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C–C coupling

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Exception to the *ortho* Effect in Palladium/Norbornene Catalysis**

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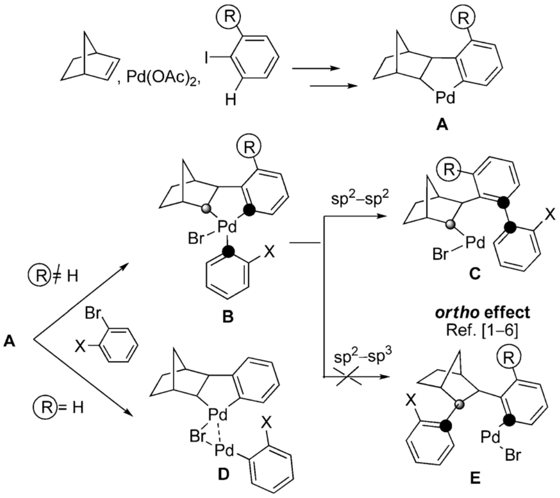
Dedicated to Professor Alfredo Ricci

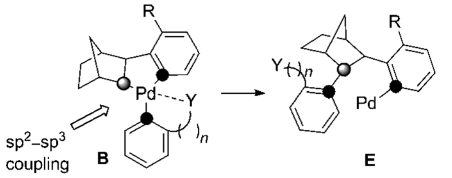
The association of palladium and norbornene opens access to a myriad of polycyclic and heterocyclic frameworks through sequential coupling reactions of aryl halides or triflates.[1] In order for the norbornene cocatalysis to lead to the desired products, one needs *ortho* substituents on the aryl halides (the so-called *ortho* effect).[2]

Density functional theory (DFT) calculations run in our group as well as in the Catellani group indicate that the role of these *ortho* substituents is to prevent reductive elimination from the bimetallic Pd^{II}–Pd^{II} intermediates of type **D** (Scheme 1). Starting from the initially formed palladacycle **A**, wherein an *ortho* group is present, the key Pd^{IV} intermediate **B** is formed and undergoes regioselective biaryl formation to give **C** rather than **E**. Our study showed that steric factors rather than electronic ones are predominant for the selectivity, and is in agreement with the variety of synthetic applications reported so far.[3,4]

Together with the Catellani group,[5] we now report the formation of adducts derived from the previously unobserved sp^2–sp^3 reductive elimination,[2,3c] that is, exceptions to the *ortho* rule. In our hands, this sp^2–sp^3 reductive elimination serendipitously happened when we worked with 2-bromophenylacetamide (Scheme 2), thus suggesting that coordinating substituents might induce different reactivities at the palladium center, and that chelation might therefore be a tool to achieve regiocontrol in palladium/norbornene catalysis.



Scheme 1. The *ortho* effect in palladium/norbornene catalysis.



Scheme 2. Chelation approach to regiocontrol; $n=1$, $Y=(C(=O)NH_2)$ for sp^2–sp^3 coupling (this work). $n=0$, $Y=NH_2$ for sp^2–sp^3 coupling (Ref. [5]).

Herein we present our synthetic results and our proposed mechanistic rationalization that arises from computational analysis of several reactive pathways.

In a typical experiment, an equimolar amount of 2-iodotoluene, norbornene, and 2-bromophenylacetamide were reacted in the presence of $Pd(OAc)_2$ (10 mol%), tri(2-furyl)phosphine (20 mol%), and Cs_2CO_3 in dry DMF. Gratifyingly, this selectively yielded 75% of the norbornene-containing dihydrophenanthrene **1a** (Table 1), which is not the product expected given the *ortho* rule.[3c,6] We sought to extend the scope of this peculiar reactivity with differently substituted aryl iodides by varying both their steric and electronic properties. Good results were obtained with alkyl or alkoxy substitutents for the formation of compounds **1a–g** (entries 1–7). Polyaryl iodides (entries 8 and 9) or aryl iodides bearing chloride or trifluoromethyl substituents (entries 10–

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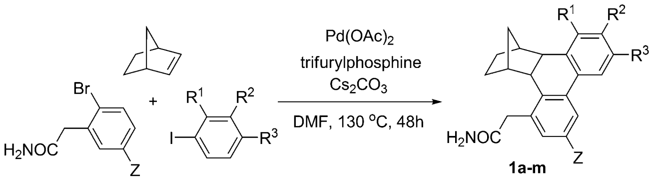
Table 1: Multicomponent synthesis of dihydrophenanthrene.



Entry[a]	Aryl iodide	Z	Yield [%][b]
1	R^1 = Me; R^2 = R^3 = H	H	**1a**: 75
2	R^1 = Et; R^2 = R^3 = H	H	**1b**: 57
3	R^1 = CH$_2$-OMe; R^2 = R^3 = H	H	**1c**: 60
4	R^1 = Me; R^2 = Me; R^3 = H	H	**1d**: 60
5	R^1 = Me; R^2 = H; R^3 = Me	H	**1e**: 82
6	R^1 = Me; R^2 = H; R^3 = OMe	H	**1f**: 65
7	R^1 = Me; R^2 = R^3 = OMe	H	**1g**: 60
8	1-iodonaphtalene	H	**1h**: 61
9	9-iodophenanthrene	H	**1i**: 81
10	R^1 = Cl; R^2 = R^3 = H	H	**1j**: 47
11	R^1 = CF$_3$; R^2 = R^3 = H	H	**1k**: 71
12	R^1 = Me; R^2 = R^3 = H	CF$_3$	**1l**: 45
13	R^1 = Me; R^2 = H; R^3 = Me	CF$_3$	**1m**: 52

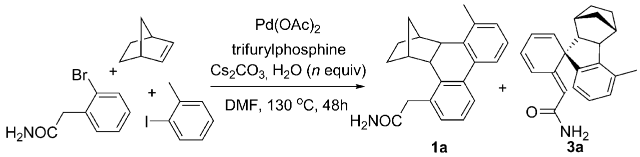
[a] Reaction conditions: ArBr (0.36 mmol, 0.045 M in DMF), ArI (0.36 mmol), norbornene (0.36 mmol), Pd(OAc)$_2$ (0.036 mmol), TFP (0.072 mmol), Cs$_2$CO$_3$ (0.72 mmol), 130 °C. [b] Yield of isolated product. DMF = dimethylformamide.

11) were also reacted successfully and led to the adducts **1h–k**. 2-Bromo-5-trifluoromethyl phenylacetamide followed a similar trend and delivered **1l–m** in reasonable yields (entries 12 and 13). Overall, the exception to the *ortho* rule proved to be at work with a variety of substituents.

Upon determining the scope of the chelation-controlled sequence, we observed that when the substrates were not carefully dried, an appreciable amount of the spiro derivative **3a** was isolated as a by-product together with the now familiar **1a** (Table 2).[7] When excess water (11 equiv relative to palladium) was added, **3a** was obtained as the sole product of the reaction (entry 3). An additional increase of the water content led to degradation. It is noticeable that at first sight, the formation of **3a** arises as a result of the *ortho* effect.

We investigated the behavior of various aryl iodides in the presence of water (eight examples, see Table S1 in the Supporting Information). Pleasingly, the palladium-mediated dearomatization leading to spirocyclic adducts proved quite general although yields remained limited (ranging from 28% to 65%).

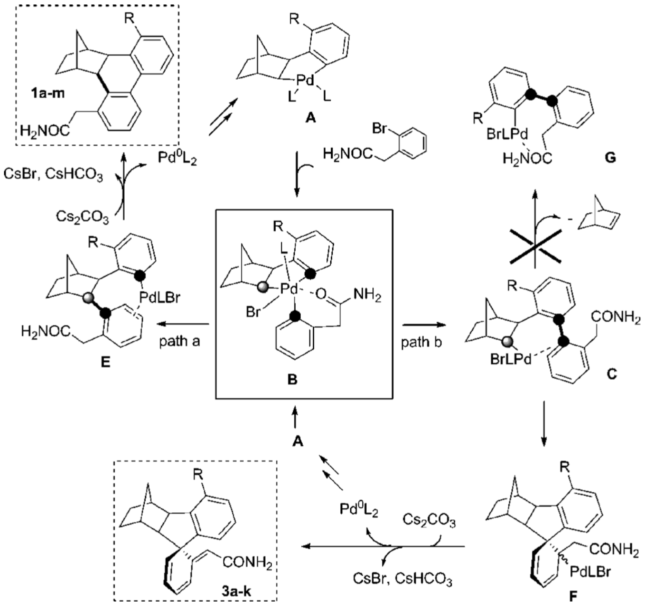
Table 2: Effect of water on the selectivity of the reaction.



Entry[a]	*n*	**1a**/**3a**[b]
1	0	1:0 (**1a** only)
2	2.5	1:1
3	11	0:1 (**3a** only; 65% yield)[c]

[a] Reaction conditions: as in Table 1 but at half the scale. [b] Determined by ^{1}H NMR analysis. [c] Yield of isolated product.

On the basis of both our theoretical results and previous studies, a hypothetical mechanism was considered (Scheme 3). The *ortho*-substituted aryl iodide and norbornene should lead to metallacycle **A** as usual.[8] **A** would then oxidatively add to 2-bromophenylacetamide to generate the Pd^{IV} complex **B**.[3a] At this point, coordination of the carbonyl moiety would form a chelate that might favor sp^2–sp^3 C–C bond-forming reductive elimination to 1,2 diaryl norbornene derivative **E**, which would undergo a second C–H activation step that would release **1a–m** and the Pd^0 complex for turnover (path a, Scheme 3).



Scheme 3. Proposed mechanistic pathways.

Somehow, water returns the reactive path back toward the traditional manifold, either through an apical ligand exchange, hydrogen bonding, or stabilization of a pentavalent Pd^{IV} species. Further on in the reaction pathway, water also appears to hamper the usual norbornene extrusion[1a,b] through β-hydride elimination, thus favoring dearomatization instead.[6]

The Pd^{IV} intermediates involved are extremely prone to reductive eliminations, and it has not been possible to isolate any putative intermediate from the reaction mixtures. We thus turned to DFT modeling to gain insight into the reactivity.

To check the feasibility of the Pd^{IV} complex **B**, we modeled oxidative additions of the aryl bromide onto the starting Pd^{II} metallacycle (with and without amide chelation) and we compared them with a bimetallic pathway alternative to Pd^{IV}. The energetic convenience of Pd^{IV} formation was confirmed, in accordance with our previous calculations.[3a] In our system the chelating substituent in the *ortho* position of the aryl bromide certainly increases the energy gap between these pathways, by both favoring the oxidative addition leading to **B** (as demonstrated recently by Vicente et al.)[3d]

and increasing the steric hindrance in the bimetallic pathway (Pd^{IV} formation results favored by more than 20 kcal mol^{-1}; see Figures S1 and S2 in the Supporting Information).

The Pd^{IV} intermediate calc-**B** obtained from oxidative addition of bromophenyl acetamide to the cyclopalladated complex **A** converged systematically on a minimum energy in which a chelate to the palladium center forms through the oxygen atom of the amide (L = tris(2-furyl)phosphine; Figure 1). In contrast to previous calculations on the octahedral Pd^{IV} complexes with an apical aliphatic or benzylic group,[3a] the chelating acetamido moiety also forces the halide to be *cis* to the norbornane unit (Figure 1, and see Figure S3 in the Supporting Information). Without water, the activation barrier to the sp^2–sp^3 C–C bond formation is lower than the barrier leading to the usual sp^2–sp^2 C–C bond formation (3.0 kcal mol^{-1}, Figure 1, levels marked with solid lines).

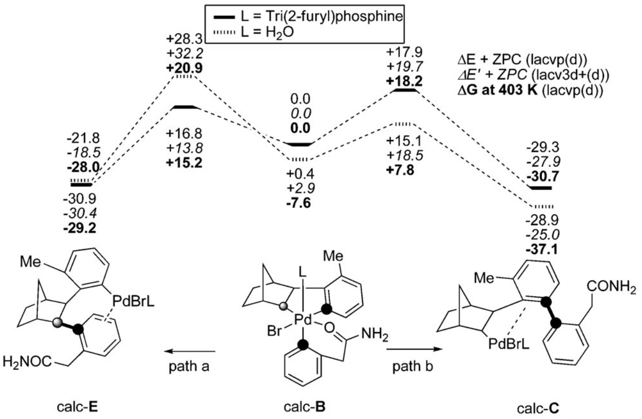


Figure 1. Calculations of the barrier energies for the sp^3–sp^2 (path a) and sp^2–sp^2 (path b) couplings starting from complex **B** having either a phosphine ligand (solid energy levels) or water (dashed levels). Values in kcal mol^{-1}. See the Supporting Information for computational details.

The chelation of the amide is released in the transition state leading to the sp^2–sp^3 coupling in the calculated phosphine-containing system (Figure 1, path a, and see Figure S8 in the Supporting Information). Therefore, the metal center is pentacoordinated. On the contrary, the chelation remains in place for the transition state of the compound showing an *ortho* effect (path b); that is the palladium atom is hexacoordinated in that case (Figure S8). We know that barriers for reductive eliminations from octahedral Pd^{IV} complexes are in general higher than those of pentacoordinated Pd^{IV} complexes,[3a] which gives a first rationale for the observed exception. To further strengthen the validity of our model, we calculated the barriers from a chelated Pd^{IV} species analogous to **B** but arising from oxidative addition of bromobenzylamine. This cascade was proven to follow the general *ortho* rule.[4] Results correlate with experiments since sp^2–sp^2 coupling is favored in this case by 5.2 kcal mol^{-1} (Figures S4 and S5 in the Supporting Information).

In addition, steric strain appears to develop more in the *ortho*-effect transition state leading to calc-**C**, as evidenced by a very short distance between the hydrogen atom *ortho* to the C–Pd bond on the benzylamide and the benzylic hydrogen atom of the norbonene β to palladium (2.01 Å; Figure S8). This second effect additionally contributes to increasing the activation energy for the sp^2–sp^2 coupling. The combined effects lead the usually disfavored sp^2–sp^3 coupling to prevail.

Water can efficiently replace the phosphine as the apical ligand and the corresponding *cis* Br/norbornene Pd^{IV} complex is stabilized because of the steric strain released in the ligand exchange ($\Delta G = -7.6$ kcal mol^{-1}, $L = H_2O$).[9] In this case (Figure 1, levels marked with dashed lines), the coordination of palladium is similar to that in the path a transition state relative to the phosphine case, but the geometry changes significantly in the path b transition state (sp^2–sp^2 coupling). The steric strain is partially released since the shortest H–H distance is now 2.08 Å. Moreover, if chelation is still present, a partial displacement of water is nonetheless observed (the Pd–O distance goes up to 2.63 Å from 2.34 Å in the path a transition state (Figure S8). Thus the metal resembles a more reactive pentacoordinated species. These two features combined restore the usual and expected energetic preference of the sp^2–sp^2 coupling over the sp^2–sp^3 coupling ($\Delta\Delta G$ of 12.1 kcal mol^{-1}), which is in perfect agreement with the experimental results. The inversion in the favored reductive elimination was found only when water replaced the phosphine. Alternative mechanisms based on pentacoordinated high-valent palladium, hydrogen bonding of water to the amide, and scrambling of the axial ligands were considered but cannot explain the reaction outcome (see the Supporting Information for details).[10]

This reaction mechanism also agrees well with the results of Table 2. Since **B** is a closed-shell, 18-electron complex, replacement of the phosphine with water likely occurs through a dissociative mechanism,[11] and the two complexes are in thermodynamic equilibrium. We postulate that a 1:1 mixture is formed when the two ligands are present in a nearly equimolar amount (Table 2, entry 2). Formation of **1** is excluded only when the excess of water is large enough to overcome the contribution of the free enthalpy of the Pd–P bond.

According to the DFT calculations, the amide moiety is therefore crucial for leading to the exception to the *ortho* rule. Chelation forces the Pd^{IV} complex into a *cis* Br/norbornene geometry, and it also likely hampers the transition state leading to sp^2–sp^2 coupling. Water can overcome this trend by reducing the steric strain and increasing the flexibility of the complex.

Downstream from the C–C coupling, 5-*exo* migratory insertion or tandem deprotonation/nucleophilic attack at the palladium center could explain the dearomatization of complex **C** (Figure 1) and the formation of products **3** via **F**. Our DFT results suggest that the former option is favored by 5.6 kcal mol^{-1} (see Figure S9 in the Supporting Information). Formation of **3** from **E** in the presence of water could be ruled out on the basis of the large energetic gap between the two nonreversible reductive eliminations from the complex **B**.[7b,12] The relative ease of this diastereoselective dearomatization (calculated barrier of +13.3 kcal mol^{-1} for **C**→**F**) is additionally confirmed since it experimentally happens faster than the usual norbornene extrusion (+20.5 kcal mol^{-1} barrier; see Figure S11 in the Supporting Information).[1,2] The latter step is usually favored by steric hindrance.[1a,b] We thus suggest that water is crucial not just for switching the favored reductive elimination from **B** but also for triggering the subsequent dearomatization, owing to its minimal size.

We found a barrier of +19.6 kcal mol^{-1} for the formation of the other diastereomer of **3**, and it is due to a clear steric interaction between the amide group and the norbornene unit (see Figure S10 in the Supporting Information). The fact that DFT predicted the observed diastereostereoselectivity for the dearomatization supports the proposed mechanism.

To conclude, we have reported the first deviation from the *ortho* effect in palladium/norbornene catalysis. DFT calculations indicate that this likely originates from the role played by a suitably placed amide group in the reductive elimination pathway involving an initially formed chelated Pd^{IV} intermediate. Addition of water restores the reaction to its normal (*ortho* rule in effect) selectivity, however it led to dearomatization. Additional work will seek to expand the synthetic applications of the chelate approach in Pd^{IV} chemistry.

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[12] Detailed computational results supporting our mechanistic rationalization in the dearomatization reaction are available in the Supporting Information.