CHEMISTRY A European Journal



Accepted Article

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To be cited as: Chem. Eur. J. 10.1002/chem.201702703

Link to VoR: http://dx.doi.org/10.1002/chem.201702703

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A Combined Experimental/Computational Study of the Mechanism of a Palladium-Catalyzed Bora-Negishi Reaction

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Abstract: Experimental and computational efforts are reported which illuminate the mechanism of a novel boron version of the widespread Negishi coupling reaction that offers a new protocol for the formation of aryl/acyl C-B bonds using a bulky boryl fragment. The role of nucleophilic borylzinc reagents in the reduction of the Pd(II) pre-catalysts to Pd(0) active species has been demonstrated. The non-innocent behavior of the PPh₃ ligands of the [Pd(PPh₃)₂Cl₂] pre-catalyst under activation conditions has been probed both experimentally and computationally, revealing the formation of a trimetallic Pd species bearing bridging phosphide (PPh₂) ligands. Our studies also reveal the monoligated formulation of the Pd(0) active species, which led us to synthesize related (η^3 -indenyl)Pd-monophosphine catalysts which show improved catalytic performances under mild conditions. A complete mechanistic proposal to aid future catalyst developments is provided.

Introduction

Palladium-catalyzed cross-coupling reactions have revolutionized synthetic organic chemistry since first breaking onto the scene in the 1970s.¹ Owing to their wide functional group tolerance, and systematic tunability by rational ligand design, these methods have been successfully transplanted from academic laboratories to industrial finechemical, pharmaceutical and agrochemical production.² The Suzuki-Miyaura coupling, in which a C-C bond is formed using an organoboron reagent, is arguably the most widely applied metal-mediated cross-coupling transformation. Here, the choice of the boroncontaining component is known to be critical for the outcome of the reaction,³ with boronic acid/esters being the most widely

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> Details on the alternative one-step synthesis of borylzinc reagents, crystallographic information, NMR spectra and computational details and tables.

> Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

used class of reagent.⁴ These compounds in turn are typically prepared by the borylation of C-halogen or C-H bonds using diboron(4) esters of general formula $B_2(OR)_4$.^{1b}

Very recently, we developed an alternative strategy for the borylation of C-X (X = Br, Cl) bonds using polar, formally anionic, borylzinc reagents,⁵ in the presence of simple and affordable palladium pre-catalysts (Scheme 1).⁶ In effect, this approach constitutes a novel boron version of the widelyapplied Negishi C-C coupling reaction. Importantly, our method has allowed us to develop the first efficient, systematic and catalytic route to acylboranes,^{7,8,9} a rare class of organoboron compound with high potential in synthetic organic chemistry.¹⁰



Scheme 1. Palladium-catalyzed borylation of aryl bromides and acyl chlorides using borylzinc reagent 1 (Dipp = 2,6-diisopropylphenyl).⁶

Many palladium-catalyzed cross coupling reactions are believed to proceed through a common catalytic cycle involving oxidative addition of the organic substrate at a Pd(0) centre, followed by transmetalation of the coupling partner and reductive elimination of the organic product, with concomitant catalyst regeneration (Figure 1).^{1a,c,d} The Pd(0) active species is usually generated via in situ reduction of a Pd(II) pre-catalyst by one of a number of potential routes. That said, it is apparent that the picture is often more complicated than this simple mechanistic model would imply, and subtle modifications to the reaction medium, for example, can lead to drastic changes in reactivity,¹¹ particularly in processes involving highly polar zinc reagents.¹² As a consequence, detailed studies have proved to be crucial in developing mechanistic understanding, which in turn can be applied to the rational design of new catalysts with enhanced performance, superior selectivity or broader applicability.

In the current contribution we present a joint experimental/computational effort to elucidate the mechanism of the novel bora-Negishi coupling which we believe may illuminate future catalyst developments. A key mechanistic aspect in most palladium-mediated organoboron reactions is the role of the added base: potentially, this is required to access a transient boron-centered nucleophile,¹³ although additional roles have

also been suggested.14 One of the benefits of the bora-Negishi system is that it allows this issue (and associated mechanistic complexities derived from the presence of the base)¹⁵ to be disregarded, since the intrinsic nucleophilicity of borylzinc reagents removes the need for external additives of this type. In addition, we report an alternative convenient one-step synthetic protocol to access airstable borylzinc reagents directly from a bromoborane, and thereby circumvent the need to use Yamashita's highly sensitive boryllithium complex (thf)₂Li{B(NDippCH)₂}¹⁶ as a precursor (see Experimental Section and Supporting Information for details). As such, this simple development significantly enhances the convenience of the bora-Negishi methodology in synthetic organic chemistry.



Figure 1. General catalytic cycle for palladium-catalyzed cross-coupling reactions (Ac = activation; OA = oxidative addition; Tr = transmetalation; RE = reductive elimination).

Results and Discussion

Catalyst pre-activation to generate Pd(0) species

Although systems based on Pd(II)/Pd(IV) pairs have been reported,¹⁷ it is well known that $L_nPd(0)$ species are the active catalysts in most palladium-mediated cross-coupling reactions. Palladium nanoparticles and other heterogeneous forms of palladium have shown outstanding catalytic properties.¹⁸ Nevertheless, according to poisoning experiments with CS₂, PPh₃ and Hg carried out during our preliminary investigation,¹⁹ such species are not the active catalyst in our system.⁶ Alternative radical pathways related to those reported by Marder²⁰ for zinc-catalyzed borylation could also be ruled out based on the borylation of organic substrates specifically designed as radical probes.⁶

Active $L_nPd(0)$ species are typically generated via the *in situ* reduction of Pd(II) salts by the action of phosphines,²¹ amines,²² hydride sources,²³ other additives,²⁴ or even by electrochemical methods.²⁵ However, despite the extensive use of air and moisture stable [Pd(PAr₃)₂X₂] pre-catalysts in cross-coupling reactions, the pre-activation mechanisms by which the active species $L_nPd(0)$ are generated are not fully understood.²⁶ In the bora-Negishi case, the strongly reducing nature of boryl derivatives of main group metals prompted us to first examine the ability of the borylzinc reagent **1** to give access to Pd(0)-phosphine species, as well as the mechanism by which these may be formed. In these and subsequent investigations we have focused primarily on the pre-catalyst [Pd(PPh₃)₂Cl₂] (**2a**), owing to its superior performance and wider substrate applicability in

the borylation of aryl bromides when compared to other Pd(II) sources.⁶



Scheme 2. Activation of $[Ph(PPh_3)_2Cl_2]$ (2a) with $[(thf)_2Zn_2(Br)_2\{B(NDippCH)_2\}_2]$ (1) to form Pd(0) active species. [B] = $[B(NDippCH)_2]$. [dvds = 1,1,3,3-tetramethyldisiloxane]

Accordingly, the reaction of 2a with 2.5 equivalents of 1 under catalytically relevant conditions (dioxane solvent, 80 °C) and in the presence of ten equivalents of the trapping agent 1,3-divinyl-1,1,3,3-tetramethyldisiloxane (dvds)²⁷ results in the quantitative formation of the stable Pd(0) monophosphine complex $[Pd(PPh_3)(\kappa^2-dvds)]$ (4) after 16 hours, with concomitant release of one equivalent of PPh₃ (Scheme 2). The reaction was monitored by ¹H and ³¹P{¹H} NMR spectroscopy (showing 45 and 66% conversion after 2 and 4 h, respectively) and clean formation of 4 was unambiguously confirmed by comparison with previous literature data.²⁸ Around 40% of the borylzinc reagent 1 was converted into haloborane, in accordance with a reduction stoichiometry which requires one boryl anion equivalent per molecule of 2a. The haloborane generated is a ca 1:6 ratio of chloroborane (5) and bromoborane (6), with the mixture thought to result from halide exchange between 1 and 2a. This observation is supported by the fact that the same reaction carried out over a period of 30 min. using variable amounts of 1 (but in the absence of dvds) leads to a mixture of products that includes [Pd(PPh₃)₂BrCl] (7) and [Pd(PPh₃)₂Br₂] (8) (Scheme 3). The nature of 7 and 8 was ascertained via ¹H and ³¹P{¹H} NMR spectroscopy by spiking with authentic samples synthesized following literature procedures.²⁹ Nonetheless, under such conditions the major product (up to 95% using 10 equiv. of 1) was the expected species $[Pd(0)(PPh_3)_2]$ (3a) (in any of its related oligomeric forms or halide adducts)^{11a}. characterized by a broad ³¹P{¹H} NMR resonance at δ_P ca. 21 ppm.^{28,30} The formulation of the Pd(0) active species was further confirmed by adding dvds or bromobenzene to these reaction mixtures, which after 10 min at 25 °C resulted in quantitative formation of the alkene adduct 4 or the oxidative addition

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Pd(PPh ₃) ₂ Cl ₂ 2a	dioxane	Pd(PPh ₃) ₂ Cl ₂	[Pd ⁰ (PPh ₃) ₂]	Pd(PPh ₃) ₂ BrCl	Pd(PPh ₃) ₂ Br ₂	Pd(PPh ₃) ₂ PhBr	[PPh ₄]ZnX ₃	[Pd] ₃
+	80 °C, 30 min	2a	3a	7	8	9a	10	11
^[B] Br thf	hf 0.5 equi	v 8	-	12%	6%	6%	15%	60%
	(B) 1 1.5 equi	v 1	48%	1%	1%	1%	8%	42%
thf 1	2.5 equi	v -	58%	-	-	<1%	6%	22%
	10 equiv	v -	95%	-	-	-	-	-

Scheme 3. Reaction of pre-catalyst **2a** with variable amounts of borylzinc **1** (${}^{31}P{}^{1}H$) NMR spectroscopic yields calculated relative to total phosphorus content). [Pd]₃ (**11**) = [(Ph₃P)₃Pd₃(µ-PPh₂)₂(µ-Br)]⁺.

product $[Ph(PPh_3)_2PhBr]$ (9a), respectively. These results demonstrate that in the absence of any external additive, borylzinc 1 is able to convert 2a into Pd(0) species (e.g. 3a) under catalytically relevant conditions.

Another interesting aspect observed during reactions of 1 and 2a is the non-innocent character of the PPh₃ ligands in experiments performed under related conditions using fewer equivalents of 1 (Scheme 3). Under such conditions, we could identify [Pd(PPh₃)₂PhBr] (9a) and [PPh₄]⁺ (10) even in the absence of bromobenzene, as minor species in variable amounts (the identities of which were confirmed by spiking with authentic standards). Moreover, even in the absence of any organic substrate to be borylated, phenylborane (12) is still formed in yields of around 20 to 30% relative to 2a. Cleavage of P-C bonds within phosphine ligands mediated by palladium has precedent in the literature, and has been associated with catalyst deactivation processes.³¹ One of the suggested mechanisms involves the formation of multimetallic species containing phosphide bridges after oxidative addition of a P-C bond at an adjacent metal centre.³² A similar mechanism of this kind (Scheme 4), which is also supported by calculations (vide infra), would be consistent with the subsequent formation of species 9a and 11. 10 could then be formed by reductive elimination of [PPh₄]⁺ from 9a.³³ At low ratios of borylzinc



Scheme 4. Proposed mechanism for the activation of PPh_3 by means of P-C cleavage via formation of a Pd dimer.

reagent 1 (vs. palladium precursor 2a), the Pd(0) species 3a could comproportionate with asyet unreacted 2a to generate a Pd dimer, which would evolve into products 9a, 10, 11 or 12 following a variety of elementary steps. In addition, the formation of these products by initial comproportionation of Pd(0) and Pd(II) is consistent with their non-observation in experiments where 3a is trapped using dvds (Scheme 2). In contrast, under higher concentrations of borylzinc reagent 1 (e.g. 10 equiv.) Pd(II) precursor 2a would rapidly be consumed resulting in clean and almost quantitative formation of 3a.

Interestingly, during these experiments usina lower concentrations of 1 we could also observe a characteristic pattern of ³¹P{¹H} resonances due to an ABB'XX' spin system $(\delta_X = 226.5, \delta_B = 19.0 \text{ and } \delta_A = 12.3 \text{ ppm}; J_{AX} = 11, J_{AB} = 91 \text{ Hz}).$ The species responsible (11) can be obtained in spectroscopic yields of up to 60% by heating dioxane solutions of 1 and 2a (in a 2:1 ratio) at 80 °C for 30 min. Increasing the amount of 1 relative to 2a decreases the amount of 11 produced in favour of [Pd(0)(PPh₃)₂] (3a) (Scheme 3). Intense red crystals of 11 could be grown from dichloromethane/hexane solutions and X-ray diffraction studies reveal that the palladium-containing component is the trinuclear bis-phosphide [(Ph₃P)₃Pd₃(µ-PPh₂)₂(µ-Br)]⁺ (Figure 2). The unit cell contains two of these tripalladium units co-crystallized with one [PPh4]+ cation (thus further confirming its formation during pre-catalyst activation), with charge balance being achieved via a rare [Zn₆Cl₁₅]³⁻ anionic cluster (see Supporting Information for details). The tripalladium cluster might be seen as an intermediate state during precatalyst reduction, with an average metal oxidation state of 4/3.



Figure 2. ORTEP diagram of cationic trinuclear component of **11** (thermal ellipsoids: 50% probability; H atoms, one of the two **11** cations present in the unit cell and [Zn₆Cl₁₅]³⁻ counter-anion omitted and phenyl groups shown in wireframe format for clarity).

It is noteworthy that an almost identical trinuclear palladium phosphide (with the exception of the bridging halide ligand and counter-anion) was reported by Dixon and co-workers to be formed on prolonged heating of thf solutions of $[Pd(PPh_3)_3CI][BF_4].^{31,34} \ ^{31}P\{^{1}H\}$ NMR spectroscopic and X-ray diffraction data closely match those measured for **11**. Despite the extensive use of $[Pd(PPh_3)_3Cl_2]$ (**2a**) as a pre-catalyst, this is to our knowledge the first time that such a palladium phosphide cluster has been observed during a catalytic cross-coupling reaction. Its potential role during catalysis will be further discussed below.

Regarding the formation of phenylborane **12** during these experiments, it is also important to note that the $[PPh_4]^+$ cation generated as per Scheme 4 could serve as one of the sources of **12**, as has previously been reported for a related C-C cross-coupling protocol.³⁵ Indeed, we could demonstrate that **1** is able to borylate $[PPh_4]^+$ (**10**) in the presence of **2a** to form phenylborane **12** and PPh₃ in yields of around 10% (Scheme 5). The low yield is attributed to catalyst poisoning by the released PPh₃, in agreement with control experiments discussed below.

$[B] \searrow Br \searrow thf$	[PPh ₄]X	2 h, 80 °C	[B] — Ph	+ PPh ₃
2^{n} Br 2^{n} [B] +	$(X = CI, ZnX_3)$	dioxane	12	
1 I	10	2a		
	1 equiv	-	0%	
	-	5 mol %	1%	
	1 equiv	5 mol %	10%	

Scheme 5. Borylation of the tetraphenylphosphonium cation using 1.



Scheme 6. Mechanisms explored for the pre-catalyst activation of 2a by 1 with free energies in kcal mol⁻¹.

In order to obtain further insight into the pathways involved in the activation of the Pd pre-catalyst 2a, DFT calculations were carried out using the M06L and M06 functionals and mixed implicit-explicit models for THF solvation (see Computational Details). The mechanism considered for the reduction of Pd(II) to Pd(0) and formation of [B]-Cl (5) ([B] = $[B(NDippCH)_2])$ was transmetalation followed by reductive elimination (Scheme 6). This mechanism is the one proposed for the reduction of Pd(II) in most cross-coupling reactions from R-Pd-X intermediates^{11a,36} and it has been experimentally and computationally validated for Negishi reactions using ZnMe2 and ZnMeCI.^{12e,I} We additionally considered the possibility of direct nucleophilic attack at chloride by $Zn[B]Br(thf)_2$ (itself generated by the fragmentation of 1), which has been suggested for related systems.37 However, all attempts to find a transition state were unsuccessful and lead us to exclude this potential pathway (see Supporting Information for more details).



Figure 3: Geometries of **TS^A2** and **T3a** showing key distances. Hydrogen atoms have been removed for clarity.

Coordination of $Zn[B]Br(thf)_2$ was only found to be possible trans to PPh₃ due to the steric bulk of the boryl ligand [B] (Scheme 6). Consistent with experimental observations (*vide infra*), this necessarily implies dissociation of one of the phosphines from **2a**, as suggested with other precatalysts of the type $[(R_3P)_2Pd^{II}(X)_2]$ bearing bulky phosphines,³⁸ and formation of **A1a**. The substitution of one phosphine by the borylzinc fragment is endoergic by 13.3 kcal mol⁻¹. Substitution of one of

the zinc-bound thf ligands by chloride has an energetic barrier of 7.9 kcal mol⁻¹ (TS^A1) and stabilizes this intermediate by 1.5 kcal mol⁻¹. Subsequent formation of the Pd-boryl bond in A3a (ΔG = 1.0 kcal mol⁻¹) requires decomplexation of Br followed by rotation of the CI-Zn[B]Br(thf) bond. A transition state for this process (TS^A2, Figure 3) was located with a free energy of 29.0 kcal mol⁻¹ above the initial reactants, which is consistent with the high temperature (80 °C) required for catalyst activation. In A3a, the boryl group is bound to both Pd and Zn, with Pd-B and B-Zn distances of 2.09 and 2.81 Å, respectively. The latter interaction is lost in the subsequent step, in which the boryl group is displaced at zinc by an external thf molecule through TSA3 (ΔG = 8.5 kcal mol⁻¹). The overall transmetalation process is exergonic by 5.2 kcal mol-1. Subsequent dissociation of ZnBrCl(thf)₂ yields the unsaturated Pd intermediate A6a, which by reductive elimination forms [B]-Cl. This reaction has a low energy barrier (3.6 kcal mol⁻¹) and is exergonic by 4.9 kcal mol⁻¹ if [B]-CI remains bonded to Pd (A7a), and by 27.7 kcal mol⁻¹ if the chloroborane is displaced by PPh_3 to give $Pd(0)(PPh_3)_2$.

To provide further evidence for the essential role of phosphine dissociation during the transmetalation process that leads to precatalyst activation, we additionally performed one of the experiments described in Scheme 3 (2.5 equiv. of 1) in parallel with an identical experiment in which 2.5 equiv. of PPh₃ were added to the mixture. While the former solution rapidly turned dark red due to the formation of tripalladium compound 11, the reaction containing additional PPh₃ remained bright yellow even after several hours at 80 °C. Both reaction mixtures were monitored by ¹H and ³¹P{¹H} NMR, revealing full consumption of precatalyst **2a** after *ca.* one hour at 80°C in the absence of added PPh₃, but only 10% consumption (and 90% unchanged **2a**) in the presence of PPh₃.

In addition, the dissociation of phosphine is consistent with the reduced activity observed when using [Pd(dppf)Cl₂] (dppf = 1,1'bis(diphenylphosphino)ferrocene) instead of [Pd(PPh₃)₂Cl₂] (2a) as the pre-catalyst,⁶ and with the formation of phosphonium salts during the reaction of 2a with 1 (Scheme 3). As described above, the formation of [PPh4]+ and 9a suggests the presence of facile routes for the oxidative addition of P-Ph bonds. We found that this reaction from the unsaturated Pd(II) and Pd(0) intermediates A6a and A7a is either not feasible or endergonic by 17 kcal mol⁻ ¹, respectively. By contrast, an oxidative P-C bond cleavage reaction at dimer D1a, (itself formed by coordination of 2a to Pd(0)-PPh₃ as proposed in Scheme 4) is exergonic (ΔG = -3.7 kcal mol⁻¹) and has a low energy barrier (11.4 kcal mol⁻¹ from D2a). This reaction takes place in two consecutive steps involving comproportionation, in which one Ph group of a phosphine ligand assists the Pd(0) to Pd(II) oxidation, followed by P-Ph oxidative addition involving the same Ph group. Oxidative addition of C-X and Y-H bonds (X = halogen, and Y = H, O, N) to Pd(I)-Pd(I) dimers has precedent in the literature.³⁹ The formation of dimeric species D1a, D2a and D3a is endergonic by 8.6, 5.8 and 4.9 kcal mol⁻¹, respectively, and indeed none of these species have ever been observed during reactions of 1 and 2a. Instead, the products experimentally characterized are 9a, 10, 11 and 12 (Scheme 3), presumably formed by further reactions of D3a with ZnX₂ and PPh₃.

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Scheme 7. Mechanism for the oxidative addition of a P-Ph bond derived from $[Pd(0)(PPh_3)_2]$ and $Pd(PPh_3)_2Cl_2$ via formation of a dinuclear Pd complex. Free energies in kcal mol⁻¹.

Oxidative addition

We previously observed that **2a** was the catalyst of choice for the borylation of bromobenzene (95% yield after 2 h reaction at 80 °C), while its tri(o-tolyl) phosphine counterpart [Pd(P(o-Tol)₃)₂Cl₂] (**2b**) was barely active (12% yield under identical conditions), and rapidly decomposed to form Pd-black (Scheme 8).⁶ By contrast, the borylation of benzoyl chloride proceeded to a similar extent with both systems.

Oxidative addition at $[Pd(0)(PAr_3)_2]$ moieties is well known and several experimental and computational studies have focused on this process.³⁵ We have experimentally observed that the reactions of bromobenzene or benzoyl chloride with freshly generated $[Pd(0)(PPh_3)_2]$ (**3a**) proceed cleanly and extremely rapidly (Scheme 2). Moreover, DFT calculations show that the



Scheme 8. Borylation of bromobenzene using pre-catalysts 2a and 2b.

oxidative addition of benzoyl chloride at either **3a** or **3b** is favoured thermodynamically by 19.1 and 3.6 kcal mol⁻¹, respectively (Scheme 9). However, while the reaction of bromobenzene and **3a** is also excergic ($\Delta G = -14.7 \text{ kcal mol}^{-1}$) the analogous process involving **3b** is almost thermoneutral (ΔG = 0.6 kcal mol⁻¹), leading indeed to a bridging dipalladium species with concomitant release of a phosphine ligand.^{35b} This is consistent with the reversible oxidative addition of bromobenzene at **3b**, with the differences compared to **3a** presumably being due to steric considerations. This equilibrium, along with the fact that the subsequent transmetalation step seems to be rate-limiting (*vide infra*) is presumably therefore responsible for pre-catalyst decomposition to palladium black in the system Ar-Br/**3b**. By contrast, the irreversible oxidative



10.1002/chem.201702703

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Scheme 9. Free energies in kcal mol⁻¹ for the oxidative addition of (i) PhBr and (ii) PhCOCI with L = PPh₃ and L = P(o-Tol)₃.

addition to ${\bf 3a}$ of bromobenzene stabilizes the Pd(II) component in the form of ${\bf 9a}.^{40}$

Transmetalation of borylzinc reagents

Transmetalation is a critical step in cross-coupling reactions and occurs via a variety of mechanisms owing to the broad variety of nucleophiles employed.⁴¹ Following the commonly cited catalytic cycle, transmetalation would be expected to take place at a Pd(II) complex itself derived from the oxidative addition of bromobenzene or benzoyl chloride to a [Pd(0)(PAr₃)₂] species. From the intermediate Pd(II) complex, a mechanism analogous to that shown in Scheme 6 might then be expected to be responsible for introduction of the boryl ligand into the coordination sphere of palladium, followed by B-C reductive elimination. To probe this hypothesis, we performed stoichiometric reactions between the previously synthesized oxidative addition products 9a (from bromobenzene) or 14a (from benzoyl chloride) and borylzinc reagent 1 under catalytically relevant conditions (Scheme 10). As expected, these reactions led efficiently to the formation of the borylated organic compounds PhB(NDippCH)₂ (12)and $PhC(O)B(NDippCH)_2$ (13), as well as $[Pd(0)(PPh_3)_2]$ (3a). Notably, the ratio of 12 to 13 obtained from the stoichiometric reaction of 14a with 1 (ca. 1.6:1) is identical to that obtained from catalytic reactions using pre-catalyst [Pd(PPh₃)₃Cl₂] (2a) (see Scheme 8), thus suggesting that 14a is indeed a competent intermediate during catalysis. In this reaction, 12 is potentially formed via CO extrusion from 14a brought about by phosphine ligand dissociation (see Supporting Information for details).



Scheme 10. Stoichiometric reactions between (a) 9a or (b) 14a and borylzinc reagent 1.

The viability of **9a** and **14a** as intermediate species in the catalytic cycle was further confirmed by comparison of their catalytic profiles with that of pre-catalyst **2a** for the borylation of bromobenzene and benzoyl chloride, respectively. To do so, we monitored the catalytic performance of the three palladium species in parallel by ¹H and ¹¹B{¹H} NMR spectroscopy: Figure 4 shows temporal profiles for each system (derived from ¹H NMR measurements) based on the consumption of the borylzinc reagent **1** (see Experimental Section for details). The catalytic

behaviour of intermediates **9a** and **14a** is almost identical to (or even slightly superior than) that of pre-catalyst **2a**, a finding which clearly supports their roles as intermediates in the catalytic cycle. We additionally assayed the trinuclear system **11** as a catalyst for the borylation of bromobenzene and found a slightly diminished but comparable catalytic performance to that of **2a** and **9a**. An induction period of around 10 min became evident for **11** to become active, which we associate with its break-up into active mononuclear Pd(0) species.



Figure 4. Reaction profiles for the borylation of bromobenzene (A) and benzoyl chloride (B) using pre-catalyst **2a**, oxidative addition intermediates **9a** and **14a** and trimetallic-Pd **11**. Reaction conditions: Reaction conditions: **1** (0.010 mmol), bromobenzene or benzoyl chloride (0.022 mmol), [Pd] (5 mol%), solvent (0.5 mL; 1,4-dioxane (A) or thf (B)), 80 °C. Reaction monitoring by ¹H NMR spectroscopy using an internal standard. Lines drawn to guide the eye.

At first inspection, it seems likely that transmetalation is the rate limiting step in the catalytic cycle since the stoichiometric oxidative addition step is rapid, while no palladium boryl species can be detected after transmetalation. At the very least, the implication is that transmetalation must occur at a significantly slower rate than subsequent reductive elimination in order that the concentrations of palladium boryl intermediates never accumulate to levels detectable by NMR. Given the trans disposition of the aryl/acyl and halide ligands in **9a/14a** we therefore decided to investigate whether the change to a cis disposition of aryl/acyl and boryl groups required for reductive elimination was occurring during the transmetalation step via ligand dissociation (as shown in Scheme 6). As an initial probe,

10.1002/chem.201702703

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we examined the reactions towards borylzinc reagent 1 of palladium complexes 15 and 16, which feature chelating phosphines, and consequently cis oriented aryl/acyl and halide ligands. Despite being electronically similar to 9a and 14a, however, formation of the borylated products proceeded at a considerably slower rate with 15/16 (Scheme 11). It seems likely (given that 15 and 16 are stereochemically pre-organized with respect to subsequent C-B reductive elimination), that it is a slower rate of transmetalation for these chelating systems which underpins this difference. This in turn can be ascribed to the high steric encumbrance around the palladium centre which would result from accommodating not only the two tertiary phosphine co-ligands but also the massively hindered boryl group. In the case of 9a/14a - featuring monodentate co-ligands - the potential for phosphine dissociation during transmetalation would reduce the degree of crowding in a manner less readily accessible to 15 and 16 due to the chelate effect conferred by the bisphosphine. Consistently, the necessity for phosphine dissociation (which was also suggested for similar mechanistic steps during pre-activation) is further implied by examining the effects on the 9a + 1 temporal profile of the presence of two additional equivalents of triphenylphosphine. Thus, the rate of consumption of 1 is very clearly inhibited by the presence of additional phosphine (Figure 5).



Scheme 11. Reaction of P(II) complexes **15** and **16** bearing chelating 1,2-(diphenylphosphino)benzene with borylzinc **1**.

These findings are in marked contrast with related studies of Negishi C-C coupling reactions using organozinc reagents of reduced steric demands compared to borylzinc **1**, for which phosphine dissociation is not a prerequisite for transmetalation to occur.^{12e,I} Moreover, it has been observed that transmetalation with ZnMe₂ is faster than with ZnMeCl in classic Negishi reactions,^{12e} while our studies reveal that bisboryl compound Zn{B(NDippCH)₂}₂ is barely active for the borylation of aryl bromides and acyl chlorides, most likely due to steric reasons.⁶ An additional advantage derived from the use of highly bulky borylzinc reagents is that no B-B homocoupling is detected - as often observed with organozinc reagents in Negishi reactions.⁴² The critical influence of sterics in our system can also be inferred from the considerably slower rates of borylation of orthosubstituted aryl bromides compared to bromobenzene.⁶

Also consistent with the necessity for phosphine dissociation, is the fact that *in situ* ³¹P{¹H} NMR spectroscopic analyses during catalytic runs using **2a** reveal resonances at δ_P *ca.* 30 ppm which we tentatively assign to mono-ligated species of general formula [Pd(PPh₃)PhX]₂ (X = Cl, Br), based on literature precedent ([Pd(PPh₃)PhX]₂, δ_P X = Cl {CD₂Cl₂: 31.6 ppm}, X = Br {CD₂Cl₂: 30.4, C₆D₆: 30.7}; [Pd(PPh₃)PhX₂], δ_P X = Cl {CD₂Cl₂: 30.9 ppm}, X = Br {CD₂Cl₂: 29.9, C₆D₆: 30.5}).⁴³ These species are only ever present in low concentration (< 20%) and the associated NMR signals disappear after reaction completion.



Figure 5. Reaction profile for the reaction between [Pd(PPh₃)₂PhBr] (**9a**) and borylzinc reagent **1** in the absence (blue circle) and the presence (orange triangle) of added PPh₃ (2 equiv). Reaction conditions: **1** (0.011 mmol), bromobenzene (0.024 mmol), **2a** (5 mol%), additional PPh₃ (10 mol%), 1,4-dioxane (0.5 mL), 80 °C. Reaction monitoring by ¹H NMR spectroscopy using an internal standard. Lines drawn to guide the eye.

In addition to these experiments, we also wanted to determine by means of calculations the feasibility of a transmetalation mechanism occurring via intermediates similar to those proposed for the pre-catalyst activation step. With this in mind, the structures/energies for species shown in Scheme 6 were computed by replacing one of the chlorides by Ph (15^{CI}). The relevant calculated energies are shown in Scheme 12. The free energies of all intermediates in which zinc-containing species are bound to Pd are higher with Ph (T1a-T5a) than with Cl (A1a-A4a). This is consistent with the lower electrophilicity expected for complexes of the type [PdL₂RCI] compared to [PdL₂Cl₂], together with the higher steric profile of Ph compared to Cl. However, once ZnBrCl(thf)₂ is dissociated from intermediate T5a direct formation of Ph-[B] takes place without any apparent energy barrier and is strongly exergonic (ΔG = - 44.6 kcal mol⁻¹). Indeed a small gain in energy of 2.5 kcal mol⁻¹ is observed by replacing the Ph-[B] by PPh₃. Attempts to calculate the transition state for the bromide/boryl ligand exchange in Pd, which is expected to be the one with the highest energy, were unsuccessful. Indeed a similar geometry to that of TSA2, was found to be a minimum with Ph instead of Cl (T3a, Figure 3) probably due to an interaction between a π -CC bond of Ph with Pd (which is not possible with Cl). The energy of this intermediate is 24.5 kcal mol-1 above 15^{cl} and 1, and the

transition states connecting it with **T2a** and **T4a** (**TS^T1**^{*f*} and **TS^T2**^{*f*} respectively) were estimated to be 27.2 and 26.4 kcal mol⁻¹ above the reactants, respectively (see supporting information). These energies suggest that a transmetalation pathway involving species **T1a-T5a** is reasonable for a reaction that takes place at 80°C. It is also consistent with the fact that electron deficient aryl rings are borylated at lower rates,⁶ which could be understood in terms of higher energies for intermediates alike **T3a** and their associated transition states. Moreover, the fact that no boryl intermediates are observed at any point in the reaction sequence is consistent with the effectively barrier-less (or very low barrier) C-B reductive elimination step leading to product formation.

Complete mechanistic cycle

Overall, the results obtained in this study together with existing knowledge of Pd-catalyzed cross-coupling reactions are in agreement with the mechanism shown in Scheme 13. in which ligand dissociation plays a pivotal role in most of the steps. During pre-catalyst activation (Ac), phosphine dissociation is required to allow the transmetalation process that leads to monoligated Pd(0) after reductive elimination of haloborane. This Pd(0) species can either be stabilized with PPh₃/P(o-Tol)₃ (a), or react either with R-X (OA) or with unreacted pre-catalyst (b). The latter is potentially the first step in a route yielding trimetallic Pd species 11, which can be seen as a reservoir of Pd(0), as well as a source of [PPh₄]ZnX₃ and trans-[PdL₂PhX] (which can enter into the catalytic cycle (c)) via P-Ph bond activation. In addition to catalyst activation, oxidative addition of R-X (OA) has been proposed in the literature to occur by monoligated Pd species, even in the case of PPh_3 co-ligands.^{40,44} The



Scheme 12. Mechanism for the transmetalation pathway from E3 with the free energies (kcal mol⁻¹) obtained for intermediates. The energies for TS^{T1} ^f and TS^{T2} ^f have been estimated by means of relaxed energy scan calculations (see SI).

electronically unsaturated and sterically unhindered [PdLRX] facilitate cis-trans isomerization, intermediates leading (reversibly) to trans-[PdL2RX] (9a, 14a) after phosphine recombination - species that are experimentally observed during catalysis. Additionally, three-coordinate Pd compounds favor CO elimination (Elim), which is evidenced during the borylation of benzoyl chloride, particularly with the PPh₃ system. Transmetalation (Tr) from such three-coordinate Pd species seems to be the rate-limiting step, yielding boryl Pd(II) intermediates. This is followed by reductive elimination (RE), which is expected to be almost barrierless and highly exoergic, consistent with the non-observation of any Pd-[B] intermediates



Scheme 13. Proposed catalytic cycle for the borylation of aryl bromides and acyl chlorides using borylzinc reagents and L2PdCl2 pre-catalysts.

Finally, taking into consideration the crucial role of mono-ligated formulation of palladium during most steps of the catalytic cycle we decided to examine the reactivity of related palladium complexes bearing a single PPh3 co-ligand. We focused on systems containing bulky η^3 -indenyl ligands, which have recently been highlighted as convenient scaffolds that use steric factors to avoid the formation of inactive Pd(I) dimers.⁴⁵ We therefore synthesized complexes [(η^3 -indenyl)Pd(PPh₃)Cl] (17) and [(η^3 -1-^tBu-indenyl)Pd(PPh₃)Cl] (18) from the reaction of PPh₃ with dimeric $[(\eta^3-indenyl)_2Pd_2Cl_2]$ and $[(\eta^3-1-^tBu-indenyl)_2Pd_2Cl_2]$, respectively (see Experimental Section for details). The catalytic performance of 17 and 18 in the borylation of bromobenzene by 1 under our standard conditions was then monitored by ¹H and ¹¹B{¹H} NMR spectroscopy (Figure 6). As expected, the initial activity increases in the order 2a < 17 < 18. The initial induction period evident in the case of 2a is consistent with that shown in Figure 2 and is therefore ascribed to pre-catalyst activation/formation of [Pd(0)(PPh₃)₂] (3a). The required phosphine dissociation is circumvented in the monoligated complexes 17 and 18 that apparently do not exhibit any

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significant induction periods. However, the indenyl pre-catalysts seem to decompose at 3% catalyst loadings without reaching reaction completion and are surpassed by the simpler and affordable **2a**, pointing to the successful stabilization of resting states of catalyst by the second phosphine ligand. Lowering the temperature to 50 °C brings about improved yields for bromobenzene borylation up to 85% using indenyl catalysts **17** and **18**, while carrying out these reactions at 25 °C clearly demonstrates the superiority of the monoligated species under milder conditions (Figure 6). Further catalyst design optimization to balance the trade-off between activity and stability are currently being investigated in our group and will be reported in due course.



Figure 6. Reaction profile for the borylation of bromobenzene using 1 catalyzed by **2a** (blue circle), **17** (red diamond) and **18** (grey triangle) at 80 (A), 50 (B) or 25 °C (B). Reaction conditions: 1 (0.010 mmol), bromobenzene (0.022 mmol), [Pd] (3 mol%), 1,4-dioxane (0.5 mL). Reaction monitoring by ¹H NMR spectroscopy using an internal standard. Lines drawn to guide the eye.

Conclusions

In summary, we propose a complete mechanistic scheme (Scheme 13) for a recently developed bora-Negishi reaction, that allows the Pd-catalyzed borylation of a variety of organic substrates. Importantly, it is the only method available for the systematic and catalytic preparation of acylboranes, which represent an unusual class of organoborane reagents of great potential in synthetic organic chemistry.⁴⁶ Experimentally, we have analyzed the mechanism by which the Pd(II) pre-catalyst is activated, isolated reaction intermediates and screened their catalytic competence, demonstrated the pivotal role of ligand dissociation and synthesized and tested alternative monoligated systems. These studies have been complemented by theoretical investigations to obtain additional insight into each step of the catalytic cycle, as well as to learn about the causes for the divergent activity observed for related systems based on PPh₃ and P(o-Tol)₃ during the borylation of aryl bromides. This joint experimental/computational effort has thus provided key mechanistic information that we believe will pave the way toward future catalyst developments for improved activity/selectivity, and broader scope. These avenues and others are currently being pursued in our laboratories.

Experimental Section

General methods and instrumentation. All manipulations were carried out using standard Schlenk line or dry-box techniques under an atmosphere of argon. Solvents were degassed with dinitrogen and dried by passing through a column of the appropriate drying agent.47 THF was refluxed over sodium/benzophenone and distilled. NMR spectra were measured in benzene- d_6 (dried over sodium or potassium and distilled under reduced pressure) or CDCl₃ (used as received). NMR samples were prepared under argon in 5 mm Wilmad 507-PP tubes fitted with J. Young Teflon valves. ¹H, ¹³C{¹H}, ¹¹B{¹H} and ¹⁹F{1H} NMR spectra were recorded on a Varian Mercury-VX-300, a Bruker Mercury Avance III HD NanoBay 400 or a Bruker Avance III 500 spectrometer at ambient temperature, and referenced internally to residual protio-solvent (1H) or solvent (13C) resonances, and are reported in ppm relative to tetramethylsilane (δ = 0 ppm). Assignments were confirmed using two dimensional HSQC and HMBC correlation experiments. Carbon signals exhibiting significant line broadening due to quadrupolar relaxation caused by the proximity of boron atoms were not reported. Chemical shifts are quoted in ppm. Solid state and solution phase infrared spectra were measured on a Nicolet iS5 FT-IR spectrometer using air sealed KBr-discs or NaCl-cells. Elemental analyses were carried out at London Metropolitan University.

Starting materials. Borylzinc reagent 1⁶ and palladium complexes **9a**,⁴⁸ **7**,²⁹ **8**,²⁹ **14a**⁴⁹ and **17**⁵⁰ were synthesized according to literature procedures. Other palladium precursors and organic substrates were obtained from commercial sources and used as received.

Zn{B(NDippCH)₂}₂ (19). In a glove box, metallic potassium (367 mg, 9.42 mmol) was cleaned to remove oxide coating and finely suspended by vigorous stirring in 20 mL of refluxing absolute *n*-hexane under an argon atmosphere. A mixture of ZnCl₂ (582 mg, 4.28 mmol) and bromoborane (Br{B(NDippCH)₂}, 20) (1000 mg, 2.14 mmol) was prepared in a glove box and removed in sealed glass vial. The mixture was then added to the suspension of potassium sand at room temperature under a flow of argon The reaction mixture was vigorously stirred for 24 h to form a dark grev suspension, filtered and dried in vacuo. NMR analysis of the crude residue showed full conversion of 20 to 47% of 19 and 53% of hydroborane (H{B(NDippCH)2}) 21. This mixture was dissolved in 9 mL of refluxing absolute n-pentane, cooled to room temperature and kept in a -26°C freezer for 48 h. Large colorless crystals of 19 formed at this point which separated by filtration, washed with 0.5 mL of absolute npentane and dried in vacuo. Yield: 280 mg, 31%. Analytical data is identical to that reported previously.5a

[(Ph₃P)₃Pd₃(µ-PPh₂)₂(µ-Br)]⁺ (11). A mixture of palladium precursor 2a (50 mg, 0.071 mmol) and borylzinc reagent 1 (43 mg, 0.036 mmol) was dissolved in dioxane (3 mL) and heated at 80 °C for one hour under argon atmosphere. The resulting dark red solution was filtered, concentrated and compound 11 was obtained after precipitation with pentane as a bright orange solid 11 (17 mg, 40%, assuming ZnBrCl2⁻ as the counteranion on the basis of elemental analysis). Crystals suitable for X-Ray diffraction analysis were grown by layering the dioxane solution with pentane and cooling the mixture at -23 °C overnight. ¹H NMR (CD₂Cl₂, 400 MHz): δ 7.41 (6 H, t), 7.37 (4 H, t), 7.20 (12 H, t), 7.13 (3 H, t), 7.09 (20 H, m), 6.80 (6 H, t), 6.75 (8 H, m), 6.59 (6 H, m). All aromatic $^{3}J_{HH}$ have values of around 7.5 Hz. $^{13}C\{^{1}H\}$ NMR (CD₂Cl₂, 100 MHz): δ 135.1 (vt, $J_{CP} = 13 \text{ Hz}$, C_{ipso}), 134.0 (t, $J_{CP} = 6 \text{ Hz}$, CH), 133.0 (d, $J_{CP} = 13 \text{ Hz}$) Hz, CH), 132.8 (t, J_{CP} = 8 Hz, CH), 132.5 (d, J_{CP} = 22 Hz, C_{ipso}), 131.5 (d, $J_{CP} = 41$ Hz, C_{ipso}), 130.5 (d, $J_{CP} = 13$ Hz, CH), 129.9 (d, $J_{CP} = 3$ Hz), 128.3 (t, J_{CP} = 5 Hz, CH), 128.2 (t, J_{CP} = 5 Hz, CH), 127.9 (d, J_{CP} = 10 Hz, CH). ³¹P{¹H} NMR (CD₂Cl₂, 162 MHz): ABB'XX' spin system ($J_{AX} = 11$, J_{AB} = 91 Hz), δ 226.5 (2 P, m, PPh₂ (PX)), 19.0 (2 P, m, PPh₃ (PB)), 12.3 (1 P, m, PPh3 (PA)). Elemental analysis found: C 52.33, H 3.47 %, calculated for C78H65Br2Cl2P5Pd3Zn C 52.85, H 3.70 %. Crystallographic data: $C_{156}H_{130}Br_{1.92}CI_{15.08}P_{10}Pd_6Zn_6$, Mr = 4032.93, monoclinic, P21/n, a = 29.2833 (3), b = 19.5660 (2), c = 33.5346 (5) Å, β = 96.388 (1)°, V = 19094.6 (4) Å³, Z = 4, ρc = 1.403 g cm⁻³, T = 150 K, λ = 0.71073 Å. 78158 reflections collected, 36679 independent [R(int) = 0.072], which were used in all calculations. R1 = 0.1113, wR2 = 0.2427 for observed unique reflections [I > $2\sigma(I)$] and R1 = 0.0884, wR2 = 0.2308 for all unique reflections. Max. and min. residual electron densities 4.00 and -1.75 e Å⁻³.

Pd(DPPBz)PhBr (**15**) (DPPBz = 1,2-bis(diphenylphosphino)benzene). **9a** (250 mg, 0.318 mmol) and DPPBz (284 mg, 0.636 mmol) were suspended in benzene (8 mL) and the reaction mixture stirred at room temperature for 16 hours under N₂ atmosphere. Pentane was added to complete precipitation, and the product was isolated after filtration and several washings with pentane giving a yellow powder (184 mg, 82%). Spectroscopic details were identical to those previously reported for the same compound synthesized by an alternative method.⁵¹

Pd(DPPBz)(C(O)Ph)Cl (DPPBz (16) 1,2bis(diphenylphosphino)benzene). 14a (150 mg, 0.194 mmol) and DPPBz (172 mg, 0.389 mmol) were suspended in benzene (5 mL) and the reaction mixture stirred at room temperature for 16 hours under N_2 atmosphere. Pentane was added to complete precipitation, and the product was isolated after filtration and several washings with pentane giving a yellow powder (103 mg, 77 %). ¹H NMR (CD₂Cl₂, 400 MHz): δ 7.03 – 7.59 (29 H, m). $^{13}C\{^{1}H\}$ NMR (CD₂Cl₂, 100 MHz): δ 134.3, 133.6 (d, ²*J*_{CP} = 13 Hz), 133.3, 132.1, 131.7, 131.0, 130.6, 130.3, 129.7, 128.9 (d, ${}^{2}J_{CP}$ = 10 Hz), 128.6 (d, ${}^{2}J_{CP}$ = 11 Hz), 128.3, 127.7 (signals due to quaternary carbon atoms were not observed). ³¹P{¹H} NMR (CD₂Cl₂, 162 MHz): δ 39.8 (d, ²J_{PP} = 42 Hz), 32.1 (d, ²J_{PP} = 42 Hz). IR (CH₂Cl₂): v(CO) 1590 cm⁻¹. Elemental analysis found: C 63.93, H 4.16 %, calculated for C37H29CIOP2Pd C 64.09, H 4.22 %.

(η³-1-/Bu-indenyl)Pd(PPh₃)Cl (**18**). Dimer (η³-indenyl)₂(μ-Cl)₂Pd₂ (80 mg, 0.130 mmol), prepared from a reported procedure,⁴⁵ and PPh₃ (68 mg, 0.260 mmol) were placed in a Schlenk flask and suspended in Et₂O (8 mL) under argon atmosphere. The suspension was stirred for two hours at room temperature, during which time the reaction mixture became homogeneous. The solution was filtered, concentrated and cooled to -23 °C overnight. Compound **18** was isolated as a brown crystalline powder (106 mg) in 71% yield. ¹H NMR (CD₂Cl₂, 400 MHz): δ 7.60 – 7.44 (15 H, m, PPh₃), 7.59 (1 H, obscured with PPh₃ singals, Ind), 7.15 (1 H, t, ³J_{HH} = 7.4 Hz, Ind), 6.93 (1 H, t, ³J_{HH} = 7.4 Hz, Ind), 6.64 (1 H, d, ³J_{HH} = 2.2 Hz, Ind), 6.35 (1 H, d, ³J_{HH} = 7.4 Hz, Ind), 4.33 (1 H, t, ³J_{HH} = 2.2 Hz, Ind),

1.65 (9 H, s, 'Bu). ¹³C{¹H} NMR (CD₂Cl₂, 100 MHz): δ 137.2 (d, $^2J_{CP}$ = 2 Hz, Ind), 136.3 (d, $^2J_{CP}$ = 5 Hz, Ind), 134.0 (d, $^2J_{CP}$ = 12 Hz, PPh₃), 132.1 (d, $^1J_{CP}$ = 45 Hz, PPh₃), 130.8 (Ind), 130.6 (d, $^4J_{CP}$ = 3 Hz, PPh₃), 128.4 (d, $^3J_{CP}$ = 11 Hz, PPh₃), 126.2, 125.8, 120.4, 116.8 (Ind), 107.9 (d, $^2J_{CP}$ = 7 Hz, Ind), 73.5 (d, $^2J_{CP}$ = 4 Hz, Ind), 34.7 (d, $^3J_{CP}$ = 5 Hz, C(CH₃)), 29.5 (d, $^4J_{CP}$ = 5 Hz, C(CH₃)). ³¹P{¹H} NMR (CD₂Cl₂, 162 MHz): δ 28.9 . Elemental analysis found: C 64.80, H 5.12 %, calculated for C₃₁H₃₁CIPPd C 64.59, H 5.42 %.

Pre-activation experiments for trappig Pd(0) species. Two set of experiments were carried out: (A) **2a** (8 mg, 0.011 mmol), borylzinc reagent **1** (16 mg, 2.5 equiv) and dvds (25 µL, 10 equiv) were placed in a Young's NMR tube inside a dry box and dissolved in dioxane (0.6 mL). The tube was heated at 80 °C and conversion was monitored by ³¹P{¹H} analysis; (b) **2a** (8 mg, 0.011 mmol) and borylzinc reagent **1** (66 mg, 10 equiv) were placed in a Young's NMR tube inside a dry box and dissolved at 80 °C for 30 min and then dvds (12 µL, 5 equiv) or bromobenzene (6 µL, 5 equiv) were added inside a dry box. Conversion was monitored by ³¹P{¹H} analysis.

Pre-activation experiments with variable amounts of 1. 2a (10 mg, 0.014 mmol) and variable amounts of borylzinc reagent **1** (0.5 to 10 equiv) were placed in a Young's NMR tube inside a dry box and dissolved in dioxane (0.6 mL). The tube was heated at 80 °C for 30 min. Conversion and selectivity data were obtained by ¹H and ³¹P{1H} NMR analysis of the crude mixtures using a capillary charged with trimethoxybenzene and P(OPh)₃ as internal standards.

General procedure for catalytic borylation. In a typical experiment borylzinc reagent 1 (12 mg, 0.010 mmol) was placed in a Young's NMR tube inside a dry box, and the corresponding organic substrate (bromobenzene or benzoyl chloride, 0.022 mmol, 1.1 equiv) then added. Palladium pre-catalyst was transferred into the mixture as a stock solution in dry 1,4-dioxane or thf (0.5 mL, 5 mol%) and the tube heated at 80 °C for up to 2 h, time during which ¹H NMR data were obtained using trimethoxybenzene as an internal standard to build the corresponding reaction profiles.

Stoichiometric experiments between 1 and Pd compounds. Borylzinc reagent **1** (12 mg, 0.010 mmol) and the corresponding palladium compound (**9a**, 16 mg, 0.020 mmol; **14a**, 15 mg, 0.020 mmol; **15**, 14 mg, 0.020 mmol; **16**, 14 mg, 0.020 mmol) were placed in a Young's NMR tube inside a dry box and dissolved in thf- d_8 or dioxane (0.6 mL). The tube was heated at 80 °C for 3 h. Conversion and selectivity data were obtained by ¹H and ³¹P{1H} NMR analysis of the crude mixtures using a capillary charged with trimethoxybenzene and P(OPh)₃ as internal standards.

Catalytic borylation of [PPh₄][X]. Borylzinc reagent 1 (27 mg, 0.022 mmol) and [PPh₄]Cl (16 mg, 0.044 mmol) were placed in a Young's NMR tube inside a dry box (in some experiments $ZnBr_2$ (10 mg, 1equiv) was also added to form ZnX_3^- in situ). Pd(PPh₃)₂Cl₂ was transferred into the mixture as a stock solution in dry dioxane (0.5 mL, 2.2 mM, 5 mol%) and the tube heated at 80 °C for 2 h. Conversion and selectivity data were obtained by ¹H NMR analysis of the crude mixture after addition of trimethoxybenzene as internal standard.

Computational details. Two different DFT functionals (M06L and M06) and basis sets (BS1 and BS2) were selected for geometry optimization and energy refinement, in order to optimize accuracy and computational cost. All stationary points were fully optimized with the pure M06L functional⁵² including dispersion, as implemented in the Gaussian09 software package (Rev. D.01).⁵³ Geometry optimizations were carried out on

the full system including solvation by THF with the continuum SMD model.54 Frequencies were computed with the aim of classifying all stationary points as either minima or transition states and determining the thermochemistry corrections, (G - E), which include the zero-point, thermal and entropy energies. BS1 was used for geometry optimizations and includes polarization functions and small-core pseudopotentials by combining the double- ζ 6-31G^{**} (C, N, O and H)⁵⁵ and LANL2DZ (Pd)⁵⁶ basis sets. Single point calculation on the optimized structures was performed by using the hybrid M06 functional, including solvation and using the triple- ζ BS2, in which Pd was described with the LANL2TZ(f) basis set $^{\rm 57}$ and C, N O and H were described with the 6-311+G** basis set,58 including polarization and diffuse functions. The free energies discussed in the text were obtained by adding the thermochemistry corrections, (G - E), at the DFT(M06L)/SMD/BS1 level, to the potential energies refined at the DFT(M06)/SMD/BS2 level. These energies were corrected for a 1M standard state...

Acknowledgements

J.C. thanks the EU 7th Framework Program, Marie Skłodowska-Curie actions (COFUND, Grant Agreement no. 267226) and Junta de Andalucía for a Talentia Postdoc. E.K. thanks the EU 7th Framework Program, Marie Skłodowska-Curie actions (PIEF-GA-2013-626441). A.N. thanks the Norwegian Research Council through the grants (221801/F20 and 250044/F20), the Center of Excellence for Theoretical and Computational Chemistry (CTCC; grant No. 179568/V30) and the Norwegian Metacenter for Computational Science (NOTUR; grant nn4654k).

Keywords: borylation • cross-coupling • borylzinc • palladium • acylborane

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