charged species may not exist in less polar organic solvents such as dioxane; (2) it remains difficult to accurately calculate the solvation free energy of a charged species in organic solvent.[23] Furthermore, the free energy change of the following reaction is calculated to be −7.3 kcal/mol in solution, which further supports the use of K[PhB(OH)$_3$] as the nucleophile.

$$K_3PO_4 + H_2O + PhB(OH)_2 \rightarrow K[PhB(OH)_3] + K_2HPO_4 \qquad (1)$$

With K[PhB(OH)$_3$] as the base, the transmetalation process is found to be composed of four elementary reactions (Scheme 3): (a) coordination of K[PhB(OH)$_3$] to **IN7** forming **IN10**; (b) dissociation of KOAc from **IN10** with the formation of a tetracoordinated Ni complex **IN11**; (c) the transmetalation itself to produce **IN12**; and (d) dissociation of B(OH)$_3$ from **IN12** to generate a tricoodinated Ni complex **IN13**. Most of the steps correspond to direct ligand association and dissociation and, therefore, should not have large barriers.

As shown in Figure 4, after coordination of K[PhB(OH)$_3$] to **IN7** the potassium cation is coordinated by one of the B−OH groups and both of the carboxyl oxygens to form **IN10**. The free energy of **IN10** is −4.4 kcal/mol. After the removal of KOAc from Ni, a tetracoordinated Ni complex **IN11** is indentified in which phenylboronic acid is bonded to Ni through one of the B−OH groups and C1 carbon. In **IN11** the C1 carbon prefers to occupy the position *trans* to PCy$_3$, presumably to minimize the steric repulsion. From **IN11** the real transmetalation transition state (i.e., **TS4**) can be readily found, whose structure is consistent with the classical four-center transition state mechanism.[11b,c] The free energy of **TS4** is +31.2 cal/mol relative to **IN7**. This energy barrier is much lower than that of base-free transmetalation (+54.7 kcal/mol). Note that in the experimental study the Ni-catalyzed reaction was carried out

Scheme 3



at 80−110 °C, an observation that can be translated to a free energy barrier of *ca.* 30 kcal/mol.[24] Thus the base-assisted transmetalation is more consistent with the experiment.

2.3. Reductive Elimination. The immediate product of transmetalation is a tetracoordinated Ni complex **IN12**, which can discharge $B(OH)_3$ to generate a tricoordinated intermediate **IN13**. Reductive elimination from **IN13** proceeds through a tricoordinated transition state **TS5**. The free energy of **TS5** is only +6.0 kcal/mol higher than that of **IN13**, indicating that reductive elimination is a very facile step. The immediate product of reductive elimination is the monoligated Ni complex **IN5**, which should exist in equilibrium with **IN1**.

2.4. Overall Mechanism. The mechanism of the full catalytic cycle includes three major steps: oxidative addition, transmetalation, and reductive elimination. The corresponding energy profiles for the three major steps are depicted in Figure 6. In oxidative addition the transition state with the highest free energy is **TS2** corresponding to oxidative addition of monoligated Ni(0) to PhOAc. The energy barrier is +22.9 kcal/mol as calculated from bis-ligated Ni(0). In the transmetalation step, the transition state with the highest free energy is **TS4**. The energy barrier is +31.2 kcal/mol as calculated from **IN7**, a noticeably stable intermediate in the full catalytic cycle. Finally, reductive elimination is found to be a very facile step. The free energy change of the overall reaction is −49.2 kcal/mol.

The results indicate that transmetalation is the rate-limiting step of the catalytic cycle. This argument appears to be supported by the following observations: (1) The energy barrier of transmetalation (+31.2 kcal/mol) is consistent with the temperature required for the transformation (i.e., 80−110 °C).[9,10] (2) Substituents on the boronic acids exert some effects on the efficiency of the transformation. Electron-deficient substituents tend to require higher reaction temperatures, whereas electron-rich ones do the opposite.[9,10] (3) Recently Shi et al. reported the Ni-catalyzed cross-coupling of aryl esters with organozinc

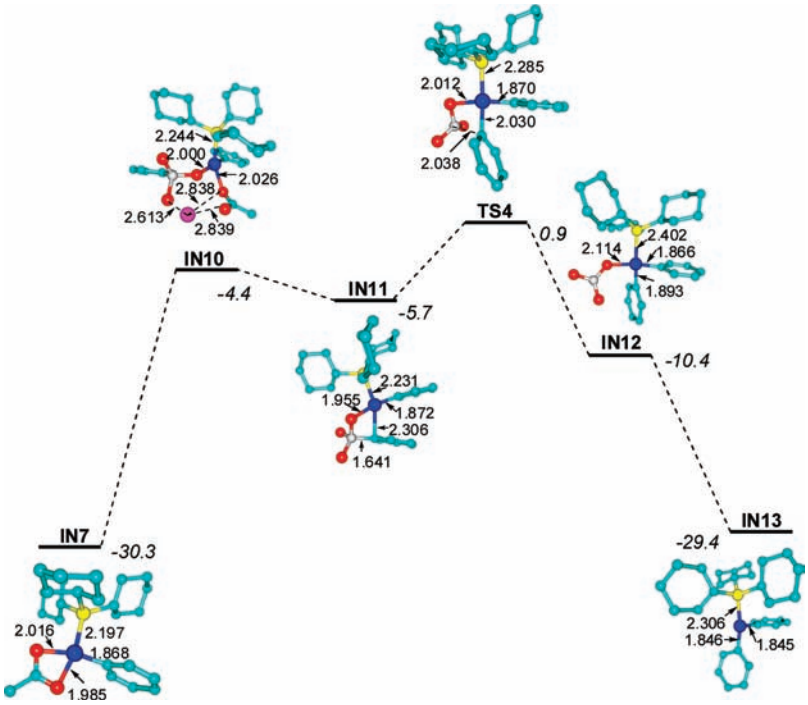


Figure 4. Energy profile for base-assisted transmetalation (Unit: kcal/mol). Green balls denote C, yellow balls denote P, blue balls denote Ni, and red balls denote O.

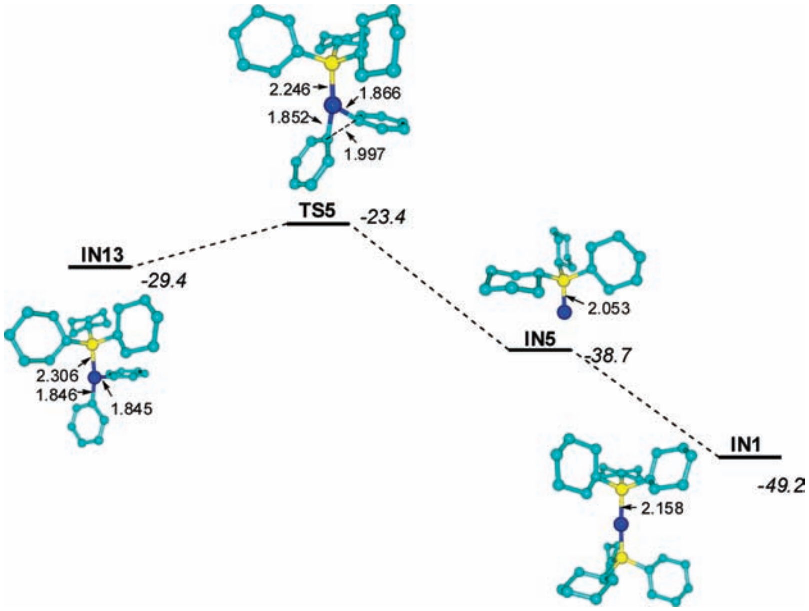


Figure 5. Energy profile for reductive elimination (Unit: kcal/mol). Green balls denote C, yellow balls denote P, blue balls denote Ni, and red balls denote O.

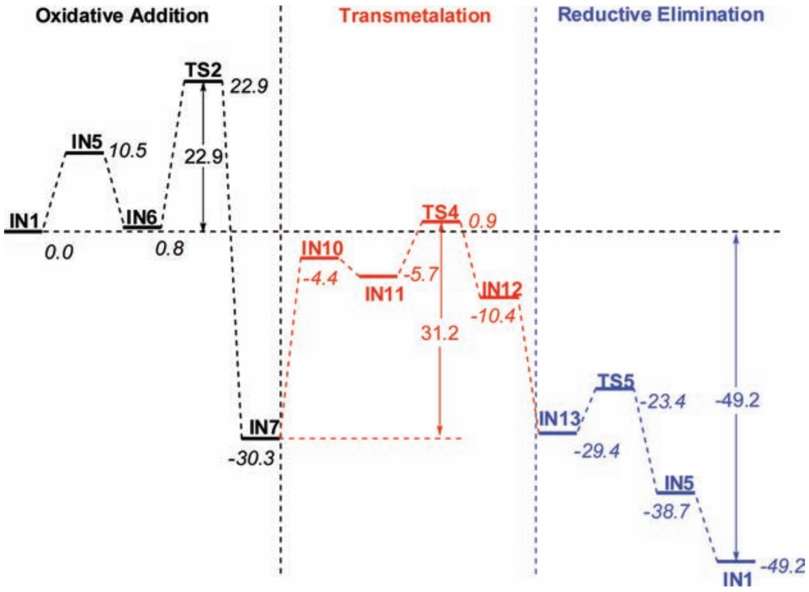


Figure 6. Energy profile for the overall catalytic cycle.

reagents under much milder conditions (*ca.* 50−70 °C).[25] Compared to Ni-catalyzed cross-coupling of aryl esters with arylboronic acids (which has to be performed under *ca.* 110 °C), it is more likely that transmetalation instead of C−OAc activation is the rate-limiting step.

3. Discussion

3.1. Oxidative Addition through Electron Transfer. In the above section, oxidative addition to Ni(0) has been assumed to proceed through a concerted, three-center addition mechanism. The same mechanism was recently examined by Nakamura et al. in their study on Ni-catalyzed cross-coupling of aryl halides with Grignard reagents.[16] Nonetheless, in some earlier studies on oxidative addition of organohalogen compounds to zerovalent d^{10} complexes, a different mechanism was proposed involving multistep successions of one-electron transfers and paramagnetic intermediates.[26] Recently Vivic and co-workers also provided evidence for Ni(I) species in the catalytic cross-coupling of alkyl iodides and bromides.[26]

To examine the possibility of oxidation addition through electron transfer in the present catalytic system, we have calculated the free energies of four reactions in solution (Scheme

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[23] (a) Fu, Y.; Shen, K.; Liu, L.; Guo, Q. X. *J. Am. Chem. Soc.* **2007**, *129*, 13510. (b) Qi, X. J.; Liu, L.; Fu, Y.; Guo, Q. X. *Organometallics* **2006**, *25*, 5879.

[24] We estimate the barrier value from the Eyring equation, i.e., $k = (k_BT/h)\exp(-\Delta G^{\ddagger}/RT)$, where k is rate constant, k_B is Boltzmann's constant, h is Planck's constant, $\Delta G^{\ddagger}$ is the activation free energy, R is the gas constant, and T is the temperature. Assuming the concentration of each reactant is 1 mol/L and the second-order rate constant k of a reaction whose half life is 24 h is 1.2×10^{-5} L/mol·s, we obtain$-\Delta G^{\ddagger}$ is 30.4 kcal/mol at 100 °C.

[25] Li, B.-J.; Li, Y.-Z.; Lu, X.-Y.; Liu, J.; Guan, B.-T.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 10124.

Scheme 4

	ΔG (kcal/mol)
$Ni(PCy_3)_2 + PhOAc \longrightarrow Ni(PCy_3)_2^{\bullet+} + PhOAc^{\bullet-}$	+44.4
$Ni(PCy_3)_2 + PhCl \longrightarrow Ni(PCy_3)_2^{\bullet+} + PhCl^{\bullet-}$	+46.5
$Ni(PCy_3)_2 + PhBr \longrightarrow Ni(PCy_3)_2^{\bullet+} + PhBr^{\bullet-}$	+18.4
$Ni(PCy_3)_2 + PhI \longrightarrow Ni(PCy_3)_2^{\bullet+} + PhI^{\bullet-}$	+12.4

4). These free energies can be used to estimate the ease of electron transfer. It is found that the electron transfer of PhOAc is slightly easier than PhCl but much more difficult than PhI and PhBr. In Kochi's study Ni(I) (as produced from direct electron transfer) was observed in large quantity when Ni(0) was treated with ArI.[25] However, with ArBr only a small amount of Ni(I) was produced, whereas with ArCl no Ni(I) was observed. The calculated free energy changes in Scheme 4 are in good agreement with Kochi's experiments. Thus we conclude that ArCl and ArOAc should prefer the concerted, three-center addition mechanism as shown in Scheme 1, although ArI and ArBr may induce the electron-transfer pathway in the oxidative addition to Ni(0).

3.2. Selectivity in C—O Bond Activation. In the cross-coupling of aryl esters, there are two C—O bonds that can be activated (Figure 1). Because the Ar—O bond is much stronger than the carbonyl C—O bond by *ca.* 20 kcal/mol,[28] it is important to ask why the former can be selectively activated by Ni. To address this problem we have examined the possible reaction pathway that involves the activation of the carbonyl C—O bond. The energy profile of this pathway, as compared to the Ar—O bond activation pathway, is shown in Figure 7.

It is found that monoligated Ni(0) can form a complex (**IN14**) with the carbonyl C═O bond. This complex is less stable than the Ni(0) complex with the phenyl ring by 0.1 kcal/mol. Oxidation addition of Ni(0) to the PhO—Ac bond proceeds through a three-center transition state (**TS6**). **TS6** (+14.2 kcal/mol) is much lower in energy than **TS2** (+22.9 kcal/mol). This observation can be readily explained by the Ar—O bond being much stronger than the carbonyl C—O bond by *ca.* 20 kcal/mol.

The immediate product of oxidation addition to the PhO—Ac bond is a three-coordinated Ni(II) complex **IN15**. It is important to notice that **IN15** (−11.5 kcal/mol) is much less stable than **IN7** (−30.3 kcal/mol). The large energetic difference between **IN15** and **IN7**, together with the large energetic difference between **IN7** and **TS2**, produces the following outcomes: (1) oxidative addition of PhO—Ac to Ni(0) is a readily *reversible* reaction, whose forward and reverse barriers are +14.2 and +25.7 kcal/mol, respectively; (2) oxidative addition of Ph—OAc to Ni(0) is an *irreversible* reaction, whose forward and reverse barriers are +22.9 and +53.2 kcal/mol, respectively.

From **IN15** we can find the transmetalation intermediates (**IN16**, **IN17**) and transition states (**TS7**) parallel to those starting from **IN7**. The free energies of all these transmetalation intermediates and transition states are considerably higher than those described in section 2.2 by *ca.* 10−20 kcal/mol. In particular, the energy difference between **IN15** and **TS7** (+33.1 kcal/mol) is larger than that between **IN7** and **TS4** (+31.2 kcal/mol) by *ca.* 2.0 kcal/mol. All these observations suggest that transmetalation from **IN15** is more difficult as compared to transmetalation from **IN7**.

Putting the results together we conclude that oxidative addition of PhO—Ac to Ni(0) is a more facile process than oxidative addition of Ph—OAc to Ni(0). However, the former process is associated with a fairly low reverse barrier, and its product does not transmetalate easily. By comparison, the latter process is an irreversible reaction, and its product transmetalates more readily. These results explain why only the cross-coupling products from the Ar—OAc activation were observed.

3.3. Possible Involvement of Nickel Carbonyls. In an early study by Yamamoto et al.,[29] zerovalent Ni complexes were found to promote cleavage of C—O bonds in phenyl carboxylates to give Ni(II) complexes such as nickel carbonyls and nickel phenoxide and other gaseous and liquid products (Scheme 5). This experimental observation is consistent with our calculation result that the RCO—OR′ bond (instead of the RCOO—R′ bond) in carboxylic esters can be selectively cleaved under mild conditions through oxidative addition. Here we explain why decarbonylation from the RCO—OR′ activation intermediate (i.e., **IN15** shown in Figure 8) does not cause a problem in the recently reported cross-coupling reactions.[9,10]

As shown in Figure 8, it is found that decarbonylation from **IN15** (through **TS8**) has an energy barrier of +18.8 kcal/mol. The product of decarbonylation is a four-coordinated Ni(II) complex (**IN18**). Reductive elimination from **IN18** to give PhOMe (through **TS9**) is found to have a very high energy barrier of +37.8 kcal/mol (or +48.8 kcal/mol as calculated from **IN15**). Transmetalation of **IN18** with phenylboronic acid is prohibited because **IN18** is coordination saturated.

Alternatively **IN18** may lose a molecule of CO to produce intermediate **IN19**. This step has a positive free energy of +0.3 kcal/mol. Reductive elimination from **IN19** to produce a carbon—oxygen bond (through **TS10**) is also found to have a very high energy barrier of +50.4 kcal/mol. Furthermore, transmetalation of **IN19** with phenylboronic acid has a very high energy barrier of +43.4 kcal/mol.

Putting the above data together, we conclude that nickel carbonyls may be produced in Ni-catalyzed transformations of aryl esters. However, nickel carbonyls cannot be easily transformed to any decomposition products, so that the alternative pathway for the Suzuki-type cross-coupling is favored and observed in the experiment.[9,10] This conclusion does not conflict with the experiment of Yamamoto and co-workers,[29] because in their experiment there was no boronic acid.

3.4. Compare the Activity of Ni and Pd. Pd was examined by Shi et al.[9] for the activation of aryl esters. The observation that only Ni, but not Pd, could catalyze the transformation poses an interesting question as to why Pd fails to activate the C—O bond. In this context we systematically calculate the free energy barriers for the oxidative addition of various C—X bonds to Ni and Pd (Table 1). To simplify the comparison we only consider the monoligated Ni(0) and Pd(0) species, which are known to be more reactive than the corresponding bis-ligated metals.[21] PMe_3 is used as ligand to represent the electron-rich phosphines,

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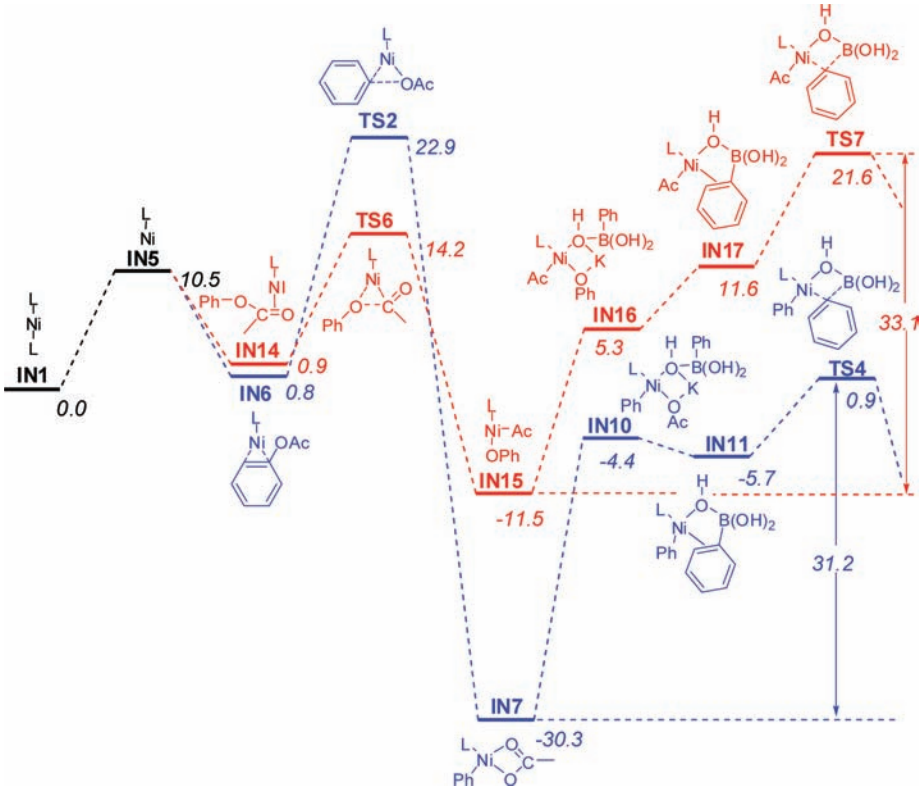
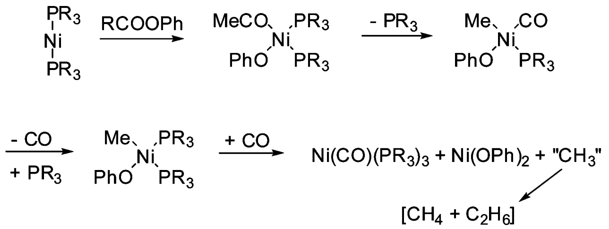


Figure 7. Compare the energy profiles for the ArO−Ac (red) and Ar−OAc (blue) activation pathways. Pathway in blue is favored (Unit: kcal/mol).

Scheme 5



although in reality a more bulky ligand[30] needs to be designed to increase the effective concentration of the monoligated species in reaction media.

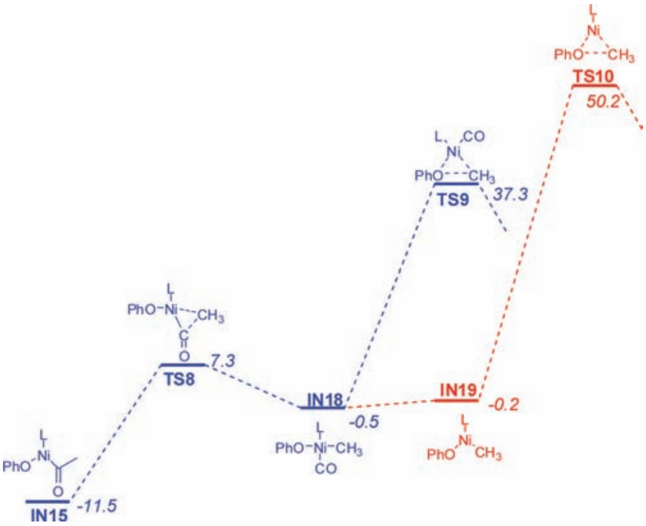
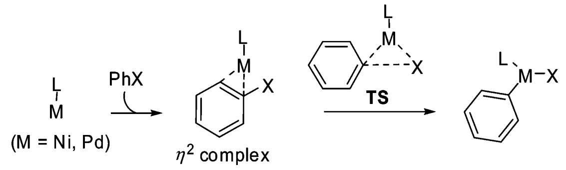


Figure 8. Possible involvement of nickel carbonyls in the transformation (Unit: kcal/mol).

Table 1. Oxidative Addition of Various Ph−X bonds to Ni(0)PMe$_3$ and Pd(0)PMe$_3$ (Unit: kcal/mol)



Ph−X	Ni(0)PMe$_3$ η^2 complex	Ni(0)PMe$_3$ TS	Ni(0)PMe$_3$ barrier	Pd(0)PMe$_3$ η^2 complex	Pd(0)PMe$_3$ TS	Pd(0)PMe$_3$ barrier
Ph−Br	−24.5	−21.2	3.3	−8.2	−4.8	3.4
Ph−Cl	−26.1	−16.5	9.6	−5.5	9.3	14.8
Ph−F	−25.9	1.8	27.7	−6.3	28.0	34.3
Ph−SAc	−26.7	−16.1	10.6	−1.9	9.5	11.4
Ph−OTf	−25.1	−20.6	4.5	−4.6	21.2	25.9
Ph−OMs	−26.1	−0.1	26.0	−3.9	24.5	28.4
Ph−OTs	−24.4	−1.0	23.4	−3.9	25.5	29.4
Ph−OAc	−23.7	2.7	26.4	−4.8	29.2	34.0
Ph−OMe	−25.4	4.2	29.5	−6.8	35.2	42.0
Ph−NHAc	−22.4	1.9	24.2	2.1	31.4	31.4

From Table 1 we find that both Ni(0)- and Pd(0)-oxidative addition reactions share the same pathway, i.e., formation of an η^2 complex followed by C−X bond activation. Formation of the η^2 complex between Ni(0) and Ph−X is highly exothermic (−22 to −27 kcal/mol). By comparison, formation of the η^2 complex between Pd(0) and Ph−X is much less so (−8 to +2 kcal/mol). These observations are consistent with Nakamura's recent study.[16]

The activation energy from the η^2 Ni-complex to the oxidative addition product increases in the order C−Br (+3.3) < C−OTf (+4.5) < C−Cl (+9.6) < C−SAc (+10.6) < C−OTs (+23.4) < C−NHAc (+24.2) < C−OMs (+26.0) < C−OAc (+26.4) <

C—F (27.7) < C—OMe (+29.5). By comparison, the activation energy from the η^2 Pd-complex to the oxidative addition product increases in the order C—Br (+3.4) < C—SAc (+11.4) < C—Cl (+14.8) < C—OTf (+25.9) < C—OMs (+28.4) < C—OTs (+29.4) < C—NHAc (+31.4) < C—OAc (+34.0) < C—F (+34.3) < C—OMe (+42.0). These trends are consistent with the available experimental observations. Evidently the Ni-mediated oxidative addition usually exhibits a lower energy barrier than the corresponding Pd-mediated process.

Note that, for Ph-OAc, Ni gives a barrier of +26.4 kcal/mol, whereas Pd's barrier is +34.0 kcal/mol. The difference between the two values suggests that Ni can more easily activate the C—OAc bond as compared to Pd. Interestingly, our calculations also show that the Ni- and Pd-catalyzed C—NHAc activations show free energy barriers of +24.2 and +31.4 kcal/mol. These values are not much higher than those for C—OAc activation, and therefore, some Ni- and Pd-catalysts may even be able to catalyze the cross-coupling of more inert substrates, i.e., aryl amides.

4. Summary

Ni-catalyzed selective activation of C—O bond opens a door for the cross-coupling reactions of aryl esters. Mechanistic studies on this newly discovered chemistry not only improve our understanding of how such interesting reactions take place but also shed important light on how to further expand their scope and utility. The present study reports the first theoretical analysis of Ni-catalyzed cross-coupling between aryl esters and arylboronic acids. As illustrated, the overall catalytic cycle is found to consist of three basic steps: oxidative addition, transmetalation, and reductive elimination. Calculations suggest that oxidative addition to Ni(0) in the presence of PCy_3 ligand should proceed through the monophosphine pathway with a barrier of *ca.* 23 kcal/mol. Transmetalation, on the other hand, proceeds *via* a base-assisted mechanism with a barrier of *ca.* 31 kcal/mol. Reductive elimination is the most facile step in the whole catalytic cycle.

The interesting selectivity between the Ar—OAc and ArO—Ac bond activations is also examined. It is found that oxidative addition of ArO—Ac to Ni(0) is a more facile process than oxidative addition of Ar—OAc to Ni(0). However, the former process is associated with a fairly low reverse barrier, and its product does not transmetalate easily. By comparison, the latter process is an irreversible reaction, and its product transmetalate more readily. These results explain why only the cross-coupling products from the Ar—OAc activation (but not from the ArO—Ac activation) were observed in experiments.

5. Computational Methodologies

All the calculations were performed with the *Gaussian03* programs.[31] The gas phase geometries of all compounds were optimized without any constraint by the density functional theory (DFT) method B3PW91[32] with the LANL2DZ+p basis set.[33] The D95v(d) basis set was used for C, H, O, B. Polarization functions were added for P ($\xi_d = 0.387$), S ($\xi_d = 0.503$), Cl ($\xi_d = 0.640$), Br ($\xi_d = 0.428$), I ($\xi_d = 0.289$), Ni ($\xi_f = 3.130$), and Pd ($\xi_f = 1.472$) to the standard LANL2DZ basis set.[34] Frequency analysis was performed after optimization to verify the minima and transition states. For compounds that had multiple conformations, efforts were made to find the lowest-energy conformation by comparing the structures optimized from different starting geometries.

Single-point electronic energies were calculated by using the B3PW91 method. The SDD[35] basis set was used for Ni, Pd, and K, and 6-311+G(2d,p) was used for other atoms. The Gibbs free energy correction from frequency calculation was added to the single-point energy to obtain the Gibbs free energy.

To calculate the solvation energies, the IEF-PCM method with the Bondi radii was used.[36] The gas-phase geometry was used for all of the solution phase calculations, as it has been demonstrated that the change of geometry by the solvation effect is usually not significant.[37] The solvation free energy was added to the gas-phase free energy to obtain the Gibbs free energy in solution. All the solution-phase free energies reported in the paper correspond to the reference state of 1 mol/L, 298 K.

Acknowledgment. This study was supported by the National Natural Science Foundation of China (No. 20602034 and 20802040).

Supporting Information Available: Cartesian coordinates of optimized structures. Detailed thermodynamic data. Full citation of ref 31. This material is available free of charge via the Internet at http://pubs.acs.org.

JA810157E

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(37) We compared the geometries optimized in gas phase and in solution for a model system, in which the PCy_3 ligand was replaced by PH_3. The results showed that both the optimized geometries and corresponding free energies were not significantly affected by the solvation (see Supporting Information).