

Research Article

A Quantum-Chemical DFT Approach to Elucidation of the Chirality Transfer Mechanism of the Enantioselective Suzuki–Miyaura Cross-Coupling Reaction

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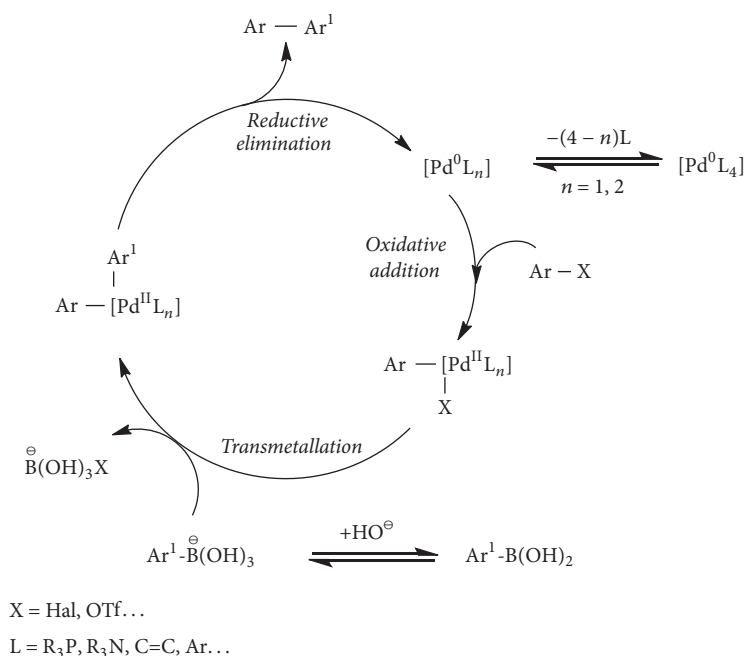
The DFT calculations of the simplified model of the asymmetric Suzuki–Miyaura coupling reaction were performed at the M062x/LANL2DZ theory level at first. It was found that enantioselective reactions mediated by the palladium complexes of chiral *C,P*-ligands follow a four-stage mechanism similar to that proposed previously as one of the most credible mechanisms. It should be underlined that the presence of substituents in the substrates and the chiral ligand at *ortho* positions determines the energies of possible diastereoisomeric transition states and intermediates in initial reaction steps. This suggests that, in practice, a sharp selection of theoretically possible paths of chirality transfer from the catalyst to the product should have a place and, therefore, the absolute configuration of the formed atropisomeric product is defined and can be predicted.

1. Introduction

Palladium mediated cross-coupling reactions constitute one of the main synthetic tools for creation of new carbon-carbon bonds [1, 2]. The carbon atoms of all types of hybridisation, possessing a variety of leaving or nonpreactivated groups, can be connected together if properly designed catalysts are used. Excellent chemical yields are usually observed in a majority of cross-coupling reactions, even those run under mild conditions. The notable progress observed during the last decade in medicinal [3–6], material [7–10], and green chemistry [11, 12] makes the issue of efficient asymmetric synthesis of drug precursors, functional materials, and fine chemicals significantly urgent, since chiral nonracemic compounds have already found wide industrial application. Among all cross-coupling reactions, only the asymmetric Heck coupling (and its several modifications, e.g., the Fujiwara-Moritani reaction and oxidative boron Heck-type reactions) is well developed [13–15]. At the same time, the enantioselective

approach to other coupling reactions still remains challenging [16–18]. Without clear understanding of the mechanism of chirality transfer from the chiral catalyst to the product, a rational design of an efficient catalyst, tailored for a given enantioselective coupling reaction, remains not possible and consequent testing of a large quantity of similar ligands will be a costly alternative [18, 19].

Herein, we are going to present the results of our computational finding of the origin of asymmetric induction in cross-coupling reactions. Since aryl-aryl bond forming cross-couplings are mechanistically quite similar, in our studies on enantioselective coupling we concentrated on the Suzuki–Miyaura reaction, which is usually applied as a method of first choice. The mechanics of the nonstereocontrolled Suzuki–Miyaura (and a few other couplings) reaction catalysed by complexes of nonchelating monophosphines has been studied in detail (Scheme 1) [20–29] and can be extrapolated to reactions catalysed by transition metal complexes of different types and to stereoselective transformations. At



SCHEME 1: Generally accepted mechanism of SM reaction.

the same time, the nature of chirality transfer still remains unclear and only general intuitive mechanistic considerations have been published to date [30].

In highly enantioselective Suzuki–Miyaura couplings, palladium complexes of significantly sterically hindered ligands are usually used [16, 18]. Accurate computer calculations of such large complexes need an extremely large computational cost. Additionally, for palladium catalysts based on regular bidentate ligands (e.g., BINAP (**I**) [31]) and monodentate ligands (e.g., oligo-aryl phosphine (**II**) and oligo-aryl phosphonites (**III**) [32]) (Figure 1), several different models of solvation and mono- and biscomplexation should be evaluated [23, 33–36]. Obviously, a discovery of subtle interactions influencing the absolute configuration of the product formed in the reaction mediated by interconverting complexes of large phosphorus ligands cannot be accurate because of many entropic issues that certainly take place but are difficult to handle. In the case of less bulky and especially bisphosphine chelating ligands, different types of 14-electron PdL_2 complexes have been postulated as active catalysts, and corresponding products of the oxidative addition reactions to such complexes have been characterised [37–40]. Thus, we decided to concentrate on highly efficient, also in asymmetric SM reactions, chiral ligands of the *C,P*-type of complexation represented by KenPhos and similar ones (**IV**) [30, 41, 42], MeO-MOP (**V**) [43], and *BisNap*-Phos (**VI**) [44] (Figure 1). These ligands form well-defined bidentate mono-P-liganded $\text{Pd}(0)$ species [45–48] with the structures formally corresponding to the 12-electron Pd-P(III) active catalysts of the SM reaction (Scheme 2, **AC**). The active catalyst is extremely reactive and readily undergoes oxidative addition reaction with aromatic halides to form intermediates with a well-defined structure **II** [49, 50].

Even such simple complexes are spatially developed and complicated enough not to allow accurate computation of their fine properties and stereochemical behaviour if the entire structure is considered. Nevertheless, in the case of catalytic systems in which substrates and ligands do not bear bending function groups (whose interaction can control the geometry of preordination intermediates) and the catalyst is a complex of the *C,P*-ligand, the geometry of the intermediates is less sensitive to the substitution pattern and several coordinational simplifications can be applied. Thus, the geometry of the palladium complexes will remain almost the same if the cyclohexyl groups situated on the phosphorus atom are replaced with methyl groups. Also, the biaryl core of the ligand can be simplified to formally chiral 6,2'-dimethylbiphenyl, and eventually 2-bromotoluene and 2-tolylboronic acid can be selected as the simplest substrates of the enantioselective cross-coupling reaction (Scheme 3). This significant simplification allows accurate DFT calculations of the entire reactions leading to the chiral (but with low racemisation energy) product [51].

With the objective of gaining insight into the origin of stereoselectivity of the selected reacting system run in aqueous media, we decided to perform DFT simulations of possible reaction paths to confirm its actual molecular mechanism and find conditions influencing the configuration of the chiral product formed.

2. Results and Discussion

2.1. Computational Procedure. The quantum-chemical calculations reported in this paper were performed on “Zeus” and “Prometheus” supercomputers in the “Cyfronet” computational centre in Cracow. The M062x [52] functional

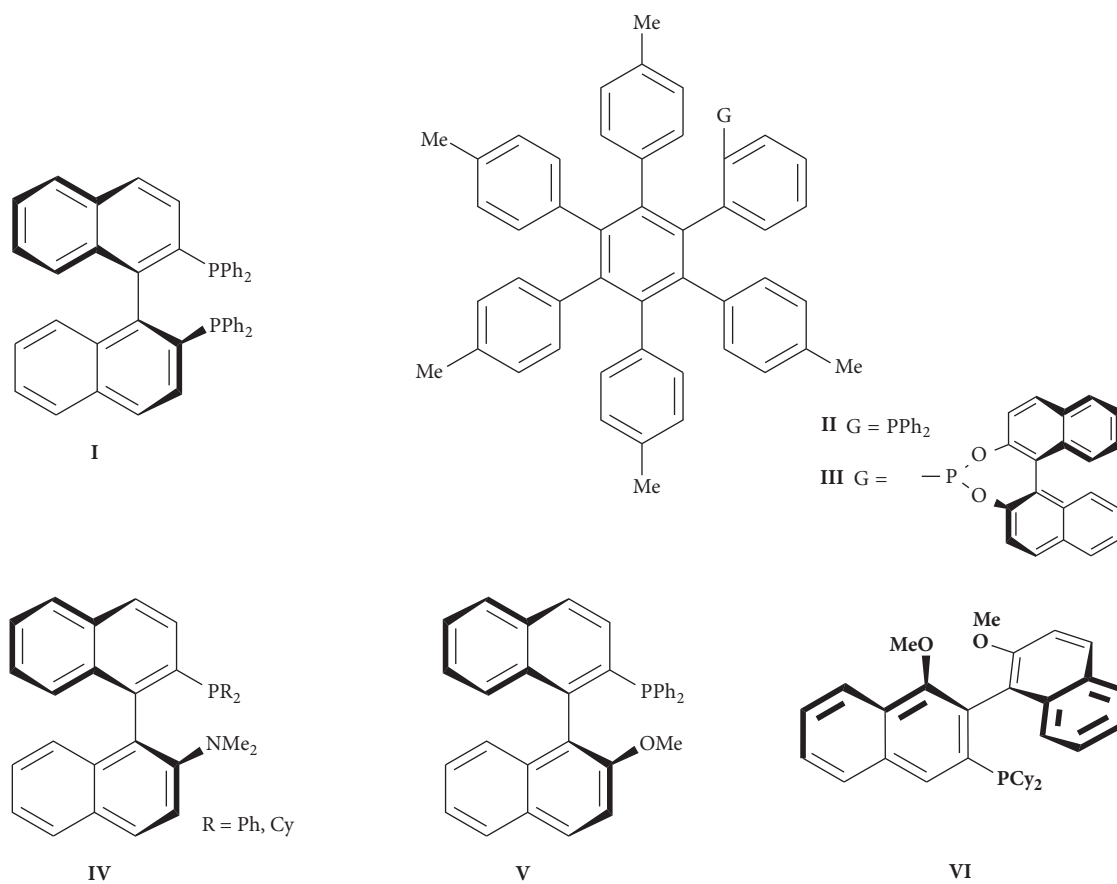
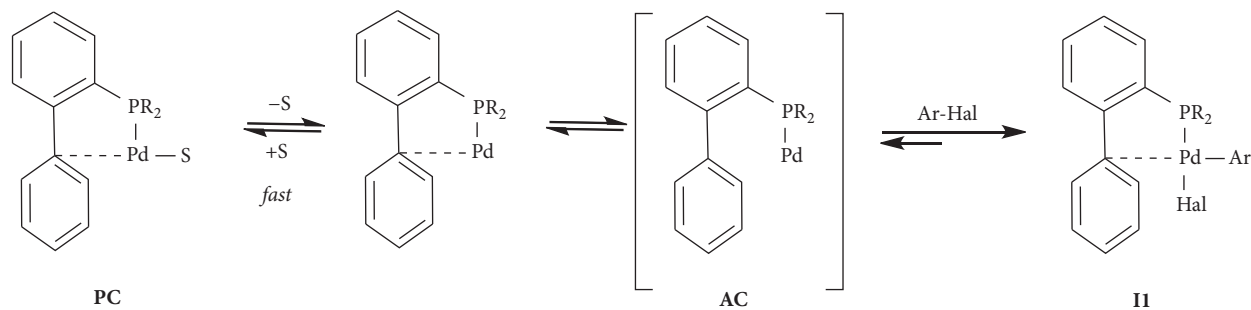


FIGURE 1: Selected chiral ligands used in SM reactions.

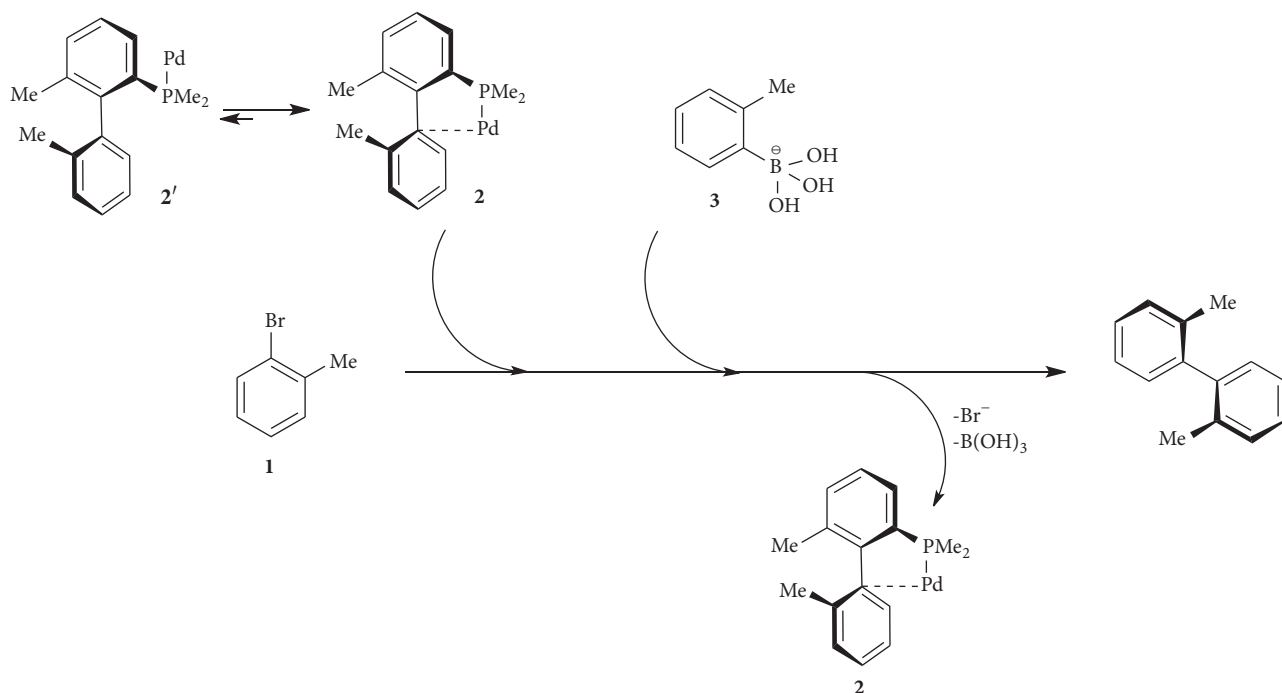


S = weakly coordinating solvent

SCHEME 2: Models of *C,P*-complexation: precatalyst: **PC**, active catalyst: **AC**, and intermediate: **II**.

implemented in the GAUSSIAN 09 package [53] was used. This functional is dedicated for precise energetic considerations [52, 54] and has been recently applied for simulation of the reaction paths of several different reactions, including aryl systems [55], phosphorus compounds [56], and halogenide-derivatives [57, 58]. Critical structures are fully optimized using basis sets: 6-31G(d) for H, C, O, B, Br, and P, as well as LANL2DZ with one *f* function for Pd and without pseudopotential. Identical basis sets have been recently used for quantitative description of similar processes involving similar chemical molecules [21]. For elementary reaction, in

which anionic species are involved, calculations using basis set with one diffusion function were performed in parallel to procedure described above. It was found that in this way practically identical critical structures were obtained. Next, we have reoptimized key, representative transition states using M06 functional, in which HF exchange contribution is significantly lower, than on the case of M062x functional. It has been found that obtained structures are very similar to those derived from M062x calculations. Thus, we concluded that the applied theory level should be recognized as wholly adequate to solve the presented problem.



SCHEME 3: Model coupling reaction.

The *Berny* algorithm was applied for optimization of the structure of the reactants and the reaction products. First-order saddle points were localized using the QST2 procedure. Stationary points were characterised by frequency calculations. All reactants and products had positive Hessian matrices. All transition states showed only one negative eigenvalue in their diagonalized Hessian matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under (IRC) calculations performed to connect previously computed transition structures (TS) with suitable minima. For the calculations of the solvent effect (presence of water), the polarizable continuum model (PCM) [59], in which the cavity is created via a series of overlapping spheres, was used. For optimized structures, thermochemical data for the temperature $T = 298\text{ K}$ and pressure $p = 1\text{ atm}$ were computed using vibrational analysis data.

2.2. Catalyst Activation. According to the widely accepted concept, monoligated coordinatively unsaturated and unstable 12-electron palladium complexes, which are formed by dissociation of bulky diphosphine (or similar) complexes, can be an active catalysts of the cross-coupling reaction (Scheme 1). In the case of *C,P*-complexes, 12-electron active catalyst is formed by dissociation of the Pd-C coordination bond (Scheme 2), and the energy of this process may influence the reaction rate. Several products of the oxidative addition possessing only one ligand at the phosphorus atom have been obtained and characterised [35, 36, 50, 60–62]. Thus, we decided to shed light on the energetic stability of the model chiral catalytic complex **2** (Scheme 3). The

M062x calculations showed that the complex with “cyclic” conformation (**2**) is more than 5.5 kcal/mol stable than the competitive structure with “extended” conformation (**2'**). This is a consequence of failure of the Pd-C complexation effect in **2'**.

Subsequently, we performed a similar study for a similar fluorinated system illustrated in Figure 2 (structures **2a** and **2a'**), in which the aryl system has a relatively more π -deficient nature. In both cases, we reached a qualitatively similar conclusion. Thus, it can be assumed that the C-Pd complexation effect is important for stabilization of the palladium-ligand complex irrespective of the nature of the substitution of aryl moiety.

A possible way to evaluate the Pd-C binding energy is “homolytic dissociation” (Figure 3) of the optimized complex structure into frozen fragments (no optimization is done for them). The uM062x/LANL2DZ calculation shows that the following fragmentation requires energy (E_1) equal to 129.97 kcal/mol (Figure 3(a)). It includes Pd-Ar and Ar-Ar binding energies. To exclude the Ar-Ar energy, similar fragmentation is needed (Figure 3(b)). In this case, the dissociation energy (E_2) is equal to 124.16 kcal/mol. The difference $E_1 - E_2 = 5.81\text{ kcal/mol}$ is due to Pd-C binding, which is close to the value derived by rotating the Ar-Ar group leading to **2'**. The total stabilization due to the presence of the Pd atom, calculated similarly by removal of the Pd atom from the complex, is 32.36 kcal/mol. Similarly, the energy of Pd-P binding was calculated to be equal to 15.16 kcal/mol. Since the Pd-C interaction is significantly weaker than the Pd-P one, we expect dissociation of Pd-P within the catalytic cycle.

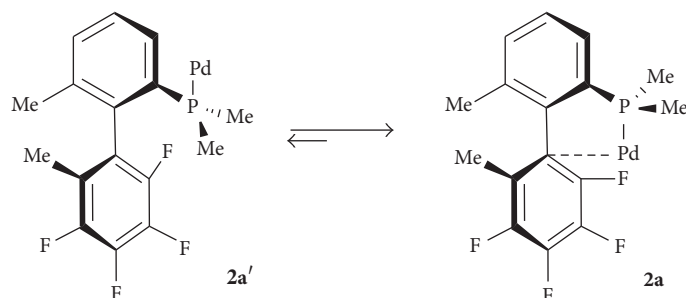


FIGURE 2: “Cyclic” (**2a**) and “extended” (**2a'**) conformations of the fluorinated C,P-complex.

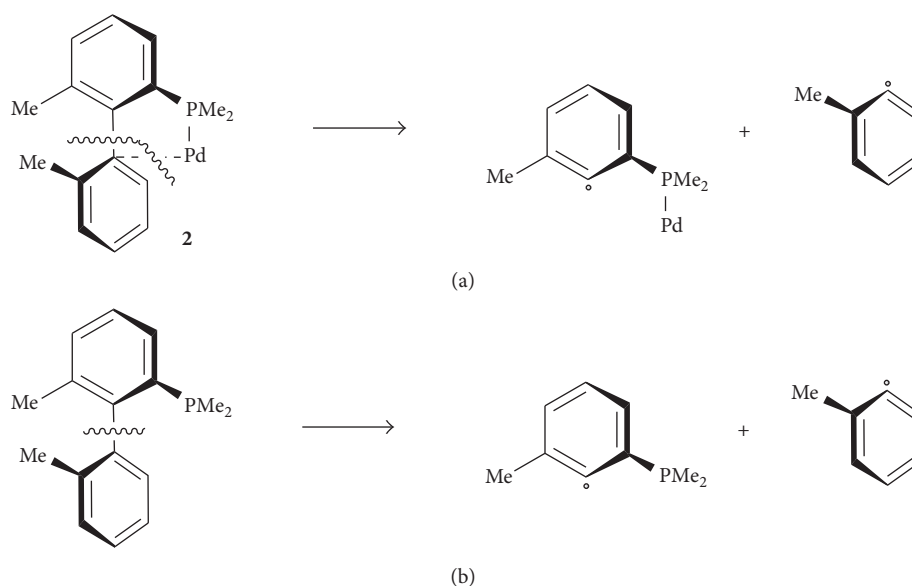


FIGURE 3: “Homolytic dissociation” of C,P-complex **2** (a) and respective phosphine ligand (b).

2.3. Oxidative Addition Step. Next, we carried out a detailed study of the mechanism of model cross-coupling involving catalyst **2**. The first stage includes formation of an adduct of 2-bromotoluene with catalyst **2** (Scheme 4). Since the palladium atom is shielded with the aromatic ring, the attack of the 2-bromotoluene molecule on the Pd atom may take place only from directions that are not shielded by the ligand. In particular, four competitive paths were found, during which the following processes take place: (1) creation of a Pd-Br bond in the direction of the axis of the P-Pd coordination bond (paths leading to adducts **5a** and **5b**, resp.) or (2) creation of a Pd-Br bond in the direction perpendicular to the axis of the P-Pd bond (paths leading to adducts **5c** and **5d**, resp.).

Thermodynamical analysis shows that in the case of all the considered paths the reaction equilibrium is evidently shifted towards the valley of the products. However, **5c** and **5d** are relatively more stable. Free Gibbs enthalpy of formation is below 29 kcal/mol for these compounds and equal to ca. 19 kcal/mol for products **5a** and **5b**. Generally,

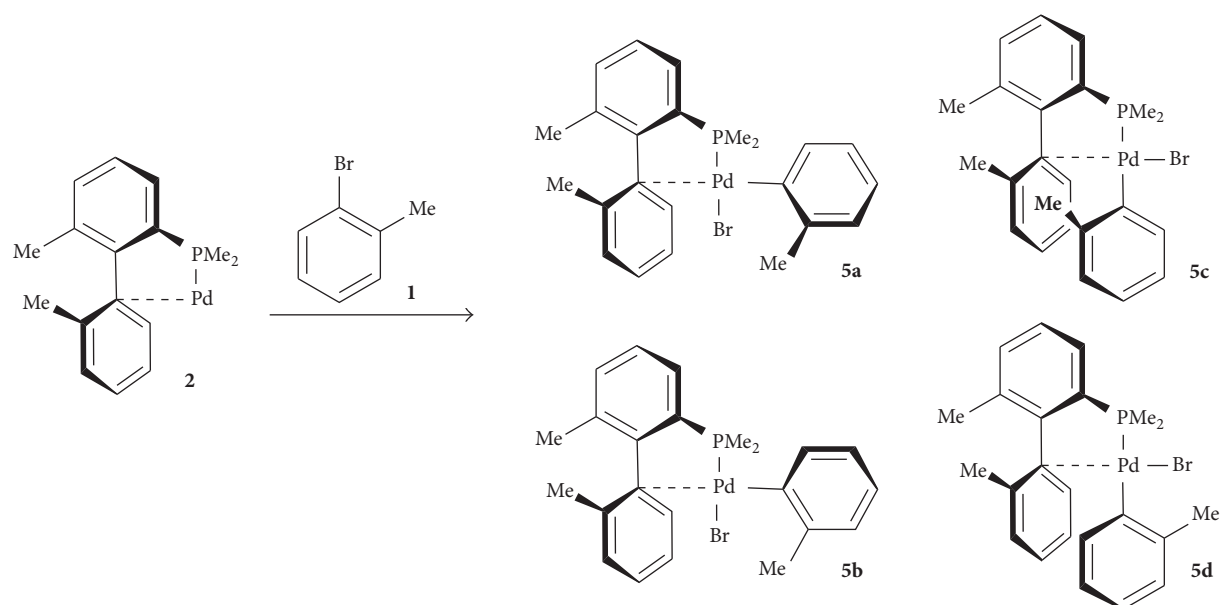
thermodynamic stability of theoretically possible products should be ordered as follows: **5c** > **5d** $\gg$ **5b** > **5a**.

Analyses of the kinetic aspects of the directions of substrate transformations indicate that the reaction proceeding according to path **C** is evidently kinetically favoured ($\Delta G^\ddagger = 0.2$ kcal/mol). Other paths should be considered as unfavourable or outright forbidden from the kinetic point of view (Figure 4).

The theoretically possible transformations between isomeric adducts **5a–d** have also been analysed. It was found that under reaction conditions all of these transitions should be considered as forbidden from the kinetic point of view, since in all of the considered cases the interconversion energy was higher than 30 kcal/mol.

Thus, it should be assumed that an isomer that is formed according to path **C** can be treated as a generally favoured structure for a wide group of reactions. This product enters the subsequent addition stages.

Two new bonds are formed within the transition state of the **1** + **2** $\rightarrow$ **5c** reaction—Pd-Br ($r = 3.246$ Å) and Pd-C_(Ar)



SCHEME 4: Theoretically possible product of the oxidative addition step.

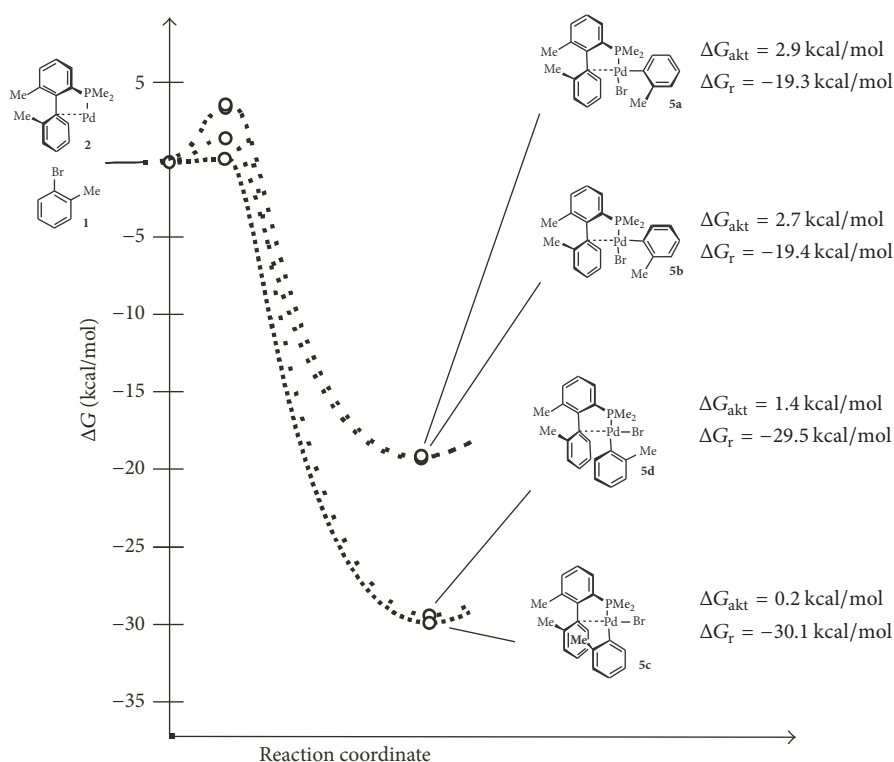


FIGURE 4: Energy profiles for competitive channels of oxidative addition reaction.

($r = 2.305 \text{ \AA}$). This is accompanied by the breakage of the $\text{Br-C}_{(\text{Ar})}$ bond ($r = 1.981 \text{ \AA}$).

In addition to our theoretical studies, the relevance of structure 5c can be confirmed by comparison of our theoretical considerations with the X-ray structures of similar *C,P*-palladium complexes (VII) [63, 64] and, additionally, with the same structure optimized using the M062x/LANL2DZ

theory level in simulated presence of water (VII'), as shown in Figure 5 and Table 1. It was found that the key angles and interatomic distances were rather similar.

2.4. Transmetalation Step. The different possibilities of transmetalation reaction that may take place in the second stage of the asymmetric SM reaction were assessed. It has

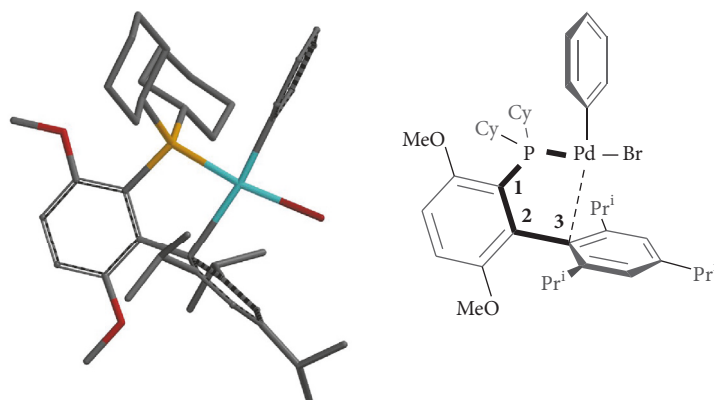
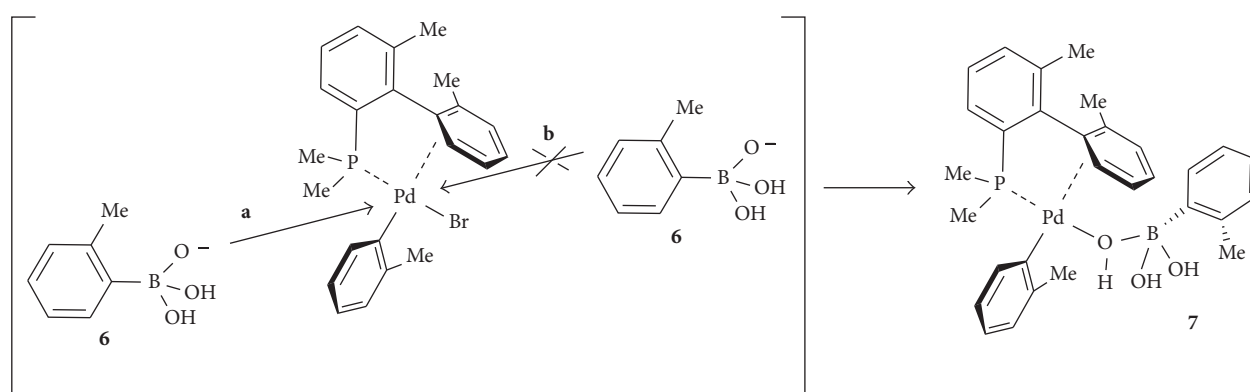


FIGURE 5: X-ray structure of complex VII [63].



SCHEME 5: Two possible paths of transmetalation.

TABLE 1: Comparison of the key geometrical parameters of complexes 5c, VII, and VII'.

Parameter	5c	VII	VII'
$r_{\text{Pd-P}}$ [Å]	2.417	2.407	2.266
$r_{\text{P-Cl}}$ [Å]	1.871	1.834	1.877
Angle _{C2-C3-Pd} [°]	103.17	106.08	106.73
Angle _{C3-Pd-P} [°]	64.73	83.71	81.15
Angle _{Pd-P-Cl} [°]	113.88	106.35	105.19

been shown that the transmetalation step in a typical SM coupling reaction does not proceed without the nucleophilic additive, which enhances the electron density at the boron atom through its coordination and formation of boron-ate adduct [20, 21, 24, 65, 66]. In an aqueous solution of inorganic bases, the role of this nucleophile may be played by

the hydroxyl anion. Thus, the second stage of the reaction includes substitution of the bromine atom with the $\text{ArB}(\text{OH})_3^-$ anion (6) (Scheme 5). The alternative reaction pathways involving the participation of neutral $\text{ArB}(\text{OH})_2$ or Pd-OH species were not favourable.

Attack of molecule 6 on the Pd atom is possible only when both methyl groups bound to phenyl rings are turned opposite to the anion approach trajectory, attack according to the “a” trajectory (Scheme 5). All attempts at finding transition stages related to the theoretically possible process of the approach of molecule 6 to the Pd atom along the “b” trajectory failed.

During the approach to the Pd atom, the 6 anion may theoretically assume various orientations. Two paths of such an approach were found, differing in the orientation of the methyl group within the anion. However, only one of these should be considered kinetically permitted. The activation barrier of the transition is 4.1 kcal/mol. This process takes place via the TS2 transition state (Figures 6 and 7). The Pd-Br bond ($r = 2.696 \text{ Å}$) of this state becomes gradually more loose, and at the same time a new Pd-O bond ($r = 2.178 \text{ Å}$) is formed. Conversion of the reacting system along the reaction coordinate leads directly from TS2 to the product 7.

During the transmetalation stage, a boric acid molecule is eliminated, with simultaneous formation of a bond between

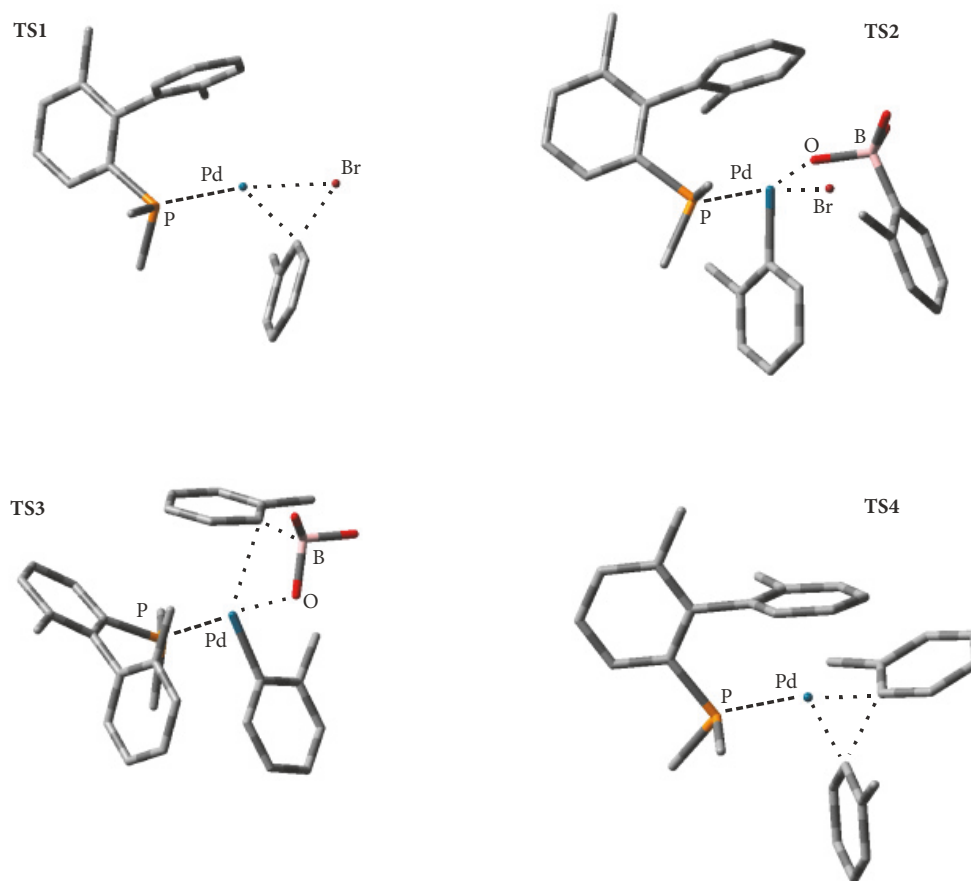
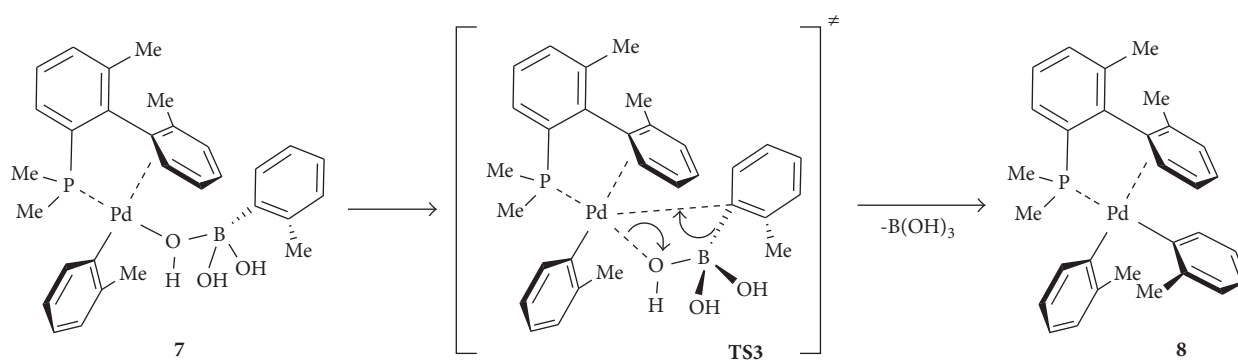


FIGURE 6: Views of transition states according to DFT calculations.



SCHEME 6: Formation of the transition stage TS3.

the palladium atom and the carbon atom of the phenyl ring introduced into the reacting system from the $\text{ArB}(\text{OH})_3^-$ molecule.

This transformation takes place through the transition state **TS3** (Scheme 6) and requires the activation barrier $\Delta G^\ddagger = 7.1 \text{ kcal/mol}$ to be overcome. As a result of a synchronous, circular electron shift within **TS3**, the bonds between the palladium atom and the oxygen atom ($r = 2.151 \text{ \AA}$) and between the boron atom and the carbon atom in position 1 of the phenyl ring become ruptured ($r = 1.632 \text{ \AA}$). This

is accompanied by formation of a new σ -bond between the phenyl ring and the palladium atom ($r = 2.676 \text{ \AA}$). It leads to formation of compound **8**.

2.5. The Reductive Elimination Stage. The last reductive elimination stage takes place via the **TS4** transition state and requires an activation barrier which is equal to 8.6 kcal/mol . Thermodynamic factors, on the other hand, favour practically an irreversible shift of equilibrium towards the product, as free enthalpy of the system decreases by over 25 kcal/mol as

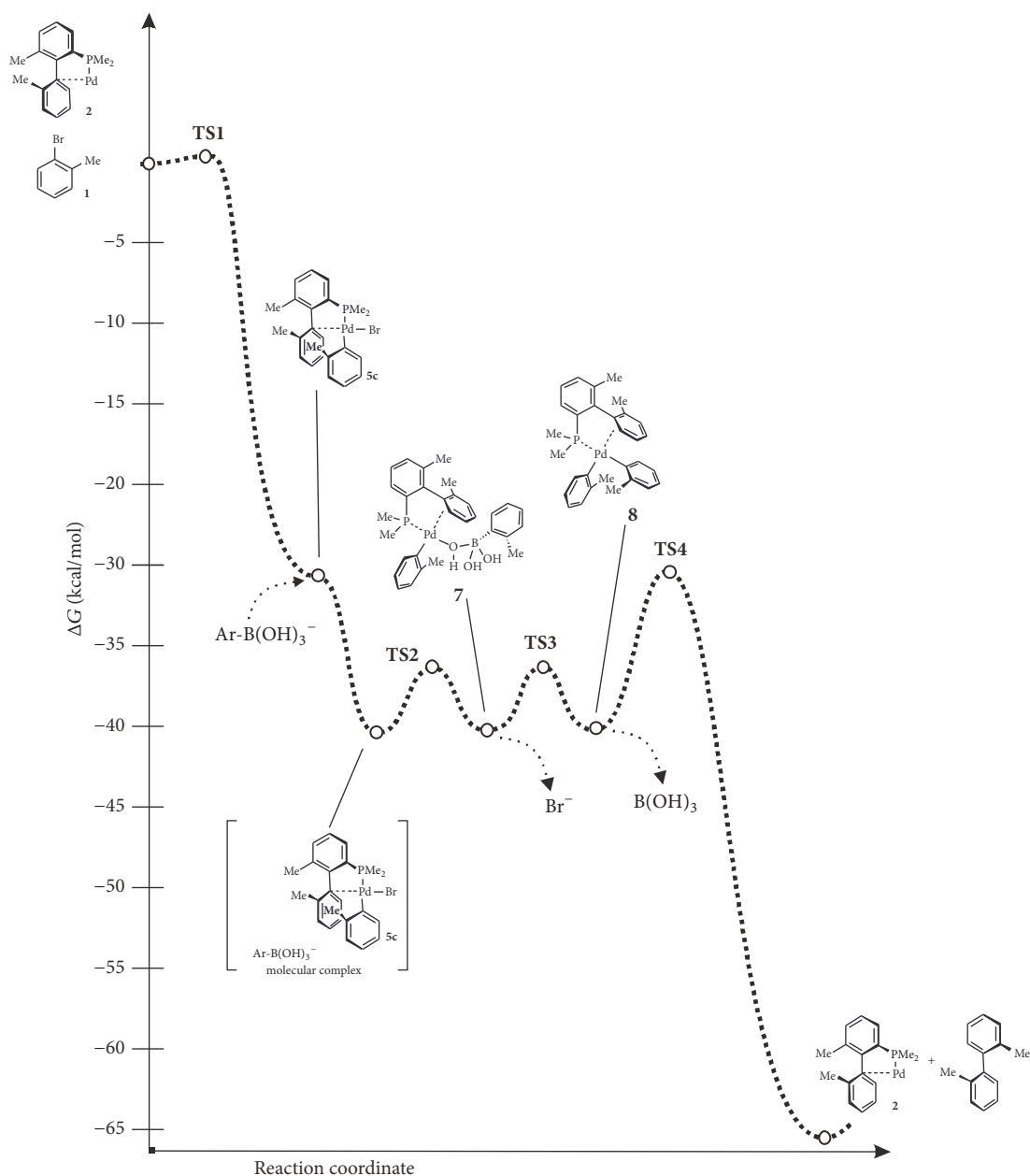


FIGURE 7: Free Gibbs energy profile for energetically preferred reaction path according to DFT calculations.

a result of this elementary reaction. Notably, the previously proposed possibility of the rotation of aryls around the Pd-Ar and Pd-Ar' bonds in **8** [30], which may yield products with an opposite absolute configuration, has a rotation barrier greater than 15 kcal/mol. Thus, this could be considered as almost forbidden and slow; hence the product configuration change at this stage of the reaction cannot be significant.

3. Conclusions

The DFT calculations performed with the simplified reaction model indicate that the palladium-catalysed process of asymmetric cross-coupling should take place according to a four-stage mechanism. It should also be stated that the

presence of substituents in the *ortho* positions of the substrates (aryl bromide and borate anion) determines a sharp selection of theoretically possible reaction directions. This means that, in practice, the conversion of the reacting system should take place according to a single reaction path only. Because rupture of existing bonds takes place simultaneously with formation of new bonds within all transition states, the entire process should take place stereoselectively and lead predominantly to one atropisomeric form. This assumption makes the task of rationalisation of the stereochemical outcome of the reaction much simpler, since only one, that is, the first reaction stage, should be analysed to predict the absolute configuration of a majority of formed biaryl products.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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