

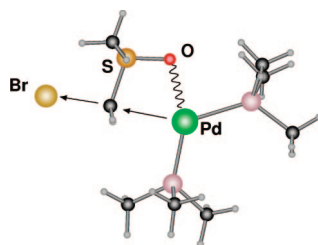
Why Is the Suzuki–Miyaura Cross-Coupling of sp^3 Carbons in α -Bromo Sulfoxide Systems Fast and Stereoselective? A DFT Study on the Mechanism

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The stereoselectivity-determining oxidative addition step in the Suzuki–Miyaura cross-coupling of α -bromo sulfoxides is analyzed computationally through DFT calculations on a model system defined by $\text{Pd}(\text{PMe}_3)_2$ and $\text{CH}_3\text{SOCH}_2\text{Br}$. Both monophosphine and bisphosphine complexes have been considered, different reaction pathways being characterized through location of the corresponding transition states. The lowest energy transition states correspond to nucleophilic substitution mechanisms, which imply inversion of configuration at the carbon, in good agreement with experimental data on the process. The energy-lowering and stereodirecting role of the sulfinyl substituent is explained through its attractive interactions with the palladium center, which are only possible in the most favored mechanisms.

1. Introduction

Formation of a C–C bond in mild conditions is one of the most challenging goals of organic chemistry. The palladium cross-coupling reaction between organohalide and organoboron compounds developed by Suzuki and Miyaura¹ is tolerant to very sensitive functions such as ester, nitrile, and amide groups² and water could be used as solvent.^{3,4} The reaction usually takes place with aryl bromide to form new $\text{Csp}^2\text{–Csp}^2$ bonds. This

reaction has been subject to several experimental and theoretical investigations^{5–9} to determine its mechanism and sensitivity to experimental conditions.

The mechanism can be divided into three steps. First is the oxidative addition of the aryl halide on the neutral palladium complex, followed by the exchange of the second aryl group from the boron moiety to the palladium complex and finally formation of the C–C bond through a reductive elimination process. The possibility of Suzuki–Miyaura cross-coupling with

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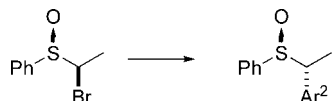


FIGURE 1. Stereospecific cross-coupling with α -bromo sulfoxide showing the inversion of the secondary carbon.

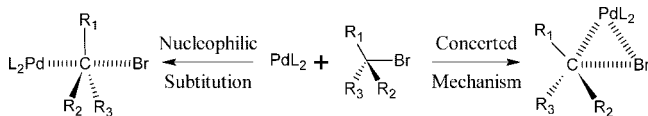


FIGURE 2. Expected transition states for the concerted and nucleophilic substitution mechanisms.

alkyl halide has been recently considered with an α -bromo sulfoxide that possesses one chiral center on the sulfur and a second chiral center on the carbon bearing the bromine atom (Figure 1).¹⁰ The cross-coupling reaction of the *syn* diastereoisomers led to retention of configuration at the sulfur center and inversion on the carbon center. Moreover it is well established that α -halo sulfoxides are very poor substrates in S_N2 reactions with the usual nucleophiles,¹¹ including Grignard reagents since they occur at the sulfur but not at the carbon center.¹² In contrast they are excellent substrates for oxidative reactions of Pd(0) thus allowing efficient Csp^3-Csp^2 cross-coupling reactions with boronic acids.¹³ It is noteworthy that Suzuki cross-coupling processes with α -halo sulfoxides are performed with good yields even in the case of secondary halides.¹⁰ The purpose of this contribution is to elucidate the mechanisms of the oxidative addition of Pd(0) to α -halo sulfoxides to clarify the effect of the sulfinyl group and to explain the stereoselectivity and the unusual reactivity observed in cross-coupling reactions with these substrates. We will focus on the oxidative addition step because our previous computational study of the full catalytic cycle on a model system had found this to be the rate-determining step, and this is where the overall acceleration should thus be observed.⁸

The stereochemistry of the oxidative addition, the first step of the cross-coupling reaction, had been first described by Stille and Lau on the secondary sp^3 carbon^{14,15} of a chiral benzyl bromide and later by Fu and co-workers¹⁶ using a chiral deuterated primary alkyl tosylate. This step was proven to be critical for the configuration of the product and, depending on the reaction conditions, inversion or retention of configuration at the carbon center was observed.¹⁷ This has been the subject of theoretical investigations and two pathways have been proposed for oxidative addition in aliphatic halides.

The first path is similar to that proposed for aryl halides and consists of the insertion of the palladium in the C–Br bond. Labeled as “concerted mechanism” (Figure 2), it leads to retention of configuration at the carbon center. Both M–X bonds are formed simultaneously in the transition state. This mecha-

nism has been shown to be operative for the cleavage of σ bonds with low polarity at metal centers.¹⁸ It takes place with retention of configuration at the carbon center. Most computational studies on oxidative addition have assumed this mechanism to be operative.^{8,19–22}

The second mechanism is the “nucleophilic attack” of Pd(0) L_n to the carbon center. This S_N mechanism, involving in fact the heterolytic cleavage of a σ bond, is favored when atoms of different electronegativity are involved. This mechanism has been considered in several computational studies on the oxidative addition of alkyl and aryl halides to transition metal centers.^{23–26} Pioneering references in this field are due to Stille¹⁴ and are related with the oxidative addition of benzyl halides to Pd(0), which is postulated to take place by a S_N2 -type process with inversion of configuration at the benzylic center. The S_N2 , a common mechanism in organic chemistry, is well-known to operate with inversion of configuration.

In this work, we will explore the two different pathways for oxidative addition in α -bromo sulfoxide systems. We will also investigate the influence of the presence of the sulfinyl substituent on each mechanism. Mono- and bisphosphine palladium complexes have been considered, as well as the role of solvent effects.

2. Computational Details

The calculations have been performed with the Gaussian 03 package²⁷ within the DFT framework (B3LYP functional^{28–30}). The standard 6-31+G(d,p) basis set was used to describe C, H, O, P, S, and Br atoms.^{31–33} Palladium was described by the large-core relativistic SDD pseudopotentials by Kuehne et al. and the associated basis set.³⁴ All structures were optimized in vacuum, and their nature (minima or transition states) was determined by frequency analysis. Connectivity between transition states and minima was checked following the eigenvector of the imaginary frequency. Solvation effects were taken into account through single point PCM calculations³⁵ with UFF atomic radii for the solute. The experimentally applied alcohol solvent is not available as such in the Gaussian03 program, and because of that we used an arbitrary solvent with a dielectric constant equal to 11.7.¹⁰ Selected calibration tests with other solvents, such as heptane and methanol, showed a gradual smooth variation of the computed energies. All provided energies in the paper correspond to potential energies in the gas phase or in solution.

To confirm the validity of the computational method, and following the kind request from referees, we carried out three sets

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of additional single point calculations. Their results are given in detail in the Supporting Information. We evaluated the performance of a larger basis set: LANL2TZ(f) for Pd³⁶ and 6-311+G(d,p) for all other atoms.³⁷ Two other functionals were tested: BP86^{38,39} and MPWB95.^{40,41} Changes in all cases had a minor effect in the key results. The critical difference between the barriers in solvent for the **conc2** and **S_N2** dissociative pathways (vide infra) of 5.9 kcal·mol⁻¹ in the initial calculation was modified to 7.2 kcal·mol⁻¹ with the larger basis set, and to 5.6 and 9.3 kcal·mol⁻¹ with the MPWB95 and BP86 functionals, respectively. The key result for the chemical interpretation is that there is a significant difference in favor of the **S_N2** pathway, and this result is reproduced by all the tested computational methods.

3. Results and Discussion

3.1. Dissociative and Associative Pathways. The model system is defined by Pd(PMe₃)₂ plus CH₃SOCH₂Br. A palladium bisphosphine has been considered as the starting point because it is present in the generally accepted picture of the catalytic cycle, although the possible departure of one of the phosphine ligands has also been considered. CH₃SOCH₂Br has been used as a simple sulfoxide. The carbon center is certainly not asymmetric, but in the computational approach we can clearly identify the eventual inversion of configuration. The use of a primary bromide instead of the experimental secondary one could have an overall effect in the absolute barrier, but the effect of the sulfinyl substituent should be equally apparent. PMe₃ has been used as the simplest possible model phosphine because the general mechanism is not supposed to be affected by its properties. Upon request from one referee, we confirmed that the results (gas phase potential energies) were unchanged when PPh₃ was used at the ONIOM(B3LYP:UFF) level^{42,43} (see the Supporting Information). The mechanism will be considered only until the transition state leading to cleavage of the C–Br bond, and no effort will be made to discuss the subsequent intermediates.

Sulfoxides are known to act as weak ligands, and thus the organic fragment CH₃SOCH₂Br (**1**) can replace one of the phosphine ligands, reacting formally with Pd(PMe₃) (**2**), or react directly with the initial bis(phosphine) species Pd(PMe₃)₂ (**3**). The identity of active catalysts as mono- or bisphosphine complexes is moreover a current topic of research.^{8,44} This will lead to two different types of reaction pathways, which will be considered separately. We will start with the dissociative pathway, which involves an initial phosphine dissociation generating a monophosphine as the active species. The next section is for associative pathways, involving the bisphosphine catalyst.

3.2. Dissociative Pathways. Computed Structures. The α -bromo sulfoxide possesses three centers through which it can coordinate to palladium: the oxygen, the sulfur, and the bromine atoms. Apart from the simple η^1 binding, coordination can occur also by an S–O η^2 mode, or by a κ^2 mode by simultaneous binding of the oxygen and bromine atoms. Four stable

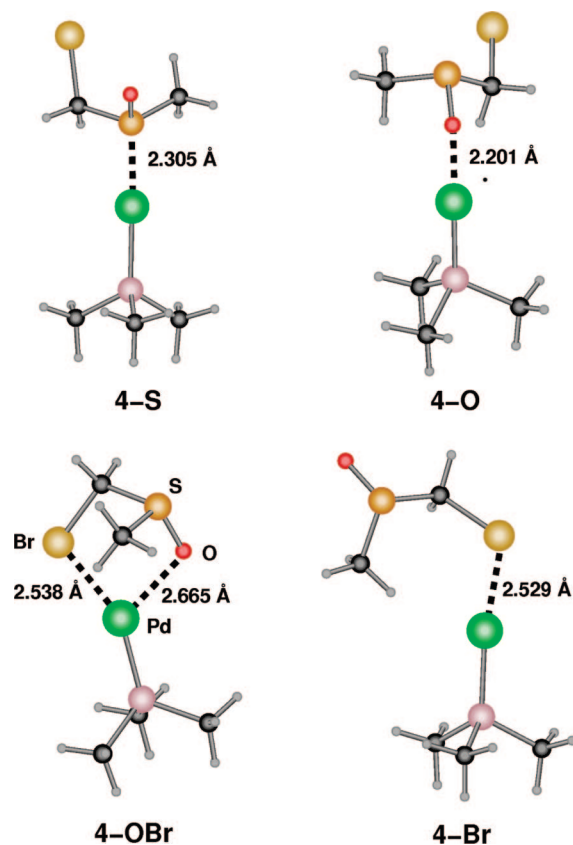


FIGURE 3. B3LYP optimized geometry of the different isomers of Pd(PMe₃)(CH₃SOCH₂Br).

Pd(PMe₃)(CH₃SOCH₂Br) adducts were identified and they are shown in Figure 3. They are labeled according to their coordination mode as **4-S**, **4-O**, **4-Br**, and **4-OBr**. The formation of each of these adducts from the Pd(PMe₃) plus CH₃SOCH₂Br system is exothermic, by values of 6.9, 7.8, 7.5, and 5.3 kcal·mol⁻¹, respectively. The existence of different possible adducts agrees with the usual behavior of sulfoxide complexes of late transition metals,⁴⁵ as is also the case for the Pd–S and Pd–O distances. **4-OBr** can be either viewed as genuine κ^2 or as a conformer of **4-Br**, because of the long Pd–O distance of 2.665 Å.

We were able to characterize four different pathways for the cleavage of the C–Br bond, each of them connected to a different adduct. The corresponding transition states are shown in Figure 4, and their relative energies with respect to the original reactants are collected in Table 1. The reaction coordinate corresponds always to the expected process, with cleavage of the carbon–bromine bonds and formation of the corresponding bonds indicated below for each case. Two of the transition states, **5-conc1** and **5-conc2**, correspond to concerted pathways. **5-conc2** is more stable (by 3.1 kcal·mol⁻¹), but they can be seen as conformers of the same structure. **5-conc1** is connected to **4-Br** and **5-conc2** to **4-OBr**. The mechanism is clearly concerted (Figure 2) with a triangular arrangement of the Pd, C, and Br atoms in the transition state. **5-conc1** and **5-conc2** differ in the arrangement of the sulfoxide substituent with respect to palladium. Though the Pd–Br and C–Br distances are similar in **5-conc1** and **5-conc2**, the Pd–C distance changes significantly from 2.528 Å to 2.812 Å (Figure 4). The Pd–O distance

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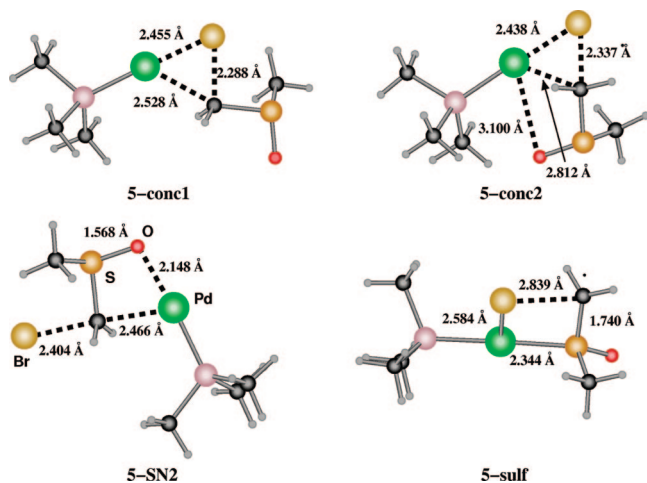


FIGURE 4. B3LYP optimized geometry of the transition states for the C–Br cleavage in the Pd(PMe₃)(CH₃SOCH₂Br) system.

TABLE 1. Relative Energies (kcal·mol⁻¹), Including Solvent Effects, of the Key Species Involved in the Dissociative Pathways^a

path	1 + 2 (reactants)	4 (adduct)	5 (transition state)	barrier
conc1	0.0	-7.8 (-15.3)	5.7 (-2.6)	13.5 (12.7)
conc2	0.0	-5.3 (-14.3)	4.3 (-5.7)	9.6 (8.6)
S _N 2	0.0	-9.0 (-18.6)	-5.3 (-10.8)	3.7 (7.8)
sulf	0.0	-6.9 (-14.9)	17.2 (10.0)	24.1 (24.9)

^a Gas phase values are included in parentheses.

in **5-conc2** (3.100 Å) seems too long for any strong interaction between both atom. It is worth mentioning the asymmetry in the formation of bonds to Pd in both paths: the Pd–Br bond is already formed in the transition state and the transition vectors correspond to the oscillation of the carbon between the palladium and the bromine. Of course, both concerted mechanisms lead to retention of configuration at the sp³ carbon. It is worth mentioning that despite the concerted nature of the path, the formation of the palladium–carbon and palladium–bromine bonds is quite asynchronous. This was confirmed through an intrinsic reaction coordinate calculation of **5-conc2**, but it is already apparent in the structure of the transition state itself. The palladium–bromine bond is nearly formed in the transition state, with a Pd–Br distance of 2.438 Å, close to values in the range of 2.4 Å expected for the bond distance between the two atoms. In contrast, the carbon is far from the equilibrium distances with either bromine or palladium. The Pd–C and C–Br distances are 2.812 and 2.337 Å in the transition state, far from the values around 2.03 and 1.96 Å corresponding to equilibrium.

The third transition state shown in Figure 4 corresponds to a different type of process—a nucleophilic substitution assisted by the coordinated atom—and is correspondingly labeled as **5-S_N2**. This mechanism, first suggested by Stille and Lau,^{14,15} has successfully explained the enantioselectivity observed in many reactions.⁴⁶ The relationship of this transition state with an S_N2 process is clear from the nearly linear arrangement of the Pd–C–Br atoms (angle of 178.4°), the similarity of the Pd–C (2.466 Å) and C–Br (2.404 Å) distances, and the nearly planar arrangement of the three other substituents at the reacting carbon. The structure of this transition state indicates that the sulfinyl group assists the oxidative addition (Pd–O distance is 2.148 Å), as will be shown below by the discussion on the

energetics. This transition state **5-S_N2** is connected to adduct **4-O** on the reactant side. On the product side, it is connected to an intermediate **6-S_N2**, included in the Supporting Information, where the anionic bromine is far away from the metal. This intermediate evolves through a low-energy barrier to the product where the bromine coordinates the cationic palladium center. In the presence of an asymmetric carbon the relative configuration at the carbon center would have been reversed by this S_N2 pathway.

There is a fourth pathway for C–Br cleavage at the palladium center that goes through transition state **5-sulf** initiated by coordination by the sulfur atom. This path is included here for completeness, because the energy barrier is noticeably higher. In **5-sulf**, the palladium does not attack the carbon of the sulfoxide but the bromine is exchanged between the carbon and the palladium through a 4-center transition state. The result is an intermediate **6-sulf** containing a S(=O)(=CH₂)(–CH₃)[–] ligand, which rearranges afterward to the usual oxidative addition product. This pathway leads in principle to retention of configuration at the carbon center, although low barrier configuration changes from the intermediate seem possible.

Energetics. Table 1 collects the computed relative energies of the key structures in each of the pathways. All relative energies are measured with respect to the reactants CH₃SOCH₂Br (**1**) plus Pd(PMe₃) (**2**). Both gas phase and solution energies are provided, and the discussion will be mostly based in the latter.

The most remarkable result is that the lowest barrier corresponds by far to the S_N2 pathway, running through transition state **5-S_N2**, 3.7 kcal·mol⁻¹ above the related adduct **4-O**. The barrier for the S_N2 path is more than 5 kcal·mol⁻¹ lower than those corresponding to the two concerted paths, with barriers of 13.5 and 9.6 kcal·mol⁻¹ for **5-conc1** and **5-conc2**, respectively. The usual preference for concerted paths⁴⁷ in aryl- and vinylhalides is thus absent for this system. The alternative path through **5-sulf** has a barrier of 24.1 kcal·mol⁻¹, more than 10 kcal·mol⁻¹ above the closest one. This path through **5-sulf** has no chemical relevance whatsoever, in agreement with its unusual features.

The stability of **5-S_N2** seems related to the coordination of the sulfinyl group to palladium through the oxygen (Pd–O distance of 2.148 Å, see Figure 4). In this transition state, there is a four-membered ring involving palladium, oxygen, sulfur, and carbon. On the contrary, the oxygen atom remains far from the palladium center in **5-conc1** (5.086 Å) and **5-conc2** (3.100 Å), unable to help efficiently the transition state of the concerted mechanism. A related hydrogen-bonding assistance of the C_{sp}³–F activation by a S_N2 mechanism has been recently reported.⁴⁸ Secondary interactions between the organic moiety and the metal center also have been reported in other cross-coupling cases involving sp² carbons,^{49,50} although they did not have the heavy mechanistic implications of the present case.

The role of solvation is the expected one. Comparison between results with and without solvent (Table 1) shows that the most sensitive barrier to the moderately polar solvent is that

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of the S_N2 path, which is reduced because of the presence of charge separation. The large change in energetics for this path could call into question the validity of the gas phase geometries for this calculation. We notice, however, that an eventual reoptimization in solution would lower the barrier for the S_N2 path, further increasing the difference between the two pathways. The gas phase geometry of the **5-S_{N2}** transition state seems in any case qualitatively correct, because it presents already a nearly linear Pd–C–Br arrangement, with maximum charge separation. The NPA (natural population analysis) charge on the bromine atom in **5-S_{N2}** is already -0.50 atomic units, on its way to -0.85 atomic units in intermediate **6-S_{N2}**.

The stabilizing interaction between palladium and oxygen in **5-S_{N2}** seems to be essentially of an electrostatic nature. This is confirmed by the natural population analysis⁵¹ of this structure, and its comparison with that of the transition state for the competing pathway **5-conc2**. The charges for the key Pd, C, Br, S, and O atoms are $+0.10$, -0.72 , -0.50 , $+1.23$, and -1.00 atomic units, respectively, in **5-S_{N2}**. The corresponding values in **5-conc2** are -0.12 , -0.75 , -0.23 , $+1.28$, and -0.97 atomic units. Charges for more atoms and all the transition states are provided in the Supporting Information. As expected, the larger difference is in the bromine center, with 0.27 electrons more in the S_N2 structure. This bromine center is departing as bromide in this mechanism, thus the charge accumulation is expected. The accumulation of negative charge in this atom means that positive charge must be spread in the rest of the molecule. In particular, the charge in palladium changes by 0.22 atomic units, from -0.12 in **5-conc2** to $+0.10$ in **5-S_{N2}**. The more chemically significant result is, however, that the oxygen has a large charge in both cases (-0.97 and -1.00 atomic units). The large charge means that oxygen is capable of strong electrostatic interactions. The small change of -0.03 atomic units between the two complexes means that charge transfer from oxygen to palladium in **5-S_{N2}** is practically neglectable. Thus, the stabilization of this transition state must be mostly electrostatic.

The nucleophilic substitution is unambiguously the most favored pathway for the oxidative addition with the monophosphine palladium complex. This suggests a highly stereoselective process leading to inversion at the sp^3 carbon, in excellent agreement with experiment. In fact, the barrier is so low in solution that the critical step may be related to the preliminary decoordination of one of the phosphines of the palladium bisphosphine complex. We will now study the effect of the presence of this second phosphine on the palladium.

3.3. Associative Pathways. Experimental studies have shown that in solution neutral palladium may have from two to five ligands.⁵² It is difficult for the computational model applied in this work to compare systems with different coordination numbers (small phosphine model, lack of entropic effects), but the consideration of at least two different coordination numbers can be significant to see if the same general behavior holds. The study of the reaction between CH_3SOCH_2Br (**1**) and the bisphosphine $Pd(PMe_3)_2$ (**3**) produced a set of pathways (**conc1**, **conc2**, **S_{N2}**, **sulf**) identical with that reported above for the reaction between **1** and **2**. The results are qualitatively similar, and because of this, they will be discussed in less detail. The reaction starts with the formation of an adduct, **7**, in this case weaker because of the higher coordination number of the metal,

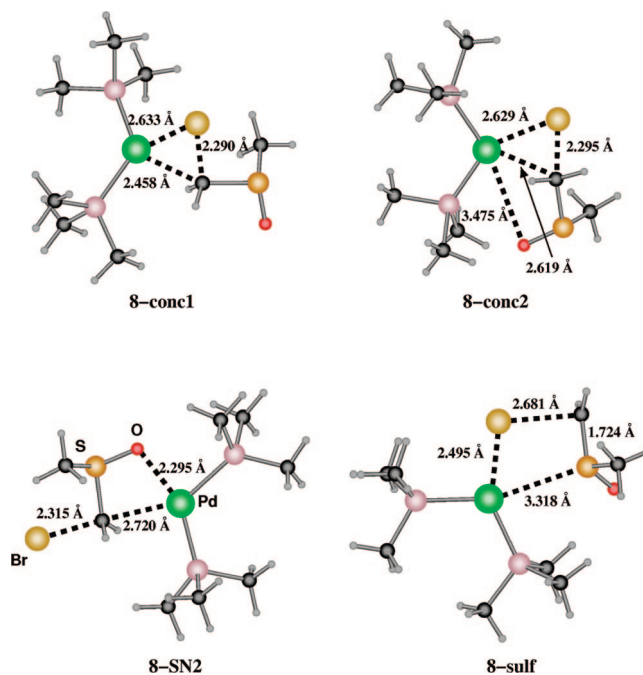


FIGURE 5. B3LYP optimized geometry of the transition states for the C–Br cleavage in the $Pd(PMe_3)_2(CH_3SOCH_2Br)$ system.

TABLE 2. Relative Energies ($kcal\cdot mol^{-1}$), Including Solvent Effects, of the Key Species Involved in the Associative Pathways^a

Path	1 + 3 (reactants)	7 (adduct)	8 (transition state)	Barrier
conc1	0.0	1.4 (–4.1)	27.6 (22.1)	26.2 (26.2)
conc2	0.0	1.5 (–3.8)	28.8 (21.2)	27.3 (25.0)
S_{N2}	0.0	5.4 (–6.4)	18.8 (13.3)	13.4 (19.7)
sulf	0.0	2.5 (–2.1)	23.1 (20.6)	20.6 (22.7)

^a Gas phase values are included in parentheses.

and continues to transition state **8**. The optimized structures for transition states **8-conc1**, **8-conc2**, **8-S_{N2}**, and **8-sulf** are shown in Figure 5, and follow the same geometrical patterns of transition states **5**, for the dissociative pathways. It is worth mentioning in any case that all these transition states lead to the cis oxidative addition product, whereas the trans product is observed experimentally.¹³ This does not seem a serious problem, because an isomerization between cis and trans product is possible and has been experimentally demonstrated.⁵³ We were able to find an additional S_N2 path, labeled as **S-S_{N2}** for this bisphosphine system, where the sulfinyl ligand coordinates to the metal through the sulfur instead of the oxygen. The features are similar to those of the (**O**)- S_N2 path, and because of this it will not be further discussed.

Table 2 presents the relative energies of the key points in the associative pathways. Again, the preference for the S_N2 path, through **8-S_{N2}**, is clear-cut, with a barrier of $13.4 kcal\cdot mol^{-1}$. The barriers for the concerted paths are about $10 kcal\cdot mol^{-1}$ higher in energy (26.2 and $27.3 kcal\cdot mol^{-1}$ for **8-conc1** and **8-conc2**) as is the barrier for the **sulf** pathway ($20.6 kcal\cdot mol^{-1}$). The barriers as a whole are higher than those for the monophosphine system. The bisphosphine system needs to close the P–Pd–P angle when going to the transition state, and that geometrical distortion must have an energy penalty. Direct comparison is in any case troublesome, because the bisphosphine complex must be in principle a more stable starting point than monophosphine.

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Other details in Table 2 follow the expected trends. Initial adducts have positive energies in solvent with respect to the reactants, but this is related to the low gas phase stability of the adducts, less than $7 \text{ kcal}\cdot\text{mol}^{-1}$. This low stability of the adducts is in turn related to the poor affinity of palladium bisphosphine for extra ligands. Solvation effects are especially important for the barrier of the $\text{S}_{\text{N}}2$ pathway, again stabilizing it because of the charge separation involved in the process.

The main conclusion of this study on the bisphosphine systems is that the $\text{S}_{\text{N}}2$ pathway is largely preferred. The preference for this pathway can be traced down to the stabilizing interactions between the sulfinyl oxygen and the metal center, which is absent in the other mechanisms. This result is analogous to that found for the monophosphine systems, and seems to point to a general behavior that would explain the experimental observation of inversion of carbon sp^3 centers adjacent to sulfinyl ligands in Suzuki–Miyaura cross-coupling.

4. Concluding Remarks

In this work we studied computationally the influence of the sulfinyl group on the oxidative addition of an α -bromo sulfoxide to a palladium complex. Both monophosphine and bisphosphine systems have been considered, and they lead to similar results. In both cases, different reaction paths have been characterized for the process through location of the transition states. The pathways corresponding to concerted oxidative addition, with retention of configuration, have reasonable energy barriers, but these are always higher than those corresponding to the nucleophilic substitution transition states that lead to inversion

of configuration. The experimentally observed stereospecificity strongly suggests that the reaction takes place through an $\text{S}_{\text{N}}2$ mechanism, which is explained by the stabilizing interaction of the oxygen (or the sulfur) atom of the sulfinyl unit with the palladium center in the corresponding transition state. This interaction is impossible in the concerted mechanisms. The favorable interactions between the sulfinyl group and palladium in the transition state explain thus the enhanced reactivity shown by the C_{α} –Br bond in α -bromo sulfoxides. Moreover, the effect of the sulfinyl substituent in the oxidative addition step is responsible for the stereochemical outcome of the whole Suzuki–Miyaura catalysis, because the rest of the steps occur with well-defined retention of configuration.

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Supporting Information Available: Full reference for the Gaussian03 program, Cartesian coordinates and summary of energetics for all stationary points, calibration tests with different basis sets and functionals, calibration tests with a larger model, and NPA charges for selected atoms and compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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