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DFT Investigation of Suzuki–Miyaura Reactions with Aryl Sulfamates Using a Dialkylbiarylphosphine-Ligated Palladium Catalyst

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Abstract

Aryl sulfamates are valuable electrophiles for cross-coupling reactions because they can easily be synthesized from phenols and can act as directing groups for C–H bond functionalization prior to cross-coupling. Recently, it was demonstrated that (1-^tBu-Indenyl)Pd(XPhos)Cl (XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) is a highly active precatalyst for room-temperature Suzuki–Miyaura couplings of a variety of aryl sulfamates. Herein, we report an in-depth computational investigation into the mechanism of Suzuki–Miyaura reactions with aryl sulfamates using an XPhos-ligated palladium catalyst. Particular emphasis is placed on the turnover-limiting oxidative addition of the aryl sulfamate C–O bond, which has not been studied in detail previously. We show that bidentate coordination of the XPhos ligand via an additional interaction between the biaryl ring and palladium plays a key role in lowering the barrier to oxidative addition. This result is supported by NBO and NCI-Plot analysis on the transition states for oxidative addition. After oxidative addition, the catalytic cycle is completed by transmetalation and reductive elimination, which are both calculated to be facile processes. Our computational findings explain a number of experimental results, including why elevated temperatures are required for the coupling of phenyl sulfamates without electron-withdrawing groups and why aryl carbamate electrophiles are not reactive with this catalyst.

Graphical abstract

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Notes

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Supporting Information

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Additional details about DFT calculations (PDF)

Cartesian coordinates for the calculated structures (XYZ)

INTRODUCTION

Transition-metal-catalyzed cross-coupling is one of the most powerful synthetic methods in modern organic chemistry.¹ In particular, Suzuki–Miyaura reactions catalyzed by palladium are used extensively in areas ranging from materials chemistry to the synthesis of natural products and fine chemicals.² Traditional Suzuki–Miyaura reactions couple a nucleophilic boronic acid with an electrophilic aryl or vinyl halide to generate a new C–C bond. However, in some cases, electrophiles generated from phenolic derivatives, which are robust, stable, and easy to synthesize from ubiquitous phenols,³ offer unique advantages for Suzuki–Miyaura reactions in comparison to aryl halides.⁴ For example, phenol-containing moieties are intermediates in many target-orientated syntheses and can be used as coupling partners after activation, when analogous halides would be difficult to access.⁵ Additionally, in some cases phenolic derivatives can act as directing groups for the prefunctionalization of the aromatic backbone of the electrophile through directed ortho metalation prior to cross-coupling.⁶ Although simple phenolic derivatives such as aryl tosylates and mesylates are extensively used in cross-coupling,^{4a,c} these moieties are not useful directing groups. In contrast, aryl sulfamates and carbamates, which are also derived from phenols, can be used as directing groups for C–H functionalization and as a consequence there is significant interest in using them as electrophiles in cross-coupling.⁶

In 2009, Garg and co-workers described the first examples of Suzuki–Miyaura reactions using aryl sulfamate electrophiles.⁷ Although they used a cheap and stable nickel precatalyst, high catalyst loadings, elevated temperatures (>100 °C), and large excesses of both the boronic acid and base were required. Subsequent work from a number of different groups has resulted in improvements to Garg's conditions, but in general the conditions for Ni-catalyzed Suzuki–Miyaura reactions involving aryl sulfamates are still harsher than those required for other electrophiles.^{5,8} Recently, we reported room-temperature Suzuki–Miyaura couplings of aryl sulfamates using an XPhos-ligated palladium precatalyst, (1-^tBu-Indenyl)Pd(XPhos)Cl (XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) (Figure 1).⁹ These reactions use relatively low catalyst loadings and do not require large excesses of either boronic acid or base. Notably, the use of the dialkylbiaryl Buchwald phosphine ligand XPhos resulted in a more active catalyst in comparison to systems supported by other monodentate phosphine and NHC ligands. Although dialkylbiarylphosphines are a privileged class of ligands for palladium-catalyzed cross-coupling reactions, which have been utilized to facilitate a large number of reactions,¹⁰ there are relatively few computational studies¹¹ on catalytic systems featuring these ligands, and a further understanding of how these ligands influence the elementary steps in cross-coupling would be valuable.

Here, we describe an in-depth computational analysis of the catalytic cycle for Suzuki–Miyaura reactions using aryl sulfamate electrophiles and a dialkylbiarylphosphine-ligated palladium catalyst. In particular, we focus on the turnover-limiting oxidative addition step, which is challenging to model due to the ability of both the substrate and ancillary ligand to bind to palladium with different coordination modes. Our analysis shows substantial differences between previous computational studies on Ni-based systems, where a five-centered transition state is proposed for oxidative addition of sulfamates,^{5,8f} and the XPhos-ligated palladium system, which proceeds through a more traditional three-centered transition state. The ability of XPhos to bind in a bidentate fashion, as a result of an additional interaction between the biaryl ring and palladium, is crucial to lowering the barrier to oxidative addition. A comparison of the transition state for oxidative addition of 1-naphthyl sulfamate to those for phenyl sulfamate and 1-naphthyl carbamate provides evidence for why these substrates require more forcing catalytic conditions (phenyl sulfamate) or cannot be successfully coupled with this catalyst (1-naphthyl carbamate). Transition state structures were also found for both the transmetalation and reductive elimination steps in the catalytic cycle, with both producing barriers far lower than those for oxidative addition. Through our computational study, we provide further understanding of the excellent activity achieved using dialkylbiarylphosphines and show the increased complexity in the oxidative addition step when aryl sulfamates are used, in comparison to traditional aryl halides. This information may prove valuable for the rational design of improved catalysts and ligands for cross-coupling reactions involving aryl sulfamates and related substrates.

COMPUTATIONAL DETAILS

DFT calculations were carried out with the meta-GGA pure M06L and hybrid M06 functionals including dispersion, as implemented in the Gaussian09 program.¹² The M06L and M06 functionals were selected due to their proven ability to accurately model transition-metal complexes, including systems where dispersion forces are important.¹³ Furthermore, M06L, as a local functional, allows for more computationally affordable experiments, which is important for the large systems studied in this work.¹³ The ultrafine (99,590) grid was used for high numerical accuracy in the calculation of the two-electron integrals. Structures were fully optimized without any geometry or symmetry constraints at the DFT(M06L) level, with the double- ζ 6-31G** basis set on all elements except palladium, which was described with the relativistic ECP-adapted LANL2DZ(f) basis set. The vibrational frequencies of the optimized structures were also computed at this level of theory with the aim of classifying the stationary points as either saddle points, i.e. transition states with a single imaginary frequency, or minima, i.e. reactants, intermediates, and products with all-real frequencies. Further, these calculations were used to determine the thermodynamic properties, including the zero-point, thermal, and entropy energies. Both the optimization and frequency calculations were performed including the solvent effects of toluene with the continuum SMD model. This model was also used to refine the energies at the DFT(M06) level with the triple- ζ 6-311G** basis set on all elements except palladium, which was described with the relativistic ECP-adapted LANL2TZ(f) basis set. The Gibbs free energy discussed in the text, G_{solv} , includes both the thermochemistry and the refined energy.

Stereoelectronic properties, including donor–acceptor interactions and steric effects, were analyzed by means of NBO6¹⁴ and NCIPLOT¹⁵ calculations, respectively.

RESULTS AND DISCUSSION

The majority of traditional cross-coupling reactions (Suzuki–Miyaura, Negishi, Stille, Hiyama–Denmark), which employ a well-defined Pd(II) precatalyst, involve the same four elementary steps regardless of the exact identity of the electrophile and nucleophile: (1) reduction of the Pd(II) precatalyst to the active Pd(0) species,¹⁶ (2) oxidative addition of the electrophile (R–X) to form a Pd(II) intermediate of the form LPd(R)(X),¹⁷ (3) transmetalation with an organometallic nucleophile (M–R') to yield LPd(R)(R'),¹⁸ and (4) reductive elimination of the two organic fragments to produce a new C–C bond (R–R') and regenerate the active Pd(0) species.^{11b,19} Each of these steps have been studied in detail, both theoretically and experimentally, but the structures and energies of the transition states for each step vary greatly depending on the specific substrates and reaction conditions, including the nature of the electrophile, nucleophile, ligand, solvent, and base. In this work we propose that Suzuki–Miyaura reactions with aryl sulfamates catalyzed by (1-^tBu-Indenyl)Pd(XPhos)Cl follow the same four steps, which are discussed in detail below. However, the unusual nature of both the electrophile and supporting XPhos ligand lead to significant differences in the structures of the transition states in comparison to those calculated for other cross-coupling reactions.

Reduction of Palladium(II) Precatalyst to Palladium(0)

Recently, we described the pathway for the reduction of complexes of the type (1-^tBu-indenyl)Pd(L)Cl to form the active (L)Pd⁰ species for cross-coupling in the presence of alcoholic solvents.^{16f} Given that the conditions employed for Suzuki–Miyaura reactions with aryl sulfamates include methanol as a cosolvent, the formation of an XPhos-ligated Pd(0) active species using (1-^tBu-indenyl)Pd(XPhos)Cl as a precatalyst is likely to follow the same pathway (see the Supporting Information for more details). Our calculations show that, as has been suggested previously,¹¹ the most stable XPhos-ligated Pd(0) species is not simply bound to the ligand through the phosphorus atom in a monodentate fashion. Instead, the Pd(0) center is stabilized through additional interactions with the carbons in the 1'- and 2'-positions of the biaryl group (Figure 2). In fact, these carbons are only 2.726 and 2.218 Å, respectively, away from the palladium center, with concurrent elongation of the C–C double bond in the biaryl ring (1.442 Å in comparison to an average of 1.405 Å in the rest of the ring). Furthermore, this interaction stabilizes the monoligated Pd(0) species considerably more than coordination of either methanol or toluene, the solvents used in catalysis (see Figure 2 and the Supporting Information for more discussion about the coordination of solvent to Pd(0)). The resulting bidentate XPhos complex can be further stabilized by coordination of toluene, $G = -4.9$ kcal mol⁻¹, or, more strongly, by coordination of the 1-(naphthyl)-*N,N*-dimethyl sulfamate substrate, $G = -8.4$ kcal mol⁻¹ (*vide infra*). Further analysis of the electronic structure of the “monodentate” and “bidentate” coordination modes is provided in a subsequent section.

Oxidative Addition

After precatalyst activation, the first step in the catalytic cycle is proposed to be oxidative addition. Although significant experimental and computational research has been performed to understand the pathways for oxidative addition in cross-coupling,¹⁷ the vast majority of this work has been performed with traditional aryl halide electrophiles and few reports have explored the oxidative addition of a C–O bond, such as those present in aryl sulfamates. Garg and co-workers computationally studied the catalytic cycle for Ni-catalyzed Suzuki–Miyaura couplings with aryl sulfamates and carbamates.⁵ They proposed that oxidative addition of an aryl sulfamate to $(PCy_3)_2Ni^0$ proceeds via initial dissociation of a PCy_3 ligand. Subsequently, activation of the aryl sulfamate occurs through a transition state containing a five-membered ring, in which an oxygen of the sulfonyl group is bound to nickel in addition to the Ni–aryl interaction. Similar pathways were proposed for related nickel systems.^{8f,20} The only work with palladium examined oxidative addition of phenyl sulfamate to $(PCy_3)_2Pd^0$ and found that it had a prohibitively high barrier of 39.7 kcal/mol after dissociation of 1 equiv of the PCy_3 ligand, suggesting that catalysis would not occur with this particular system.⁵ This is consistent with our experimental results.^{9b} In contrast to the bis-ligated $(PCy_3)_2Pd^0$ system previously studied, the active catalyst when (1-^tBu-indenyl)Pd-(XPhos)Cl is used is likely a monoligated XPhos-supported Pd(0) species (*vide supra*) and therefore we explored oxidative addition of aryl sulfamates to this species.

The substrate used to initially investigate oxidative addition was 1-(naphthyl)-*N,N*-dimethyl sulfamate, as this compound readily undergoes coupling at room temperature.^{9b} Initial binding of the substrate to **PdXPhos_Bi** to form an η^2 -naphthyl sulfamate complex is exoergic by 8.4 kcal/mol, and the complex maintains the “bidentate” binding mode of the XPhos ligand (Figure 3, **OA_1**). The 1-naphthyl sulfamate substrate is bound through the C1–C2 π bond with Pd–C bond lengths of 2.198 and 2.183 Å, respectively. Although the secondary ligand interaction is not as significant in **OA_1** as it is in **PdXPhos_Bi**, the ligand maintains the same conformation, with Pd–C bond distances of 2.929 and 2.804 Å to C1' and C2', respectively.

From **OA_1**, several transition states were found that model the breaking of the C_{aryl} – $O_{sulfamate}$ bond with concurrent formation of new Pd– C_{aryl} and Pd– $O_{sulfamate}$ bonds. The cleavage of the S–O bond of the sulfamate, which is not observed experimentally, was also explored (see Figure S3 in the Supporting Information). Transition states for breaking of the C_{aryl} – $O_{sulfamate}$ bond with the XPhos ligand in both “monodentate” and “bidentate” coordination modes were modeled. When the “monodentate” XPhos conformation is present, the classical three-center transition state obtained with aryl halides¹⁷ was found but gives a high barrier for oxidative addition of 43.6 kcal/mol (Figure 4, **OA_3C_MD**). When a five-center transition state is employed, with the sulfonyl oxygen bound to the palladium center, the barrier decreases to 39.6 kcal/mol (Figure 4, **OA_5CO_MD**). These results for the “monodentate” XPhos conformation are consistent with those described by Garg for nickel complexes with the five-membered ring having a lower barrier.⁵ However, the oxidative addition barrier for palladium is decreased even further when the nitrogen atom of the sulfonyl group stabilizes the five-membered transition state (35.0 kcal/mol; Figure 4, **OA_5CN_MD**). Moving to the “bidentate” ligand binding mode yielded three further

transition state structures. When the ligand binds in this fashion, the five-centered transition state with the sulfonyl nitrogen bound had a slightly higher barrier (36.4 kcal/mol, **OA_5CN_BD**) in comparison to **OA_5CN_MD**. However, switching to a five-centered transition state with the sulfonyl oxygen yielded a lower barrier to oxidative addition (32.3 kcal/mol, **OA_5CO_BD**). Finally, in contrast with Garg's studies, the three-membered transition state (**OA_3C_BD**) is the lowest in energy and yields an oxidative addition energy barrier of 25.5 kcal/mol. Notably, this barrier is consistent with a reaction occurring at room temperature on a time scale of hours. While the biaryl interaction in Buchwald type ligands has been shown to stabilize monoligated Pd(0) species in multiple cases,²¹ there are only a few reports^{11,17x} where a "bidentate" binding mode stabilizes an oxidative addition transition state (*vide infra* for further details). Additionally, the switch between a three-membered transition state and a five-membered transition state for the oxidative addition of aryl sulfamates is similar to results from Houk and co-workers for the oxidative addition of aryl pivalates to nickel(0) supported by either monodentate or bidentate phosphine ligands.²²

Further examination of the lowest energy oxidative addition transition state, **OA_3C_BD**, shows that the elongation of the sulfamate C_{aryl}-O bond is significant; in the transition state, this bond is 1.687 Å, in comparison to 1.397 Å in free 1-(naphthyl)-*N,N*-dimethyl sulfamate. Although XPhos maintains the same conformation as that found to stabilize the monoligated Pd(0) complex, the biaryl interaction is less pronounced, with Pd-C bond distances of 2.979 and 2.801 Å for C1' and C2', respectively. These are similar to those found in **OA_1**. The product of oxidative addition (**OA_Prod**) is a Pd(II) naphthyl sulfamate species that is -9.5 kcal/mol in energy lower than the starting materials (**PdXPhos_Bi** and 1-(naphthyl)-*N,N*-dimethyl sulfamate). In **OA_Prod**, only one of the oxygens from the sulfamate is bound (Pd-O = 2.161 Å) and the "bidentate" conformation of XPhos is maintained (Pd-C1' = 2.909 Å, Pd-C2' = 2.763 Å; elongation of C1'-C2' to 1.420 Å). In contrast, the oxidative addition product in Garg's Ni(PCy₃)₂ system, (PCy₃)Ni(aryl)(sulfamate), features a κ^2 -sulfamate ligand where two of the sulfonyl oxygen atoms are bound to the Ni(II) center, presumably in part because the ligand cannot adopt a bidentate conformation.⁵

Coupling reactions with 1-(naphthyl)-*N,N*-dimethyl sulfamate proceeded to completion at room temperature with various boronic acids.^{9b} However, phenyl-*N,N*-dimethyl sulfamate is a more challenging substrate, which requires elevated temperatures (80 °C) to afford high yields. For the purpose of comparison, we also calculated the barrier for oxidative addition of phenyl-*N,N*-dimethyl sulfamate to **PdXPhos_Bi** (Figure 5). Unsurprisingly, the energy barrier to oxidative addition is considerably higher (27.6 kcal/mol), consistent with our experimental results.

Transmetalation

After oxidative addition, the next step in the proposed catalytic cycle is transmetalation. Conventionally two pathways for the initial steps have been proposed for transmetalation in Suzuki-Miyaura reactions in the presence of protic solvents (Figure 6).^{18m,n} (a) The protic solvent is deprotonated and undergoes ligand substitution with the halide or pseudohalide at the metal center. The coordinated deprotonated solvent then acts as a Lewis base toward the organoboron nucleophile to form a boronate species bound to the palladium center. (b) The

deprotonated solvent reacts directly with the boronic acid to form a boronate, which then undergoes a ligand metathesis reaction with the halide or pseudohalide to coordinate to the palladium (Figure 6). Although considerable experimental and computational work has been dedicated to determining the specific pathway for transmetalation,¹⁸ it can vary depending on the exact reaction conditions (metal, ligand, type of organoboron, base). Therefore, it is difficult to predict which pathway a new system will follow and both routes were considered in this work.

For our Suzuki–Miyaura reactions using aryl sulfamates, the experimental conditions employed methanol as a cosolvent, in addition to K_2CO_3 as the base.^{9b} These conditions ensure that methoxide, OMe^- , is the base during catalysis. Solvent effects, which are especially relevant in this step due to the participation of small anions, were introduced with a mixed model combining implicit toluene solvation (SMD method continuum) with explicit molecules of methanol within the first solvation sphere of the system (see the Supporting Information for further details).

Comparing the thermodynamics between pathways a and b does not yield any significant differences between the two routes. Reaction of **OA_Prod** with 1 equiv of OMe^- yields a new Pd–OMe bond and a complex that is 4.5 kcal/mol below the starting reactants (pathway a, Figure 6). Likewise, reaction of the base with 4-(methoxyphenyl)boronic acid to form a reactive four-coordinate boronate species is downhill by 3.1 kcal/mol. Both of these pathways ultimately lead to **TM_1**, which is exoergic by 14.1 kcal/mol in comparison to the ground state **PdXPhos_Bi** and 4.6 kcal/mol lower in energy than **OA_Prod**. Furthermore, due to the complexity of the system, reliable calculations to model the kinetics of pathways a and b were not possible and as a consequence we are unable to provide a definitive answer on whether transmetalation follows pathway a or b. Nevertheless, on the basis of previous work^{18a–l} and the fact that formation of **TM_1** is thermodynamically favorable, it is likely that the barrier to form this species is small. Recently, Denmark and co-workers have comprehensively explored transmetalation in Suzuki–Miyaura reactions.²³ They have shown that the generation of an activated boronate species may not be necessary for transmetalation to occur, with certain conditions allowing for transmetalation directly from the boronic acid. However, for our specific system, the pathway for transmetalation directly from the boronic acid is higher than that shown in Figure 7, meaning that formation of a more active boronate species is required (see the Supporting Information).

In Figure 7, the lowest energy pathway for transmetalation from **TM_1** is shown. In this pathway, **TM_1** is the only structure that maintains the secondary interaction with the XPhos ancillary ligand ($Pd-C1' = 2.871 \text{ \AA}$, $Pd-C2' = 2.837 \text{ \AA}$). Subsequently, **TM_1** undergoes a rearrangement in which an OH group of the nucleophile binds to the palladium center and displaces the secondary interaction of XPhos to form **TM_2**. This process is endoergic by 2.9 kcal/mol. The transition state structure for the transfer of the 4-methoxyphenyl group from boron to the palladium center (**TM_TS**) is only 8.9 kcal/mol higher in energy than the lowest energy structure, **TM_1**. The incipient Pd–C bond distance is 2.182 Å, while the B–C bond has elongated to 2.075 Å (in comparison to 1.608 Å in **TM_2**). This transition state relaxes to yield a product that is a four-coordinate palladium intermediate, **TM_Prod**, with the two aryl groups cis to each other. This structure is 20.4 kcal/mol lower in energy than the

starting reactants. Overall, our calculations demonstrate that the turnover-limiting step for the palladium-catalyzed Suzuki–Miyaura of aryl sulfamates is not transmetalation, as has been proposed in related nickel-catalyzed reactions.⁵

Reductive Elimination

Reductive elimination, which is the final step in the proposed catalytic cycle, is initiated by dissociation of methoxyboronic acid from the transmetalation product, **TM_Prod**. This process generates a three-coordinate species that is endoergic by 1.7 kcal/mol from **TM_Prod** (**RE_1** in Figure 8). Subsequent ligand rearrangement generates a pseudo-four-coordinate palladium center (**RE_2**) that is 18.5 kcal/mol more stable than **RE_1**. In **RE_2** the XPhos ligand again binds in a “bidentate” fashion. As has been suggested previously,^{11b} the biaryl motif of the Buchwald-type ligands aids the reductive elimination process by forcing the two organic fragments to be in close proximity to each other.

The C···C distance in **RE_1** is 2.804 Å, in comparison to 2.686 Å in **RE_2**. Furthermore, the C–Pd–C bond angle decreases to 82.63° for **RE_2** in comparison to 88.14° in **RE_1**. The transition state structure for reductive elimination (**RE_TS_BD**) is only 7.6 kcal/mol higher in energy than **RE_2**, yielding the lowest energy barrier of the three elementary steps in this catalytic cycle. In contrast, the reductive elimination transition state found when XPhos is in the “monodentate” coordination mode (**RE_TS_MD**) produces a barrier of 20.2 kcal/mol, 12.6 kcal/mol higher than **RE_TS_BD**. This again demonstrates the advantage of using a ligand which can form weak secondary interactions with the palladium center. The **RE_TS_BD** transition state connects to a species (**RE_Prod**) in which the overall product of cross-coupling, 1-(4-methoxyphenyl)naphthalene, is still bound to the palladium center through the C–C double bond of the methoxyphenyl moiety. This species is significantly downhill (62.5 kcal/mol) from the starting reagents, consistent with previous work from Garg,⁵ and facile dissociation of the biaryl presumably regenerates **PdXPhos_Bi**.

Oxidative Addition of Aryl Carbamates

While the (1-^tBu-indenyl)Pd(XPhos)Cl precatalyst could couple a wide range of aryl sulfamates, it was not capable of coupling aryl carbamates.^{9b} As the turnover-limiting step in reactions with aryl sulfamates is oxidative addition, we calculated the barrier for oxidative addition of 1-(naphthyl)-*N,N*-dimethyl carbamate to **PdXPhos_Bi** (Figure 9). Initial binding of the 1-naphthyl carbamate substrate to **PdXPhos_Bi** is exoergic by 8.9 kcal/mol (**OA_{carb}_1**). The structure of **OA_{carb}_1** is very similar to that found for the 1-naphthyl sulfamate analogue, featuring an η^2 -naphthyl carbamate with Pd–C bond distances of 2.201 and 2.207 Å, in addition to the “bidentate” XPhos conformation (Pd–C1' = 2.935 Å, Pd–C2' = 2.868 Å). A similar three-centered transition state to **OA_3C_BD** was found for oxidative addition of the aryl carbamate (**OA_{carb}_TS**). It features “bidentate” coordination of the XPhos ligand, and the Pd–C and Pd–O bond distances are similar to those calculated in **OA_3C_BD**. Nevertheless, despite the similarities in structure, the barrier to oxidative addition for the 1-naphthyl carbamate is much greater than for 1-naphthyl sulfamate (31.9 kcal/mol vs 25.5 kcal/mol, respectively). This trend is consistent with our experimental results and is in agreement with aryl sulfamates possessing weaker C_{aryl}–O bonds in comparison to the analogous aryl carbamates. Similarly, calculations also suggest that the

barrier for oxidative addition of aryl carbamates to nickel(0) species is higher than the corresponding barrier for aryl sulfamates.^{5,24} Interestingly, the product of aryl carbamate oxidative addition (**OA_{carb}_Prod**) is endoergic by 6.5 kcal/mol in comparison to the lowest energy structure (**OA_{carb}_1**). Therefore, carbamate oxidative addition is both kinetically and thermodynamically disfavored, although in catalysis if the kinetic barrier for oxidative addition could be overcome the thermodynamic favorability of subsequent steps in the catalytic cycle would presumably drive the catalytic reaction.

Electronic and Steric Effects on the Oxidative Addition Step

The results presented above indicate that oxidative addition is the turnover-limiting step in cross-coupling reactions involving aryl sulfamates catalyzed by an XPhos-ligated palladium catalyst. Therefore, understanding the electronic and steric effects of the substrate on this step may provide useful guidelines for the design of more efficient catalysts. The graphical representation of the oxidative addition energy barriers associated with transition states **OA_3C**, **OA_5CO**, and **OA_5CN** (Figure 10) shows an opposite trend for the mono- and the bidentate coordination modes of XPhos. While the five-center transition state with N bound to palladium yields the lowest barrier when XPhos coordinates to palladium in a “monodentate” fashion (**OA_5CN_MD**), the three-center transition state yields the lowest barrier with the “bidentate” coordination of XPhos (**OA_3C_BD**). Computational experiments replacing XPhos by PMe_3 suggest that **OA_5CN_MD** would be the lowest transition state in a purely monodentate system (Figure S6 in the Supporting Information).

Natural bond orbital (NBO) analysis on **OA_3C_MD**, **OA_5CO_MD**, and **OA_5CN_MD** suggests that the higher stability of the latter transition state is due to the stronger electron donation of the N(sp) lone pair to the empty $\text{Pd-C}(\sigma^*)$ orbital. The stabilization energy (SE) obtained from second-order perturbation analysis for this interaction is 13.1 kcal/mol in **OA_5CN_MD**, whereas the analogous $\text{O(sp)} \rightarrow \text{Pd-C}(\sigma^*)$ donation in **OA_5CO_MD** is weaker with $\text{SE} = 10.0$ kcal/mol, in line with the higher barrier associated with the latter transition state. This stabilizing interaction is not present in the highest energy state **OA_3C_MD**.

In the lowest energy transition state, **OA_3C_BD**, the XPhos ligand is bound not only to palladium by the phosphorus atom but also through a secondary interaction with the C1' and C2' atoms of the biaryl motif (Pd–C bond distances of 2.98 and 2.80 Å, respectively; see Figure 2 for labels). This interaction is also observed in several Pd(0) and Pd(II) intermediates along the catalytic pathway, with the shortest Pd–C_{biaryl} distances ranging from 2.22 to 2.87 Å. In the NBO analysis of **OA_3C_BD**, this interaction is defined as a donation from a $\text{C}=\text{C}(\pi)$ orbital of the XPhos biaryl to the $\text{Pd-C}(\sigma^*)$ orbital of the forming bond, with a small SE of 4.5 kcal/mol. This weak interaction is seen in the noncovalent interaction plot (NCIPLLOT) of this transition state (Figure 11). The blue isosurface derived from the reduced density gradient reveals the presence of these interactions between palladium and the XPhos biaryl. These are weaker in the five-center transition states **OA_5CO_BD** and **OA_5CN_BD**, as shown by the longer Pd–C_{biaryl} distances of 2.98 and 3.24 Å and the smaller SEs of 4.1 and 0.6 kcal mol^{−1}, respectively. The SEs for the electron donation of the lone pairs in O and N to palladium are also lower than those in the

“monodentate” transition states: 8.0 and 6.8 kcal/mol, respectively. Further, the local NBO charges in the sulfamate and carbamate of the lowest-energy transition states (Table S2 in the Supporting Information), -0.46 and -0.47 au, respectively, account for the lower barrier found in the former case (Figures 3 and 9), due to the higher ability of the sulfamate in stabilizing the charge. In contrast, the small and similar charges of the aryl fragments in the phenyl and naphthyl sulfamate transition states, 0.03 and -0.05 au, respectively, do not account for the lower barrier in the latter case (Figures 3 and 5). This may instead be due to the more numerous CH- π interactions with the larger naphthyl ring (Figure 11).

A comparison of the NCI plots of the **OA_3C_BD** and **OA_3C_MD** transition states clearly shows more attractive interactions between palladium and the biaryl group in the former (Figure 11). The presence of these interactions highlights the relevance of dispersion forces in this system, which, in our DFT model, are accounted for by the M06L and M06 functionals. In addition, the $\text{PCC}^{\text{biaryl}}$ angle in **OA_3C_MD** is distorted to 131.1° , which, in contrast with the 121.6° in **OA_3C_BD**, is clearly larger than the ideal sp^2 angle (120°), due to the steric repulsion between the cyclohexyl and biaryl rings. These intramolecular interactions within the ligand suggest that the conformational change of XPhos from “bidentate” to “monodentate” has an energy cost, regardless of its coordination to the palladium sulfamate system. This was confirmed by optimization of the “monodentate” and “bidentate” conformations of the ligand with no metal present (Figure 12), which showed an energy difference of 8.4 kcal/mol in favor of the “bidentate” conformation. These results suggest that **OA_3C_BD** yields the lowest energy barrier by combining the most stable conformation of XPhos with the strongest XPhos-Pd noncovalent interactions.

Overall, our results indicate that the efficiency of **PdXPhos_Bi** in cross-coupling reactions with aryl sulfamates, in contrast to bis-ligated PdL_2 systems previously tested,^{5,9b} originates from the extra stability provided by noncovalent interactions with the XPhos biaryl motif. These interactions stabilize the monoligated PdL form of the catalyst, which is intrinsically more reactive than the PdL_2 form.²⁵ New catalyst design based on monoligated PdL systems should focus on increasing electron donation to palladium either from the ligand, if coordinated in a “bidentate” manner, or from the leaving group of the electrophile, if monodentate coordination of the ligand is preferred.

CONCLUSIONS

In this study we have used DFT to show that the mechanism for **PdXPhos_Bi**-catalyzed Suzuki–Miyaura reactions involving aryl sulfamate electrophiles likely follows the traditional cross-coupling pathway: oxidative addition, transmetalation, and reductive elimination. As is the case for many palladium-catalyzed cross-coupling reactions, oxidative addition was found to be the turnover-limiting step. Analysis of the pathway for oxidative addition shows that the coordination modes of both the aryl sulfamate and the XPhos ancillary ligand have a significant effect on the energy barrier. Notably, a secondary interaction between the palladium center and the biaryl motif of the XPhos ligand significantly stabilizes the lowest energy transition state for oxidative addition. Nevertheless, despite the beneficial properties of the XPhos scaffold, the barrier to oxidative addition with aryl carbamates was found to be prohibitively high, which is consistent with our inability to

experimentally couple these substrates using an XPhos- supported palladium precatalyst. The secondary interaction between XPhos and palladium is also important in stabilizing the monoligated Pd(0) active species and assisting in lowering the barrier for reductive elimination. Our results demonstrate the crucial role that secondary interactions play in the high activity of Buchwald type ligands for cross-coupling and also suggest that increasing the electron density at the metal center is required for developing systems that will couple less activated phenolic derivatives. This is the focus of ongoing research in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

First examples of room-temperature Suzuki–Miyaura couplings with aryl sulfamates catalyzed by palladium, as described in ref^{9b}.

Figure 2.

Equilibria between bidentate XPhos- and solvent-bound Pd(0) species. Coordination of two molecules of solvent to species with X-Phos bound in a monodentate fashion is energetically unfavorable (see the Supporting Information).

Figure 3. Gibbs free energy profile, in kcal/mol, for the oxidative addition of 1-(naphthyl)-*N,N*-dimethyl sulfamate to **PdXPhos_Bi**.

Figure 4.

Transition states found for the oxidative addition of 1-(naphthyl)-*N,N*-dimethyl sulfamate to the XPhos-ligated Pd(0) catalyst and their Gibbs energies relative to reactants.

Figure 5. Gibbs free energy profile, in kcal/mol, for the oxidative addition of phenyl-*N,N*-dimethyl sulfamate to **PdXPhos_Bi**.

Figure 6.
Diverging pathways available for **OA_Prod** to undergo transmetalation.

Figure 7.
Gibbs free energy profile, in kcal/mol, for transmetalation between 4-(methoxyphenyl)boronic and **OA_Prod**.

Figure 8.

Gibbs free energy profile, in kcal/mol, for the reductive elimination of 1-(4-methoxyphenyl)naphthyl from the transmetalation product.

Figure 9.
Gibbs free energy profile, in kcal/mol, for the oxidative addition of 1-(naphthyl)-*N,N*-dimethyl carbamate to **PdXPhos_Bi**.

Figure 10.

Graphical representation of the $\Delta G^\ddagger$ values (kcal/mol) for all oxidative addition pathways located with “monodentate” (**MD**, in blue) and “bidentate” (**BD**, in red) conformations of the XPhos ligand.

Figure 11. NCIPlot of the **OA_3C_BD** (left) and **OA_3C_MD** (right) transition states. The isosurfaces of the reduced density gradient show the intramolecular nonbonding (green) and attractive (blue) weak interactions. Element color code: orange (Pd), purple (P), yellow (S), red (O), blue (N), gray (C).

Figure 12.

Metal- and substrate-free equilibrium between the possible conformations of XPhos found in the oxidative addition transition states.