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Mechanism of the Palladium-Catalyzed Addition of Arylboronic Acids to Enones: A Computational Study

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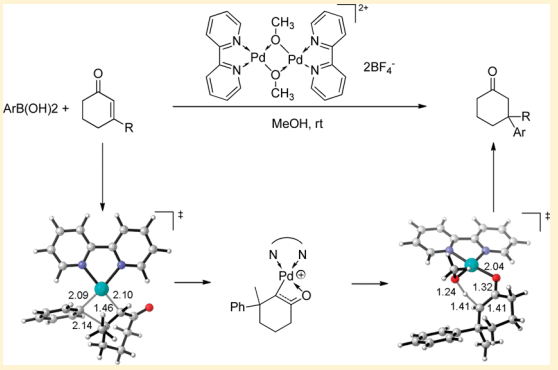
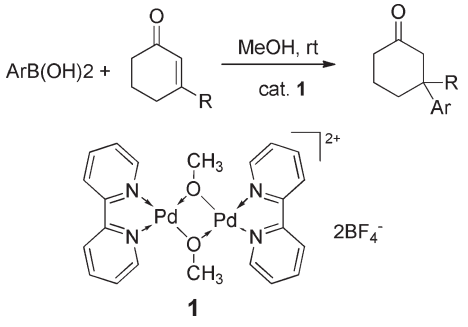
Supporting Information

ABSTRACT: The palladium(II)-catalyzed addition of arylboronic acids to β,β-disubstituted enones has been investigated with the BP86 density functional. The results show that the mechanism requires three steps: transmetalation, alkene insertion, and protonation. The alkene insertion is the rate-determining step. For unactivated alkenes, the Heck-type β-hydride elimination is more favored than protonation.



INTRODUCTION

Transition-metal-catalyzed 1,4-additions of organometallic compounds to enones have been studied for several decades.[1] Rh-catalyzed conjugate additions of organoboron,[2] -silicon,[3] and -tin reagents[4] to α,β-unsaturated carbonyl compounds were developed first. In 1981, the palladium-catalyzed 1,4-addition of ArHgCl or $SnAr_4$ to enones was reported,[5] although these reactions were of limited value because of the formation of Heck-type coupling products by β-hydride elimination.[6] In 2003, Miyaura reported a series of conjugate additions of arylboronic acids to enones, catalyzed by a cationic palladium(II)/phosphine complex.[7] Recently, Lu used the bipyridine ligand for palladium(II)-catalyzed conjugate additions of arylboronic acids to enones.[8] The Pd(II)/bipyridine-catalyzed addition of arylboronic acids to β,β-disubstituted enones takes place at room temperature, and only 0.5 mol % of Pd(II) catalyst is required.[9]



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There are no examples of reactions with alkenes with these conditions. When 3-methoxycyclohex-2-enone is used as the substrate, only 3-phenylcyclohex-2-enone is generated. The palladium(II)-catalyzed conjugate additions of arylboronic acids to enones are widely used in organic synthesis,[10] but there are few theoretical investigations of mechanism.[11] We have performed DFT calculations on the mechanism of this reaction and explained why this type of reaction cannot happen for unactivated alkenes and 3-methoxycyclohex-2-enone.

COMPUTATIONAL METHODS

BP86,[12] which can give accurate geometric and energetic results for transition metals[13] with a standard 6-31G(d) basis set (SDD basis set for palladium), was used for geometry optimizations. Solvent effects were considered by single-point calculations on the gas-phase stationary points with the integral equation formalism of the polarizable continuum model (IEFPCM).[14] All of the values given below are Gibbs free energies in methanol solvent.

RESULTS AND DISCUSSION

Figure 1 shows the free energies for the formation of the phenylpalladium compound **5** by transmetalation. The phenylpalladium complex **5** is the active catalyst in the coupling reaction. The relative free energy of complex **5** is set to zero in the subsequent calculations on the catalytic cycle summarized in Figure 2.

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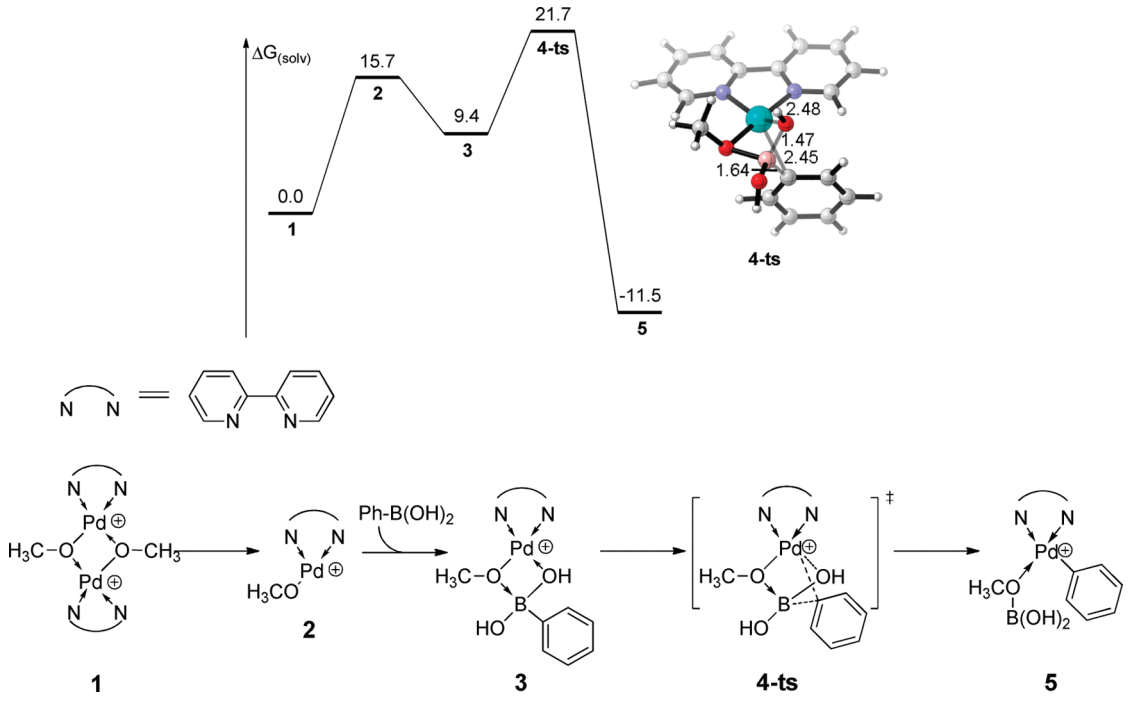

Figure 1. Catalyst loading step. The values are the relative free energies in methanol solvent.

Figure 2 shows the free energy profile and steps involved in the catalytic cycle for addition of the phenyl group to the enone. The geometries of two important transition structures are shown. Complex **8** is formed by dissociation of borane and coordination of the cyclohexenone. Complex **8** isomerizes to complex **9** with a 16.4 kcal/mol free energy increase because the coordination by the alkene is weaker than that by the carbonyl oxygen. Addition of the aryl-Pd to the enone via transition state **10-ts** gives η3-coordinated intermediate **11**. Transition state **10-ts** is the turnover-determining and stereochemistry-determining process in the presence of a chiral ligand. The barrier of this step is 26.0 kcal/mol. In the alkene insertion step, the oxygen atom is not coordinated to palladium. The competitive alkene insertion gives the Heck-type compound[15] **13** via transition state **12-ts**. The free energy of **12-ts** is 3.1 kcal/mol higher than **10-ts**. Coordination of methanol to palladium and proton transfer from methanol occurs via transition state **15-ts**. The cross-coupling product **17** is released from **16** with 12.7 kcal/mol free energy increase. The intermediate **2** re-enters the cycle after the reaction with the boronic acid as shown in Figure 1.

Experimentally, only enones are substrates, and there are no examples of reactions of unactivited alkenes. We have explored the reactivities of alkenes to understand why they are so much less reactive and why Heck type reactions are not observed. Figure 3 shows the catalytic cycle for the reaction of 1-methylcyclohexene **18**. The alkene **18** coordinates to **6** only with a 5.3 kcal/mol free energy decrease. The aryl palladium adds to the alkene via transition state **20-ts**. This is a relatively low energy process and leads to the agostic complex **21**. The geometry of **20-ts** is similar to **10-ts**. The relative free energy of **20-ts** is 13.1 kcal/mol higher than **19**; this difference is similar to the energy difference for the change of complex **9** to **10-ts**. Methanol coordination and proton transfer occur at a very high energy via transition state **23-ts**. This is 25.3 kcal/mol higher than the proton transfer in the enone because the Pd−C bond is broken, and the new C−H bond is not formed in transition state **23-ts**. The barrier of β-hydride elimination is only 3.5 kcal/mol via transition state **25-ts**, and only this reaction will be observed.

When 3-methoxycyclohex-2-enone is the substrate, only 3-phenylcyclohex-2-enone **36** is generated. We studied the competition between protonation to form the addition product **32** and β-methoxy elimination that leads to the observed substitution product **36**. As shown in Figure 4, calculations show that after the alkene insertion η3-coordinated intermediate **28** is formed. We explored whether **28** could be protonated by methanol or could instead eliminate methanol to form the substitution product. For protonation, methanol coordinates to palladium to form complex **29**, and the barrier to subsequent proton transfer is 10.0 kcal/mol via transition state **30-ts**. Intermediate **31** can dissociate to form product **32** and methoxy palladium complex **2** that reacts with boronic acid and re-enters the catalytic cycle to form the active catalyst **5**.

The isomerization of **28** to form complex **33** is a much more favorable process than reaction with methanol to form complex **29**. Methoxy elimination from **33** via **34-ts** involves a 3.5 kcal/mol lower energy than reaction via **30-ts**. The dissociation to form product **36** is more favorable than the formation of **32**. Thus, β-methoxy elimination is favored both kinetically and thermodynamically, and **36** is the only product found experimentally. Essentially, the unimolecular reaction of **28** is favored over the bimolecular reaction with methanol.

The reaction of 3-phenylcyclohexenone, **36**, is unsuccessful. The free energy profiles for the addition of **5** to **36** are shown in Figure 5. The palladium complex coordinated to the oxygen of the enone to give complex **37** as found earlier for 3-methylcyclohexenone, where **8** is formed. Addition of the aryl-Pd to

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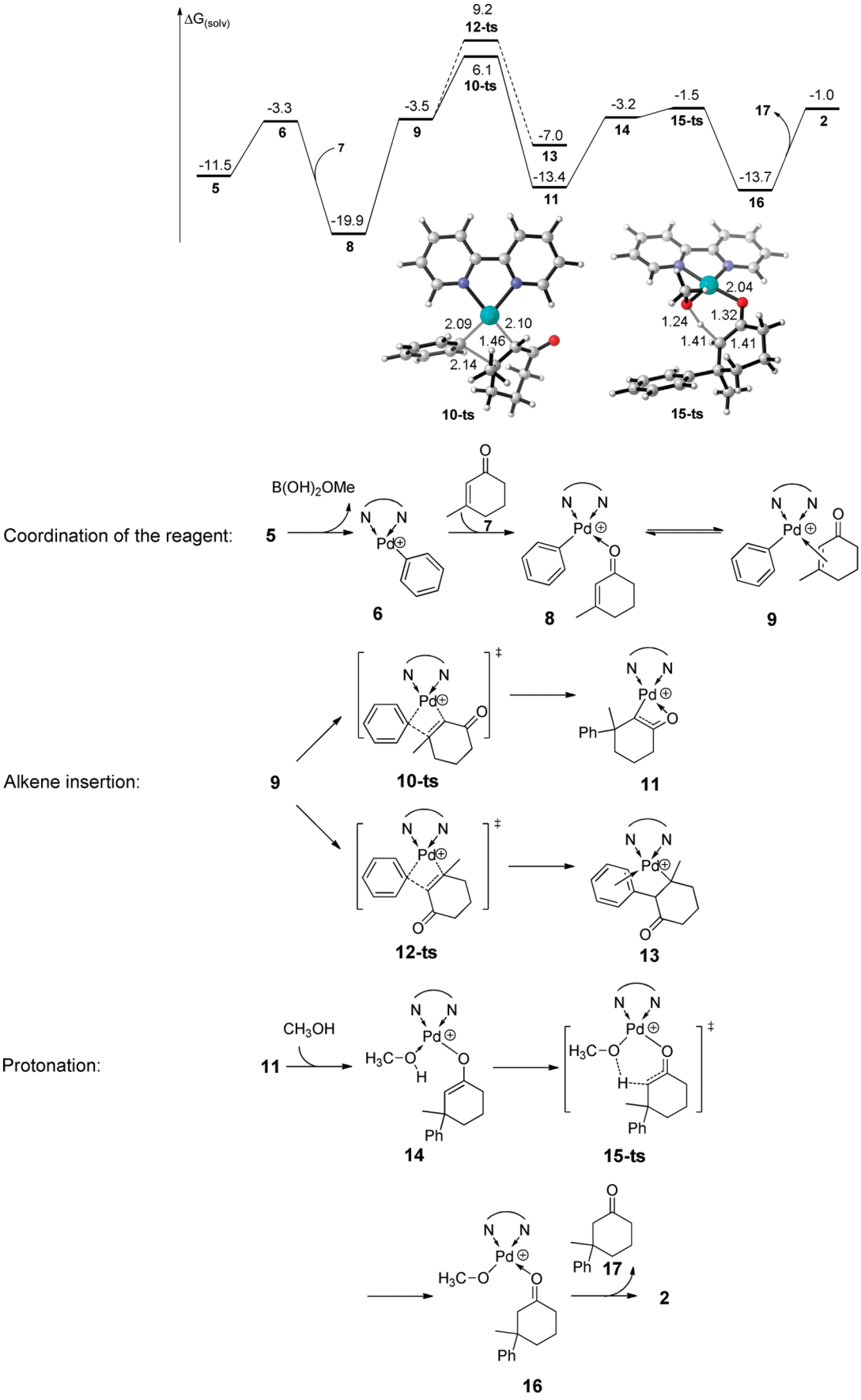

Figure 2. Reaction pathway and free energy profile of the palladium-catalyzed coupling reaction. The values are the relative free energies in methanol solvent.

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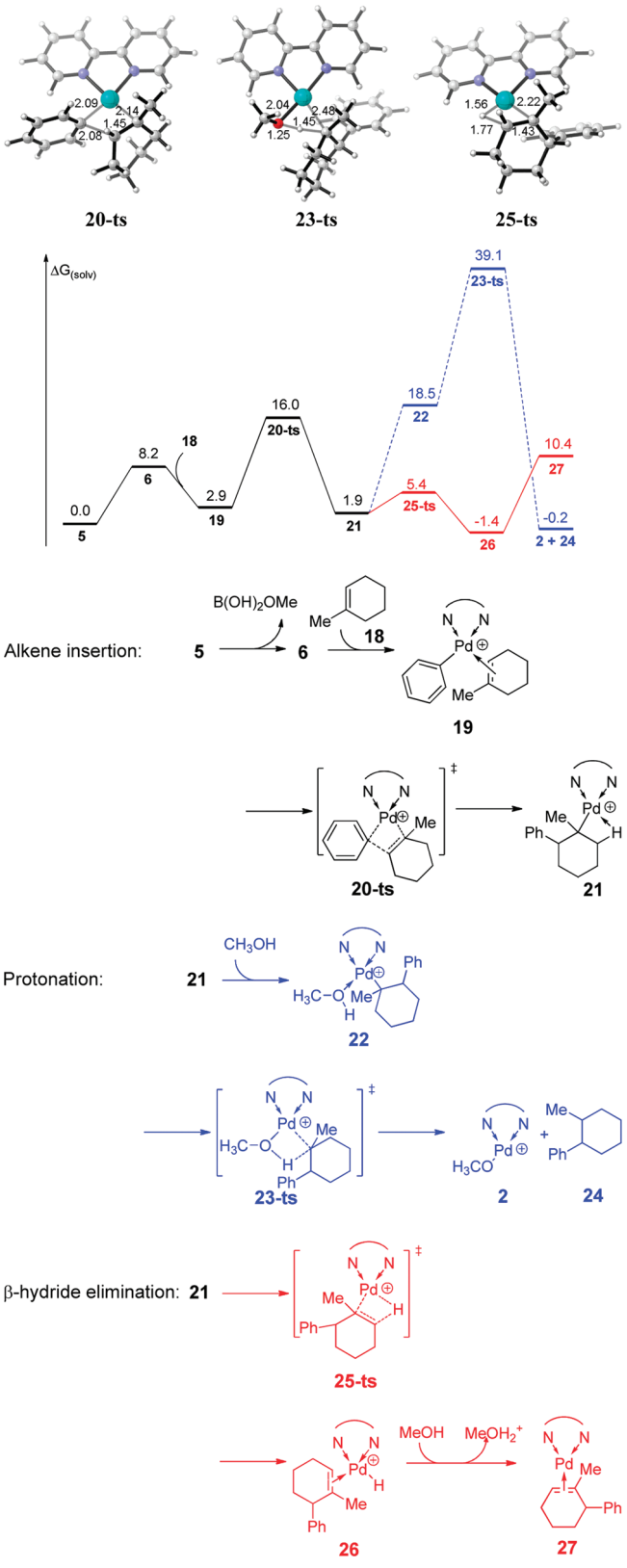

Figure 3. Protonation and β-H elimination reactions.

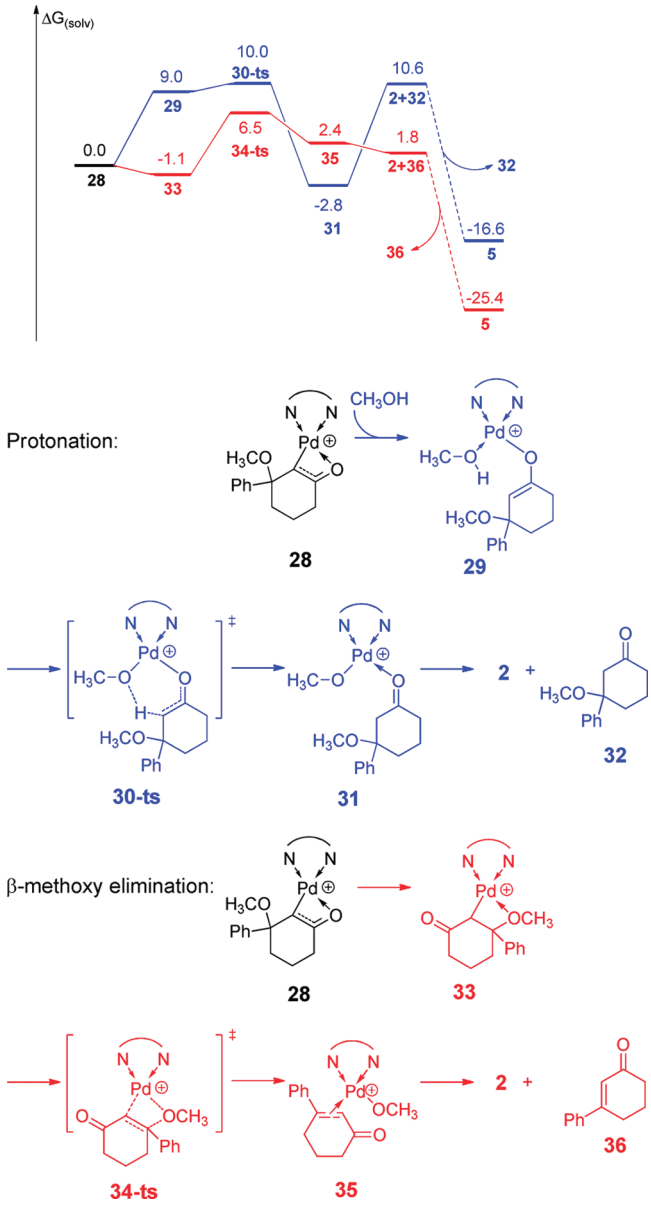

Figure 4. Competition between protonation and β-methoxy elimination.

the enone via transition state **38-ts** gives η3-coordinated intermediate **39**. The barrier of this step is 31.7 kcal/mol, which is 5.7 kcal/mol higher than that for **10-ts**. In transition structure **38-ts**, the C═C double bond of enone is increased to 1.48 Å, and the conjugation between the enone and phenyl group is interrupted. The hydrogenation energy of phenyl enone **36** is 1.8 kcal/mol less exothermic than of methyl enone **7**;[16] addition to **36** is disfavored.

CONCLUSION

The palladium(II)-catalyzed addition of arylboronic acids to β,β-disubstituted enones has been investigated with density functional theory. The mechanism involving enone insertion, protonation, and transmetalation proposed by Lu has been verified. The turnover-determining step is the enone insertion via the 4-membered transition state **10-ts**. Some competitive pathways are compared, and we have explained why the addition product is favored for the normal substrates but the substitution product is favored for 3-methoxycyclohex-2-enone.

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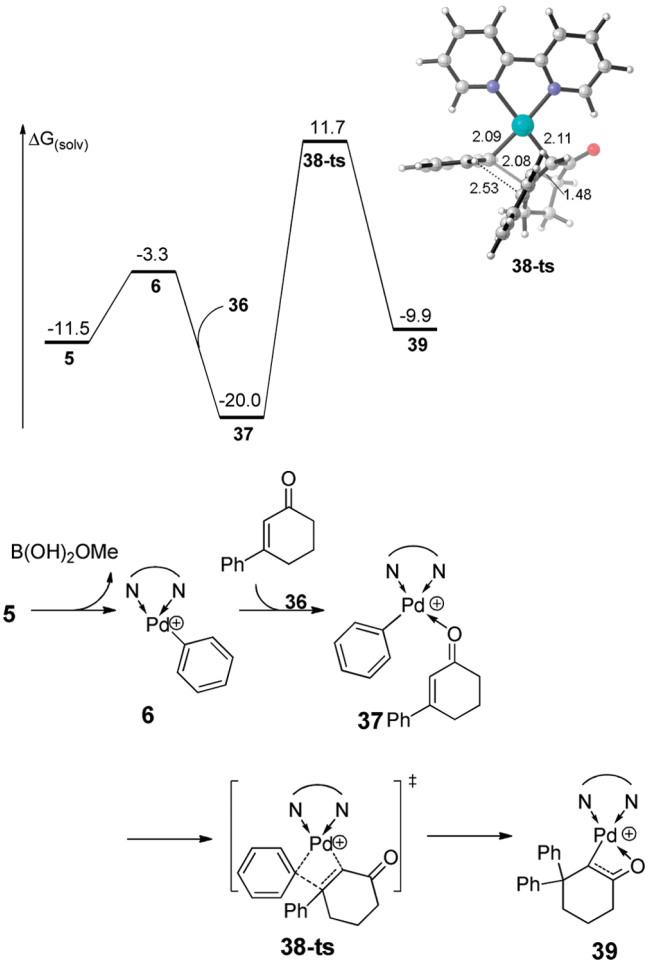

Figure 5. Reaction pathway and free energy profile of the palladium-catalyzed coupling reaction of 3-phenylcyclohexenone **36**. The values are the relative free energies in methanol solvent.

■ ASSOCIATED CONTENT

Supporting Information. Cartesian coordinates and energies of all reported structures and full authorship of Gaussian 03. This material is available free of charge via the Internet at http://pubs.acs.org.

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