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Competitive and Selective Csp^3–Br versus Csp^2–Br Bond Activation in Palladium-Catalysed Suzuki Cross-Coupling: An Experimental and Theoretical Study of the Role of Phosphine Ligands

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Dedicated to Professor José Barluenga on the occasion of his 70th birthday

Abstract: Phosphine ligands have been demonstrated to have an effect on reactivity and selectivity in the competitive intramolecular palladium-catalysed Suzuki–Miyaura coupling of dibromo sulfoxide **1a** possessing two different hybridised electrophilic carbons. It was found that the bromine bond to the sp^3-hybridised carbon is selectively replaced in the presence of unhindered phosphines such as PPh_3 or xantphos. The use of hindered phosphine ligands such as P(*o*-tol)$_3$ and P(1-naphthyl)$_3$ reversed the selectivity, conducting the cross-coupling at the Csp^2-Br. Identical trends were observed in external competition experiments carried out with bromomethyl sulfoxide and different substituted bromoarenes. DFT and DFT/MM calculations showed that the selectivity observed is mainly due to the different facility of the ligands to dissociate. Bisphosphine catalysts favour coupling at the sp^3 carbon, whereas monophosphine catalysts prefer the sp^2 carbon.

Keywords: cross-coupling · density functional calculations · ligand effects · palladium · reaction mechanisms · selectivity

Introduction

Palladium-catalysed coupling of aryl or vinyl halides or pseudohalides with orgamometallics represents a consolidated method for achieving the formation of C–C bonds.[1] However, selective transformations, despite being of high interest for organic synthesis, have been much less explored in comparison. Regio- and stereoselectivity, in the context of palladium-catalysed cross-coupling reactions, are mainly, but not exclusively,[2] derived from the different reactivities of the electrophiles towards the oxidative addition step, in most cases the turnover-limiting step in the catalytic cycle.[3] In this way, the largely *trans*-selective monosubstitution, in the Pd-catalysed cross-coupling of 1,1-dihalo-1-alkenes, is attributed to steric effects exerted by carbon substituents, which favour oxidative addition to the palladium atom *trans* to carbon substituents in the β-position.[4] Unfortunately, disubstitution is sometimes an undesirable side reaction. On the other hand, the regioselective monoarylation of unsymmetrical dihaloarenes[5] is based on the well-known differences in the leaving group aptitude[6] of halides and pseudohalides. Even with bromoaryl triflates, the selective displacement of either bromide or triflate is possible through the appropriate selection of the palladium ligands.[2,7] Recently, a computational study analysed the ligand control of the regioselectivity with respect to two Csp^2 positions (chloro and triflate).[8] It was found that a monophosphine catalyst would promote the coupling at the C–Cl bond, whereas a bisphosphine catalyst would promote the coupling at the C–

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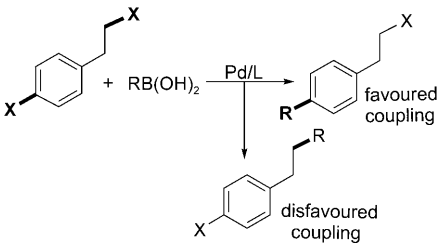
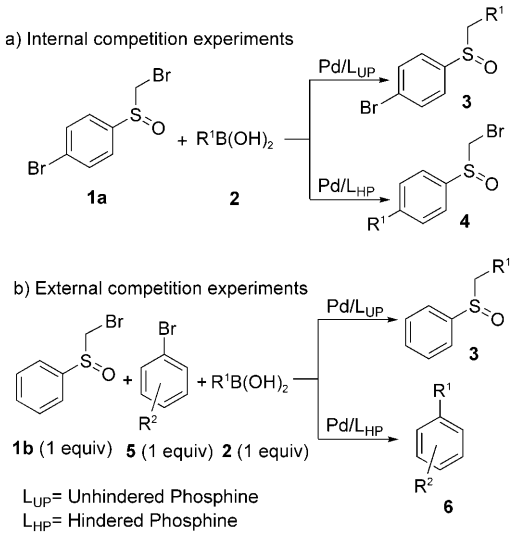
OTf bond. A more sophisticated example of selective coupling at a desired position has recently been provided in the palladium-catalysed cross-coupling of dibromobenzenes with Grignard reagents, in which the reaction takes place at the less favourable site because of the binding properties of the phosphine ligand.[9] The mechanism and details of the process have been studied by several computational groups.[10]

The effect of substituents in the aromatic ring accelerating (electron acceptors) or retarding (electron donors) the oxidative addition of palladium complexes into carbon–halide bonds was established many years ago,[11] but it is still an active field of work.[12] In addition, the hybridisation of the carbon atom that undergoes the oxidative addition also plays a role in the relative reactivity. The slow oxidative addition of alkyl halides to palladium and the favoured competing β-hydride elimination reaction are probably the main reasons for the lack of success with this kind of substrate until relatively recently, when Fu[13] conducted diverse palladium-catalysed coupling reactions successfully in unactivated alkyl halides using sterically hindered electron-rich phosphines. These ligands have been postulated to be particularly effective for couplings, because the steric demand facilitates dissociation to a monophosphine adduct, to which the substrate undergoes rapid oxidative addition as a result of the electron richness of the phosphine.[14] Even in the case of alkyl electrophiles activated by a neighbouring carbonyl group (α-halocarbonyl compounds), special conditions and ligands are usually required to achieve the cross-coupling reaction, despite the lack of β-hydrogen, which circumvents the β-hydride elimination.[15] Therefore, all precedents concerning differences in reactivity between aryl/vinyl halides and alkyl halides in palladium-catalysed cross-coupling reactions indicate a high reactivity for the former and a low reactivity for the latter (Scheme 1), with the exception of



Scheme 1. Relative reactivity of aryl and alkyl halides in palladium-catalysed cross-coupling reactions.

benzyl halides.[16] Despite the striking difference in the reactivity associated with the hybridisation of the carbon in the electrophilic partner, there have been no systematic studies exploring and exploiting this significant selectivity in palladium-catalysed cross-coupling reactions. As continuation of our research into palladium-catalysed Suzuki–Miyaura reactions with α-bromomethyl sulfoxides,[17] we have carried out a study to account for the relative reactivity of (SO)sp^3 and sp^2 C–Br bonds. Both internal and external competition experiments have been performed (Scheme 2).



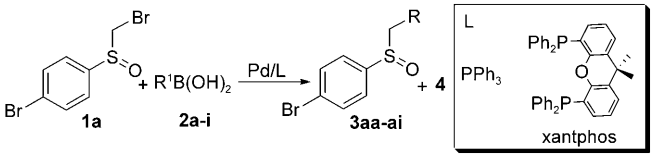
Scheme 2. Selective palladium-catalysed Suzuki–Miyaura coupling.

In this paper we show that the presence of a sulfoxide group in the α-position with respect to the sp^3 carbon activates the sp^3 C–Br bond enough to compete with aryl bromides under ligand control, and allows a better general understanding of the oxidative addition process.

Results and Discussion

Internal competition experiments were performed with dibromo sulfoxide **1a** possessing two different hybridised electrophilic carbons. For this substrate, we found that the proper selection of the phosphine ligand present in the palladium catalyst enables a competitive Suzuki–Miyaura reaction, which can be directed with high selectivity to either the sp^3 or sp^2 carbon atoms (Scheme 2). Monoarylated compounds were the only products formed without contamination with the double arylation derivatives, which were not detected in any case. As far as we are aware, the results reported herein are the first examples of a palladium-catalysed cross-coupling reaction being accomplished with a high degree of selectivity in the aryl or the alkyl electrophilic centre through a simple change in the catalyst ligands. Initially, we applied the same reaction conditions that we determined previously as optimal for analogous α-bromo sulfoxides (THF, CsF, 65 °C).[17] Under these conditions, the cross-coupling reaction of the sulfoxide derivative **1a** with boronic acid **2a**, catalysed by Pd^0/PPh_3, took place almost exclusively at Csp^3 to give the monoarylated product **3aa** in moderate yield. Both $[Pd(PPh_3)_4]$ and $Pd(OAc)_2/PPh_3$ (Table 1, entries 1 and 2) were efficient catalysts for the reaction, which was general for a range of boronic acids **2a–f** (Table 1, entries 1–7). Aryl boronic acids **2a–d** afford α-arylated sulfoxides **3aa–ad** (Table 1, entries 1–5) in moderate yields, whereas the sterically hindered **2e** (Table 1, entry 6) and the electron-poor boronic acid **2f** (Table 1, entry 7) provided the corresponding cross-coupling products in a slightly lower

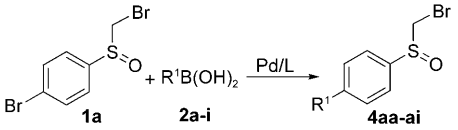
Table 1. Competitive palladium-catalysed Suzuki coupling at Csp^3.



Entry	Method[a]	R^1	**3** (yield [%])	**4** (yield [%])
1	A	C_6H_5	**aa** (50)	**aa** (4)
2	B	C_6H_5	**aa** (48)	**aa** (4)
3	A	4-$MeOC_6H_4$	**ab** (69)	**ab** (5)
4	A	3-$MeOC_6H_4$	**ac** (60)	**ac** (5)
5	A	4-BrC_6H_4	**ad** (50)	**ad** (2)
6	A	2-MeC_6H_4	**ae** (40)	**ae** (7)
7	A	4-$CF_3C_6H_4$	**af** (37)	**af** (3)
8	A	2-thienyl	**ag** (0)	–
9	A	3-thienyl	**ah** (0)	–
10	A	Me	**ai** (0)	–
11	C	C_6H_5	**aa** (90)	–
12	C	4-$MeOC_6H_4$	**ab** (91)	–
13	C	3-$MeOC_6H_4$	**ac** (89)	–
14	C	2-MeC_6H_4	**ad** (23)	–
15	C	4-BrC_6H_4	**ae** (83)	–
16	C	4-$CF_3C_6H_4$	**af** (90)	–
17	C	2-thienyl	**ag** (88)	–
18	C	3-thienyl	**ah** (95)	–
19	C	Me	**ai** (0)	–

[a] Method A: $[Pd(PPh_3)_4]$, 16 h; Method B: $Pd(OAc)_2/PPh_3$ (1:1), 16 h; Method C: $Pd(OAc)_2$/xantphos (1:1), 5 h.

Table 2. Competitive palladium-catalysed Suzuki-coupling at Csp^2.



Entry	Method[a]	R^1	**4** (yield [%])
1	D	4-$MeOC_6H_4$	**ab** (69)[b]
2	D	3-$MeOC_6H_4$	**ac** (65)[c]
3	E	C_6H_5	**aa** (92)
4	E	4-$MeOC_6H_4$	**ab** (99)
5	E	3-$MeOC_6H_4$	**ac** (89)
6	E	2-MeC_6H_4	**ad** (94)
7	E	4-BrC_6H_4	**ae** (80)
8	E	4-$CF_3C_6H_4$	**af** (86)
9	E	2-thienyl	**ag** (94)
10	E	3-thienyl	**ah** (96)
11	E	Me	**ai** (0)
12	F	C_6H_5	**aa** (76)
13	F	4-$MeOC_6H_4$	**ab** (85)
14	F	3-$MeOC_6H_4$	**ac** (75)
15	F	4-BrC_6H_4	**ad** (62)
16	F	2-MeC_6H_4	**ae** (50)
17	F	4-$CF_3C_6H_4$	**af** (72)
18	F	2-thienyl	**ag** (40)
19	F	3-thienyl	**ah** (61)
20	F	Me	**ai** (0)

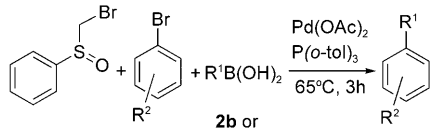
[a] Method D: $Pd(OAc)_2/PCy_3$ (1:1), 4 h; Method E: $Pd(OAc)_2/P(o\text{-tol})_3$ (1:1), 3 h; Method F: $Pd(OAc)_2/P(1\text{-naphthyl})_3$ (1:1), 16 h. [b] **3ab** (31%). [c] **3ac** (27%).

yield. Thus, the steric and electronic properties of the boronic acids affected the yields of the corresponding products **3**. However, the selectivity was almost complete. Heteroaryl (Table 1, entries 8 and 9) and alkyl boronic acids (Table 1, entry 10) were non-reactive under the assayed conditions.

Owing to the high selectivity but moderate activity of the precedent catalyst, we next examined complexes with bisphosphines. Of the bisphosphines tested [2,2′–bis(diphenylphosphino)–1,1′–binaphthyl (binap), 1,1′-bis(diphenylphosphino)ferrocene (dppf), 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane (dppp)] only (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (xantphos) was active. Like PPh_3, xantphos drives the reaction to Csp^3, but now the selectivity was complete and the reactivity was considerably enhanced. Both yields and reaction times were remarkably improved for all the boronic acids tested (Table 1, entries 11–13 and 15–18), with the exception of the sterically hindered boronic acid **2e** (Table 1, entry 14). Thus, the cross-coupling products arising from the parent compound **2a** and different substituted boronic acids were obtained with excellent yields (83–91%). Even heteroaryl boronic acids **2g** and **2h** (Table 1, entries 17 and 18), which were inert under the $[Pd(PPh_3)_4]$ catalyst, could be coupled with high yields (85 and 95%) by $Pd(OAc)_2$/xantphos. On the other hand, the use of monophosphine ligands of high basicity and bulkiness reversed the selectivity (Table 2). So, the relatively bulky trialkyl monophosphine PCy_3 showed a preference for the sp^2 electrophilic carbon, although selectivity was only moderate (Table 2, entries 1 and 2). The trend was amplified when encumbered triaryl monophosphines were used as palladium ligands. $Pd(OAc)_2/P(o\text{-tolyl})_3$ (Table 2, entries 3–11) and $Pd(OAc)_2/P(1\text{-naphthyl})_3$ (Table 2, entries 12–20) serve as efficient catalysts for the cross-coupling process at Csp^2, affording the corresponding biaryl derivatives **4**. $P(o\text{-tolyl})_3$ was seen to be the best ligand, leading to the coupled derivatives **4aa–ai** (Table 2, entries 3–11) with excellent yields for a broad range of aryl boronic acids. Once more, the selectivity depended exclusively on the palladium ligands, and was the same for electron-rich, electron-poor aryl, and heteroaryl boronic acids. To demonstrate substrate specificity, external competition experiments were also performed. To this end, we designed a series of experiments in which mixtures of sulfoxide **1b** and bromoarenes **5a–i** with representative substitution patterns were allowed to react with boronic acids **2b** or **2f** containing either an electron-rich or an electron-poor aromatic ring (Tables 3 and 4). A very satisfactory intermolecular selectivity was also found in these competitions. The reaction of mixtures of bromo sulfoxide **1b** and bromoarenes **5** containing an electron-donor (**5a–e**) or electron-acceptor substituent (**5f–i**) with boronic acids in the presence of $Pd(OAc)_2/P(o\text{-tolyl})_3$ gave exclusively biaryls **6** from the Csp^2–Csp^2 bromoarene–boronic acid cross-coupling (Table 3). Bromo sulfoxide **1b** was recovered unchanged in the experiments. Then, complete ligand-induced selectivity was achieved, which did not depend on the electronic character of the substituents at the coupled partner.

As expected, the reverse selectivity, that is, the formation of the Csp^3–Csp^2 cross-coupling products, was achieved in

Table 3. $Pd(OAc)_2/P(o\text{-tol})_3$-catalysed Suzuki coupling. External competition experiments.

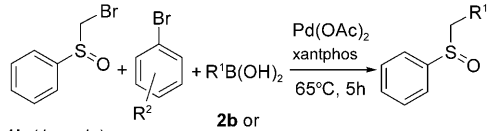


1b (1 equiv) **5** (1 equiv) **2b** or **2f** (1 equiv) **6**

Entry	**2**	**5** (R^2)	**6** (yield [%])
1	**f**	**a** (H)	**af** (84)
2	**f**	**b** (4-OMe)	**bf** (46)
3	**f**	**c** (2-Me)	**cf** (38)
4	**b**	**d** (4-Me)	**db** (40)
5	**b**	**e** (2-NH_2)	**eb**(46)
6	**f**	**e** (2-NH_2)	**ef** (46)
7	**f**	**f** (4-Cl)	**ff** (75)
8	**f**	**g** (4-CF_3)	**gf** (92)
9	**b**	**h** (4-CN)	**hb** (48)
10	**f**	**h** (4-CN)	**hf** (66)
11	**b**	**i** (3-CN)	**ib**(60)
12	**f**	**i** (3-CN)	**if** (84)

the competitive experiment when P(*o*-tolyl)$_3$ was substituted by xantphos as the phosphine ligand in the palladium catalyst (Table 4). The ligand control of the selectivity was also general, with the single exception of the coupling of bromoarenes containing a CN group (Table 4, entries 9–12).

Table 4. $Pd(OAc)_2$/xantphos-catalysed Suzuki coupling. External competition experiments.



1b (1 equiv) **5** (1 equiv) **2b** or **2f** (1 equiv) **3**

Entry	**2**	**5** (R^2)	**3** (yield [%])
1	**f**	**a** (H)	**bf** (89)
2	**f**	**b** (4-OMe)	**bf** (63)
3	**f**	**c** (2-Me)	**bf** (62)
4	**b**	**d** (4-Me)	**bb** (80)
5	**b**	**e** (2-NH_2)	**bb**(59)
6	**f**	**e** (2-NH_2)	**bf** (65)
7	**f**	**f** (4-Cl)	**bf** (64)
8	**f**	**g** (4-CF_3)	**bf** (74)
9	**b**	**h** (4-CN)	**bb** (40)[a]
10	**f**	**h** (4-CN)	**bf** (37)[b]
11	**b**	**i** (3-CN)	**bb**(59)[c]
12	**f**	**i** (3-CN)	**bf** (54)[d]

[a] **6hb** (37%). [b] **6hf** (32%). [c] **6ib** (25%). [d] **6if** (22%).

The 3- and 4-bromobenzonitriles are highly activated substrates in the oxidative addition step,[10] and the formation of a mixture of the Csp^3–Csp^2 and the Csp^2–Csp^2 cross-coupling products takes place in this case. In fact, the Csp^3–Csp^2 coupling still predominates, but the selectivity is low. However, we should note the broad scope of the ligand control of the selectivity by xantphos, (Table 4 entries 1–8) as even with bromoarenes bearing electron-withdrawing groups such as CF_3 (Table 4 entry 8), the coupling occurs with complete Csp^3–Csp^2 bond-forming selectivity.

The selectivity observed between sp^2 and sp^3 carbons due to ligand change was explored by computational means. The oxidative addition of **1a** to the palladium catalyst with the PPh_3 (method A) and P(1-naphthyl)$_3$ (method F) ligands was studied. PPh_3 was chosen as an example of a less hindered phosphine, producing mainly the activation of the Csp^3 product, and P(1-naphthyl)$_3$ was used as an example of a hindered phosphine with similar electronic effects producing only the Csp^2-activated product. The combination of two metal complexes and two activation types yields four pathways to investigate. This number was doubled because we also considered the possibility of monophosphine or bisphosphine complexes.

The enthalpies of the adducts and transition states for each of the eight computed pathways are collected in Table 5. The species are labelled as **M*nth***, in which **M** is the phosphine: **A** for P(Ph_3) and **F** for P(1-naphthyl)$_3$; ***n*** is the number of phosphines involved: **1** for $Pd(PR_3)$, and **2** for $Pd(PR_3)_2$; ***t*** is the nature of the species: **add** stands for adduct before the transition state, and **ts** for the transition state; and ***h*** shows the hybridisation of the activated carbon: **3** for sp^3 carbon and **2** for sp^2. Values are enthalpies in solution (ΔE_{sol}) relative to the reactants ($Pd(PR_3)_{1,2}$ plus **1a**) at infinite separation.

Table 5. Relative enthalpies [kcal mol^{-1}] of the adducts and transition states in the eight computed pathways for the **1a**+$Pd(PR_3)_n$ reaction.

	PPh_3		P(1-naphthyl)$_3$	
Csp^3	**A2add3**	7.1	**F2add3**	5.6
	A2ts3	17.3	**F2ts3**	18.6
	A1add3	−5.7	**F1add3**	−3.2
	A1ts3	−0.9	**F1ts3**	1.7
Csp^2	**A2add2**	9.0	**F2add2**	7.1
	A2ts2	20.5	**F2ts2**	23.3
	A1add2	−4.4	**F1add2**	−0.7
	A1ts2	−1.6	**F1ts2**	0.4

Table 5 shows the energies and transition states for the reaction of each complex with the two possible C–Br bonds. A clear pattern emerges in that the sp^3 carbon is preferred for the **A2ts3/2** (17.3 vs. 20.5 kcal mol^{-1}) and **F2ts3/2** (18.6 vs. 23.3 kcal mol^{-1}) systems, whereas the sp^2 carbon is preferred for the **A1ts2/3** (−1.6 vs. −0.9 kcal mol^{-1}) and **F1ts2/3** (0.4 vs. 1.7 kcal mol^{-1}) complexes. The nature of the preferred product does not correlate directly with the type of ligand (**A** vs. **F**), but with the coordination number (**1** vs. **2**). This may seem at odds with the experimentally observed dependence of product nature with the type of ligand. However, the ligand type and the coordination number are correlated.

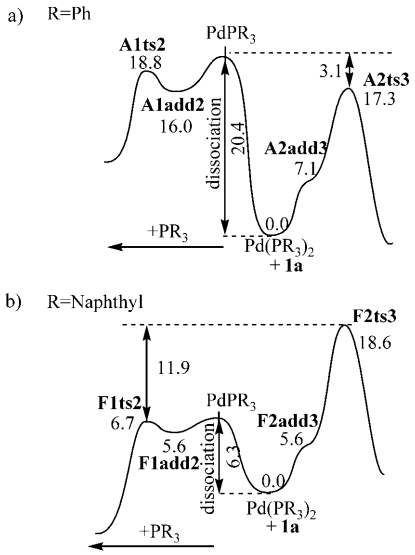
The bisphosphine complexes can dissociate one of the phosphine ligands to form the monophosphine complex. This $Pd(PR_3)$ complex is more reactive, but its formation de-

pends on the equilibrium described in Equation (1). Bulky phosphines displace the equilibrium to the right.[10,18]

$$Pd(PR_3)_2 \rightarrow Pd(PR_3) + PR_3 \quad (1)$$

The computed dissociation enthalpy energy of one phosphine from the bisphosphine complex is 20.4 kcal mol^{-1} for $Pd(PPh_3)_2$ and 6.3 kcal mol^{-1} for $Pd(P(1\text{-naphthyl})_3)_2$. It is important to note that this is a rough estimation. These energies are usually method-dependent, solvent and other molecules in the reaction media can play a role, as well as entropy effects, which are difficult to estimate accurately. The dissociation free energies in solution, which contain the entropic correction from ideal gas statistical thermodynamics, are 7.3 kcal mol^{-1} for $Pd(PPh_3)_2$ and −14.1 kcal mol^{-1} for $Pd(P(1\text{-naphthyl})_3)_2$. As expected, the inclusion of entropic effects favours the dissociation, although it is probably overestimated. We think, however, that the difference between both ligands is significant, and is furthermore easily explained by the different steric bulk.

Putting together the four most favoured pathways in Table 5 and the estimated phosphine dissociation energies reported above, the profiles in Scheme 3 can be obtained.



Scheme 3. Computed enthalpy profiles of the oxidative addition step for each of the two ligands considered.

For the case of the PPh_3 ligand, competition between the pathways going through **A2ts3** and **A1ts2** has to be considered (Scheme 3a). The estimated cost of the dissociation of the phosphine is 3.1 kcal mol^{-1} higher than **A1ts3**. Then, the Csp^3 activation with the bisphosphine system is preferred over the Csp^2 activation with the monophosphine catalyst, in agreement with experiment.

For the $P(1\text{-naphthyl})_3$ system, the comparison is between pathways through transition states **F1ts2** and **F2ts3** (Scheme 3b). The low dissociation energy of the $Pd(P(1\text{-naphthyl})_3)_2$ (6.3 kcal mol^{-1}) makes the dissociation favoured over **F2ts3. F1ts2** is located just 6.7 kcal mol^{-1} above the $PdP(1\text{-naphthyl})_3$ + **1a**, resulting in a stabilisation of 11.9 kcal mol^{-1} over **F2ts3**. These results show that for this ligand the activation of the sp^2 carbon is favoured through phosphine dissociation,[19] again in agreement with experiment.

These theoretical results seem to correlate well with the experimentally observed behaviour of other phosphines. The other monophosphines experimentally considered (PCy_3, $P(o\text{-tol})_3$) behave like $P(1\text{-naphthyl})_3$, as they are bulkier than PPh_3. They also provide a straightforward explanation for the behaviour of the xantphos ligand, which, being bisphosphine, probably remains as such, and presents a similar behaviour to $Pd(PPh_3)_2$. The lack of reactivity of other bisphosphines (dppp, dppf, dppe) remains unexplained, but it could be related to some step of the catalytic cycle other than the oxidative addition.[10,20]

The remaining question relates to why monophosphine complexes activate the sp^2 centres preferentially and bisphosphine complexes react more easily with sp^3 centres. This might be unexpected, as typical S_N2-like transition states with Pd–O interactions seem to be more sterically hindered than concerted ones, and monophosphine complexes are less hindered overall than bisphosphine species. The structures for the optimised transition states of the preferred pathways, **A2ts3** and **F1ts2**, are shown in Figure 1.

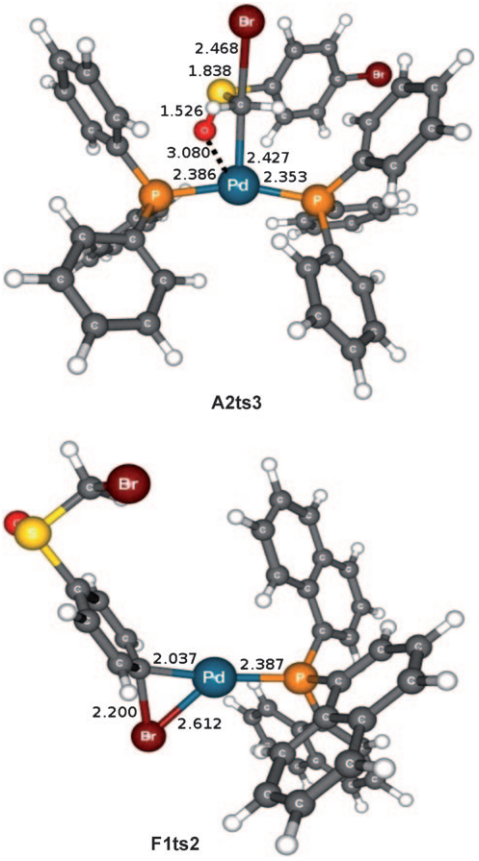


Figure 1. Optimised geometries of the transition states for the lowest energy pathways **A2ts3** and **F1ts2**. Selected distances are given in Å.

These transition states are representative of S_N2 and concerted mechanisms. The two possibilities, as well as alternative conformations, were tested for each of the systems considered, and only the lowest in energy are reported here.

A2ts3 corresponds to an S_N2-like mechanism with an almost linear Pd-C-Br arrangement. This is representative of all the transition states found for the activation of the sp^3 carbon in this work. Remarkably, the bending of the P-Pd-P bond angle is minimal in this structure, although this possibility was considered in the starting point of our geometry optimisations. In contrast, the **F1ts2** transition state corresponds to a concerted process, with simultaneous formation of the Pd–C (2.037 Å) and Pd–Br (2.632 Å) bonds. This is also the case for the other sp^2 carbon activations. Interestingly, the interaction of the sulfoxide oxygen and palladium seems quite weak in **A2ts3**, with a distance of 3.080 Å. The approach of oxygen to palladium seems hindered by the presence of the two phosphine ligands. For the monophosphine case, the distance is much shorter. For instance, in **A1ts3** (see Figure 2), it is 2.162 Å. In spite of this, sp^3 activation is preferred only for bisphosphine systems. Therefore, this palladium–oxygen interaction, which had been suggested by us as critical in the oxidative addition of α-bromo sulfoxides,[21] does not seem to play a key role in the current selectivity problem.

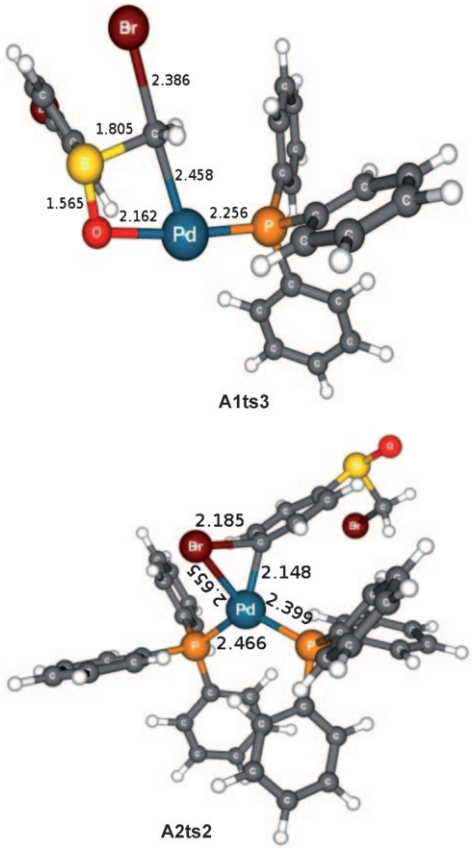


Figure 2. Optimised geometries of the transition states for the competing pathways **A1ts3** and **A2ts2**. Selected distances are given in Å.

In order to get a deeper insight, we decomposed the relative energy of the transition state with respect to the reactants in distortion and interaction terms. This same technique was applied recently by Schoenebeck and Houk to analyse the results of the competitive oxidation of C–Br and C–OTf bonds at palladium centres.[8] This type of analysis is also known as activation strain model,[22] and it is essentially the first step of other well-known energy decomposition analyses.[23]

For the four cases involving PPh_3 (**A1ts2**, **A1ts3**, **A2ts2**, **A2ts3**), the relative potential energies of the transition states in the gas phase were decomposed in distortion (ΔE_{dist}; from the substrate **1a** and the catalyst $Pd(PPh_3)_n$) and interaction (ΔE_{int}) terms by computing the energy of the separate fragments $Pd(Ph_3)_n$ and **1a** at the geometry of the transition state. The results are summarised in Table 6.

Table 6. Decomposition of gas phase potential energies ($\Delta E^{\neq}_{gas}$) in distortion (ΔE_{dist}) and interaction (ΔE_{int}) terms. Energies [kcal mol^{-1}] are relative to **1a**+$Pd(PPh_3)_n$.

	$\Delta E^{\neq}_{gas}$	ΔE_{dist} Total ($Pd(PPh_3)_n$+**1a**)	ΔE_{int}
A1ts2	−12.2	22.6 (2.3+20.3)	−34.8
A1ts3	−10.7	23.3 (0.9+22.4)	−34.0
A2ts2	11.6	38.2 (17.7+20.5)	−26.6
A2ts3	10.5	35.3 (4.6+30.7)	−24.8

The analysis is carried out on gas-phase energies for simplicity; the values follow the same trends as the enthalpy values in solution discussed in the rest of the work. For the monophosphine species, **A1ts2** and **A1ts3**, distortion and interaction terms contribute to a similar extent to the energy difference between the transition states. The activation of the sp^2 carbon is favoured by 0.7 in terms of distortion, and by 0.8 in terms of interaction, resulting in a total difference of 1.5 kcal mol^{-1} between the transition states. A different situation is observed for the bisphosphine species **A2ts2** and **A2ts3**. The interaction term still favours sp^2 activation by 1.8 kcal mol^{-1} (−26.6 vs. −24.8 kcal mol^{-1}), but this is more than compensated by the distortion term, strongly in favour of sp^3 activation by 3.9 kcal mol^{-1} (35.3 vs. 38.2 kcal mol^{-1}). Thus, the key lies in the distortion terms for the bisphosphine systems.

Further decomposition of the distortion term in the components for each reactant is clarifying. The main difference is in the metal complex side. ΔE_{dist} of the catalyst is 17.7 kcal mol^{-1} for **A2ts2** and just 4.6 kcal mol^{-1} for **A2ts3**.

The concerted transition state **A2ts2** needs to distort the $Pd(PPh_3)_2$ fragment more than the S_N2 transition state **A2ts3**. In **A2ts2** (Figure 2), the concerted cleavage of the Csp^2–Br bond tends to occupy two coordination sites on palladium, and this forces the P-Pd-P angle to close down to 120.4°, from the approximately linear value in the reactant. In **A2ts3** (Figure 1), only the carbon coordinates to the metal centre because of the S_N2 nature of the transition state. The P-Pd-P angle remains as large 160.2°, and the distortion energy is much smaller.

Conclusion

We have shown that the selection of the phosphine–palladium catalyst allows the achievement of total selectivity in cross-coupling with bifunctional substrates with Csp^3 and Csp^2 electrophilic carbon atoms. Similar results were obtained in the case of external competitive experiments. It is worth noting that there are no precedents of selective palladium-catalysed cross-coupling reactions of this type, in which substitution is selective at either the sp^3- or sp^2-hybridised carbon. The observed differences in the behaviour of xantphos are also remarkable if compared with other bisphosphines, as is its efficiency at promoting cross-coupling reactions involving Csp^3 electrophilic centres, which could lead to further applications in this challenging field.

The computational results show that the key to selectivity is the coordination number in the catalyst. Bisphosphine catalysts favour the activation of the sp^3 carbon, while monophosphine catalysts favour the activation of the sp^2 carbon. In the concerted transition state for sp^2 activation, the substrate occupies more space in the palladium coordination sphere, an optimal arrangement for monophosphine catalysts. The case of sp^3 carbons is different, because in the S_N2 transition state the substrate occupies only one position in the palladium coordination sphere, thus fitting better with bisphosphine catalysts.

Experimental Section

Palladium-catalysed competitive Suzuki–Miyaura reaction with 1-bromo-4-(bromomethylsulfinyl)benzene (1a), general procedure: A mixture of sulfoxide **1a** (0.04 mmol), boronic acid **2** (0.8 mmol), CsF (1.6 mmol), $Pd(OAc)_2$ (0.04 mmol) and the appropriate phosphane ligand (0.04 mmol) in THF (10 mL) was added to a flask fitted with a reflux condenser and stirred at 65 °C under nitrogen. After the appropriate time, the mixture was cooled to room temperature, quenched with water (10 mL), and extracted with diethyl ether (2×15 mL) and dichloromethane (3×15 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The crude material was purified by flash column chromatography.

External competition experiments with bromomethyl sulfoxide 1b and aryl bromides 5, typical procedure: A dry and N_2-flushed Schenk flask was charged with bromomethyl sulfoxide **1b** (0.4 mmol), aryl bromide **5** (0.4 mmol), CsF (0.8 mmol), $Pd(OAc)_2$ (0.04 mmol) and the appropriate phosphine ligand (0.04 mmol) in THF (10 mL). When the stirred mixture reached 65 °C, boronic acid **2** (0.4 mmol) was added in one portion. After the appropriate time, the mixture was cooled to room temperature, quenched with water (10 mL), and extracted with diethyl ether (2× 15 mL) and dichloromethane (3×15 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by flash column chromatography.

Computational details: Method A and monophosphine species on method F were treated with quantum mechanics (QM); bisphosphine species on method F (**F2add3**, **F2ts3**, **F2add2**, and **F2ts2**), were treated with quantum mechanics/molecular mechanics (QM/MM), namely ONIOM.[24] QM calculations and QM partitions were carried out with the B3LYP[25] DFT functional as implemented in Gaussian 03.[26] The basis sets used were the standard split-valence polarised 6–31+G(d,p)[27] for P, S, O, Br, C, and H, except for C and H atoms of the phosphine ligands for which 6–31G(d) was used. SDD valence basis sets with the associated effective core potentials were used for palladium.[28] The MM part of the ONIOM calculations consisted of the outer ring of each naphthyl substituent, and was treated with the UFF method.[29] Frequency calculations of all the minima and transition states were performed to confirm their nature. Single-point calculations with the polarisable continuum model (PCM)[30] were used to model the solvent effects (tetrahydrofuran $\varepsilon = 7.58$). Gaussian 03 default options were chosen, but individual spheres were placed on all hydrogen atoms to obtain a more accurate cavity. All energies reported in the text correspond to enthalpies, with solvation effects included unless otherwise stated. Some free energies in solution are presented in the text; these energies were computed applying the free-energy corrections in the gas phase to solvent energies obtained from the PCM calculation. Free energies in the gas phase are provided in the Supporting Information.

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