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Solvent/Base Effects in the Selective Domino Synthesis of Phenanthridinones That Involves High-Valent Palladium Species: Experimental and Theoretical Studies

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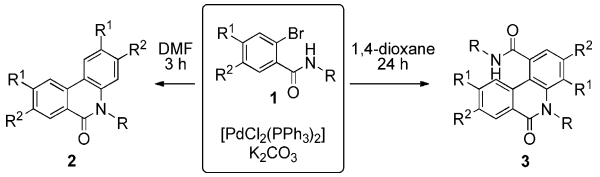
In memory of Professor François Tillequin

Abstract: The domino reaction of *o*-bromobenzamides **1a–m** in the presence of K_2CO_3 and the $[PdCl_2(PPh_3)_2]$ catalyst granted a selective access to phenanthridinones **2** or to the new 1-carboxamide phenanthridinones **3** depending on the solvent, DMF or 1,4-dioxane, respectively. Investigations of the reaction parameters provided the first example of a direct correlation between the base dissociation and the solvent polarity on the selectivity observed. Moreover, mechanistic studies (NMR spectroscopy and ESI-MS monitoring) allowed us to characterize Pd^{II} palladacycle **4** and biaryl species as common intermediates for these two domino processes. On that basis, C-(sp^2)–C(sp^2) bond formation is envisaged by generation of a Pd^{IV} complex after oxidative addition of **1** into Pd^{II} palladacycle **4**, a rationale that is supported by DFT calculations. A general catalytic cycle is proposed to account for these observations.

Keywords: basicity · density functional calculations · domino reactions · phenanthridinones · reductive coupling

Introduction

The biaryl subunit constitutes a very important template for many fields of chemistry, as it is found in natural products, pharmaceuticals, agrochemicals, catalysts, as well as materials (polymers).[1] The widespread need for such motifs led to the development of several efficient preparative methods that are typically based on C(sp^2)–C(sp^2) bond formation between two aryl moieties. Classical approaches involve transition-metal-catalyzed cross-coupling reactions and, in recent years, Pd-mediated C–H activation and direct arylations.[2,3] Besides, the formation of the biaryl axis may represent the key event of metal-catalyzed domino processes.[4] Several examples of preparation of heterocycles-containing biaryls have been reported, either in an inter- or intramolecular fashion.[5] In this context, we recently described[6] the Pd-catalyzed selective formation of phenanthridinones **2**[7] or unprecedented 1-carboxamide phenanthridinones **3**, from readily available *o*-bromobenzamides **1**, depending on the solvent, DMF or 1,4-dioxane, respectively (Scheme 1). Beyond the potential applications of these compounds in medicinal chemistry,[8] the mechanistic aspects of these catalytic reactions are of fundamental value. Some crucial issues remain to be addressed and their understanding should give some profitable data for other related Pd-catalyzed reactions. Up to now, there has been no firm mechanistic evidence for the formation of the biaryl axis in this type of domino processes. A possible Pd^{II}–Pd^{II} transmetalation pathway has been proposed on the basis of DFT calculations.[9] However, the generation of high-valent Pd intermediates could also be invoked. Moreover, the formation of tricycles **2** and **3** is totally selective, and one may wonder whether this selectivity is only governed by the solvent polarity, or by others factors such as the base, also involved in



Scheme 1. Pd-catalyzed coupling of *o*-bromobenzamides.

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the discrimination between *ipso* substitution and direct arylation routes.

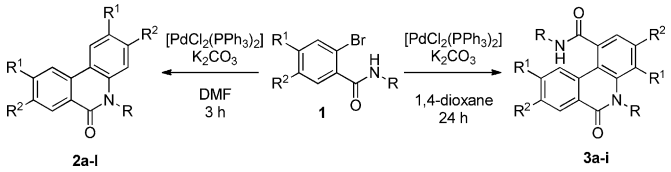
Because these Pd-mediated domino reactions raised many questions with regards to the mechanism involved, a detailed experimental and theoretical study was carried out and the results are presented herein.

Results and Discussion

Reaction scope: To investigate the scope of the title reactions, a wide array of *o*-bromobenzamides **1a–m** that differ in their N-protecting groups (R: benzyl, *p*-methoxybenzyl (PMB), allyl, methyl) and in the substituents at the aromatic ring (R^1 and R^2: OCH_3, OCH_2O, Cl, NO_2, H) were engaged. As shown in Table 1, the reaction is totally selective depending on the solvent. The nature of the N-protecting group does not influence the outcome of the reaction (Table 1, entries 1, 4, 9, and 10), except in the case of the allyl group with which a double bond isomerization was observed in 1,4-dioxane (entries 10–12).[10] The best yields were obtained when the aromatic core was substituted by electron-donating groups such as methoxy and methylenedioxy (entries 2, 3, 5, 6, 11, and 12). The presence of a deactivating group such as chlorine or an electron-withdrawing group such as nitro induced low to moderate yields (entries 7, 8, and 13). Moreover, in the latter case, the corresponding debrominated benzamide was isolated (entry 13).[11]

The reactions were carried out using different Pd complexes (Pd^0 and Pd^{II}). The results were found very similar, regardless of the Pd source.[6]

Table 1. Reaction scope.



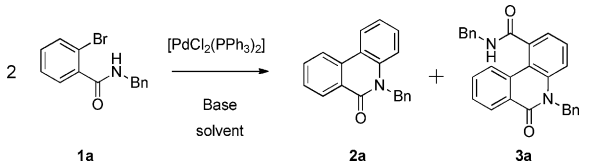
	Substrate	Substituents	Product, yield [%][a] in DMF	in dioxane
1	**1a**	R = Bn; $R^1 = R^2 = H$	**2a**, 55	**3a**, 49
2	**1b**	R = Bn; $R^1 = R^2 = OCH_3$	**2b**, 88	**3b**, 63
3	**1c**	R = Bn; R^1, $R^2 = OCH_2O$	**2c**, 91	**3c**, 80
4	**1d**	R = PMB; $R^1 = R^2 = H$	**2d**, 71	**3d**, 48
5	**1e**	R = PMB; $R^1 = R^2 = OCH_3$	**2e**, 80	**3e**, 82
6	**1f**	R = PMB; R^1, $R^2 = OCH_2O$	**2f**, 99	**3f**, 80
7	**1g**	R = Bn; $R^1 = H$; $R^2 = Cl$	**2g**, 54	**3g**, 43
8	**1h**	R = PMB; $R^1 = H$; $R^2 = Cl$	**2h**, 46	**3h**, 61
9	**1i**	$R = CH_3$; $R^1 = R^2 = H$	**2i**, 90	**3i**, 80
10	**1j**	R = allyl; $R^1 = R^2 = H$	**2j**, 55	–[b]
11	**1k**	R = allyl; $R^1 = R^2 = OCH_3$	**2k**, 80	–[b]
12	**1l**	R = allyl; R^1, $R^2 = OCH_2O$	**2l**, 95	–[b]
13	**1m**	R = PMB; $R^1 = H$; $R^2 = NO_2$	–[c]	–[d]

[a] Reaction conditions: $[PdCl_2(PPh_3)_2]$ (5 mol%), K_2CO_3 (3 equiv), *o*-bromobenzamide (1 equiv), DMF or 1,4-dioxane (20 mL) at 155 or 105 °C, respectively. [b] *E*/*Z* isomerization of the double bond of **1j–l** was observed. [c] The debrominated amide was isolated from the reaction mixture. [d] *p*-Methoxybenzaldehyde was isolated as the major product.

The influence of the temperature was next studied. The same selectivity was observed when heating the reaction in an oil bath or by microwave irradiation. Moreover when the reaction was carried out in 1,4-dioxane and heated at a temperature close to the boiling point of DMF under microwave irradiation, phenanthridinones **3** were exclusively formed. Thus the selectivity of these reactions is not governed by thermal or microwave effects.

We next focused on the influence of the carbonate base on the selectivity of the reaction (Table 2). Three bases were selected: Na_2CO_3, K_2CO_3, and Cs_2CO_3, which exhibit increasing salt solubility.[12] In addition, THF, which is a common solvent in Pd chemistry, was chosen for its intermediate polarity between DMF and 1,4-dioxane. In the absence of base, no reaction occurred, thereby outlining the crucial role played by the alkaline agent in these processes (Table 2, entry 1). In 1,4-dioxane, **3a** was exclusively obtained when using Na_2CO_3 or K_2CO_3 (entries 2 and 3). By contrast, a mixture of **2a** and **3a** was isolated with the more easily dissociated Cs_2CO_3 (entry 4). In THF, compound **3a** was obtained with weakly dissociated Na_2CO_3, whereas the use of more soluble Cs_2CO_3 led to phenanthridinone **2a** (entry 2 versus 4). By contrast, K_2CO_3 led to a mixture of the two tricycles (entry 3). Interestingly, the use of THF as solvent resulted in a significant increase in the yields of **2a** or **3a**. In DMF, a selectivity opposite to that observed in 1,4-dioxane ensued: a mixture of compounds **3a** and **2a** was formed with Na_2CO_3, and **2a** was isolated as a sole product using either K_2CO_3 or Cs_2CO_3. Thus, for the first time, a direct correlation between the base dissociation and the solvent polarity could be established. A diagonal line can be drawn in Table 2 that highlights a complementarily between the base and the solvent for maximizing the selectivity. The combination of a poorly soluble carbonate and a weakly polar solvent constitutes a weakly dissociating medium in which 1-carboxamide phenanthridinones **3** are preferentially formed. Conversely, the association of a more soluble base with a polar solvent establishes a dissociating medium that favors the formation of phenanthridinones **2**.

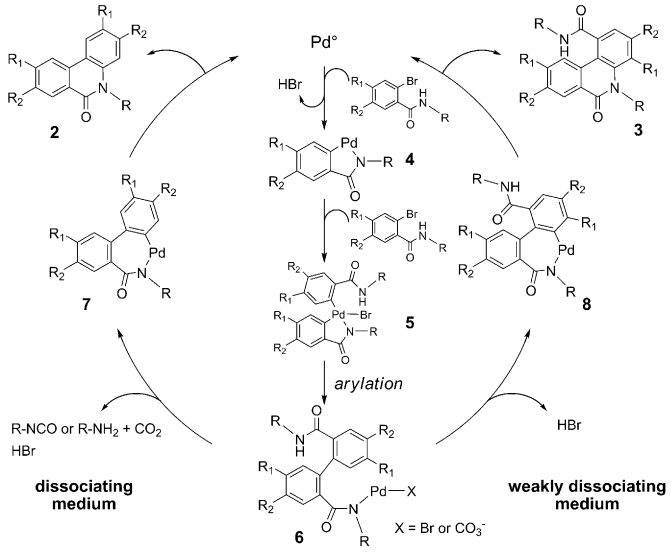
Table 2. Role of the base.[a]



	Base	Product (global yields [%]/selectivity) in dioxane	in THF	in DMF
1	no base	no reaction	no reaction	no reaction
2	Na_2CO_3	**3a** (traces)	**3a** (86)	**3a**/**2a** (64/1:3.3)
3	K_2CO_3	**3a** (49)	**3a**/**2a** (56/1:1.4)	**2a** (55)
4	Cs_2CO_3	**3a**/**2a** (69/1.5:1)	**2a** (90)	**2a** (80)

[a] Reaction conditions: $[PdCl_2(PPh_3)_2]$ (5 mol%), K_2CO_3 (3 equiv), *o*-bromobenzamide **1a** (1 equiv), dioxane, THF or DMF (20 mL) at 100, 60, or 150 °C, respectively.

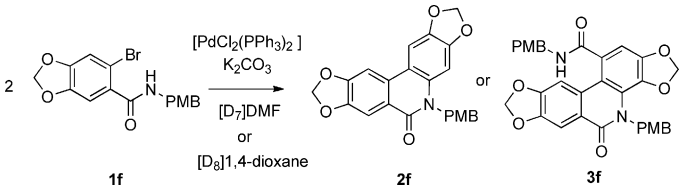
From these results and previous observations,[7a,b,13] overlapping catalytic cycles were initially proposed (Scheme 2).[6] After oxidative addition of the in situ generated Pd^0 species into the C(sp^2)–Br bond, HBr elimination led to the corresponding Pd^{II} palladacycle **4**.[14] Then, oxidative addition of a second *o*-bromobenzamide unit occurred to generate a transient high valent Pd^{IV} complex **5**.[15] The latter could furnish, after reductive elimination, the corresponding biaryl–Pd^{II} intermediate **6**. Consequently, depending on the reaction medium, two different pathways can be envisaged for the intramolecular N–C(sp^2) bond formation: 1) in a dissociating medium, ligand exchange between bromine and carbonate occurs, followed by an *ipso* substitution and elimination of an isocyanate unit; 2) in a weakly dissociating medium, a direct arylation leads to the formation of tricycle **3**.



Scheme 2. Mechanistic rationale (ligands are omitted for clarity).

However, some events proposed in these catalytic cycles have to be clarified. First, the formation of the biaryl axis from a Pd^{II} palladacycle such as **4** and an arylhalide is not well established.[16] Most commonly, the Pd^0/Pd^{II} redox pair is preferred to the Pd^{II}/Pd^{IV} one.[9,17,18] Besides, Pd^{III} complexes were recently recognized as putative intermediates in catalysis, particularly in some Pd-catalyzed reactions previously suggested to proceed by means of Pd^{II}/Pd^{IV} redox cycles.[19] In these cases, the addition of an oxidant such as $PhI(OAc)_2$ proved necessary.[20] Secondly, the possible coexistence of two reaction pathways according to the medium should be explored. Lastly, the exact implication of the base in these processes has to be rationalized.

Mechanistic investigations—NMR spectroscopy and mass spectrometry (ESI-MS) monitoring: To gain further insights into the mechanism of these reactions, we have made some attempts to detect the reaction intermediates by means of NMR and ESI-MS spectroscopy. Toward this end, the reactions were directly performed in an NMR spectroscopy tube and heated at 120 °C for [D_7]DMF, or 90 °C for [D_8]1,4-dioxane within the NMR spectrometer (Scheme 3).[21] Free induction decay (FID) acquisitions were achieved every 30 min. When a significant modification was observed by ^{1}H NMR spectroscopy, an aliquot of the reaction mixture was analyzed by ESI-MS. Benzamide **1f** was selected for these experiments because it reacts in high yields (see Table 1) and displays structural probes such as the methylenedioxy moiety and the PMB CH_2 group.[22]



Scheme 3. NMR spectroscopy and ESI-MS monitoring of the transformation of **1f**.

Reaction in [D_7]DMF: The reaction was first carried out with an excess amount of Pd catalyst (1.2 equiv of [$PdCl_2(PPh_3)_2$]). In the absence of base, no reaction occurred, as shown previously (Table 2, entry 1). The signals that corresponded to **1f** were clearly observed in the ^{1}H NMR spectrum, and the baseline was straight (see the Supporting Information). Immediately after addition of K_2CO_3 (3 equiv), the baseline was markedly modified, thus demonstrating the crucial role of the base in the generation of Pd^0 species. After one hour, signals attributable to Pd^{II} intermediates that resulted from oxidative addition into the C(sp^2)–Br bond were observed in ESI-MS(−) (Figure 1).

These complexes are readily identifiable by their characteristic isotope pattern. In particular, cluster peaks that corresponded to $[ArPdBr-H]^-$ and $[ArPd(PPh_3)Br-H]^-$ were detected (*m*/*z* 470 and 735, respectively). These complexes were accompanied by $[ArPdCl-H]^-$ and $[ArPd(PPh_3)Cl-H]^-$ species that resulted from a halogen exchange (*m*/*z* 426 and 688, respectively), which is a consequence of the over-stoichiometric addition of [$PdCl_2(PPh_3)_2$]. Observation of these insertion products is fully in line with the expected mechanism. In ESI-MS(+), a cluster peak attributable to palladacycle **4** (*m*/*z* 652 $[M+H]^+$) was detected (Figure 2). The observed isotope pattern for this cluster matches well with its calculated one. Thus, ESI-MS analysis supports the formation of both $[ArPd^{II}X]$ and palladacycle species in the reaction mixture, which are probably in equilibrium.[23]

Evolution of the reaction shows complete consumption of amide **1f** with exclusive formation of the dehalogenated amide **9** (Scheme 4). Neither biaryl nor tricycle were observed in mass spectroscopy or isolated after chromatography.

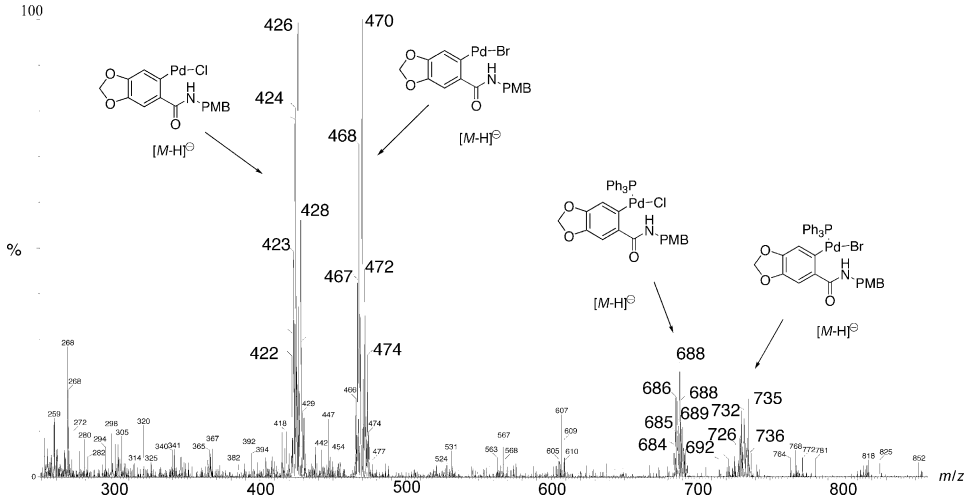


Figure 1. ESI-MS(−) spectrum after one hour ([D_7]DMF).

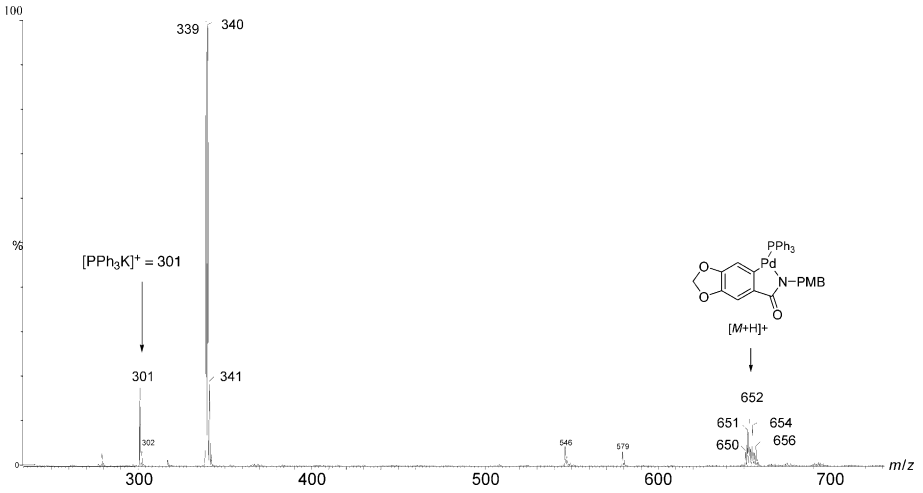
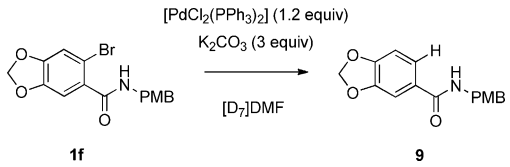


Figure 2. ESI-MS (+) spectrum after one hour ([D_7]DMF).

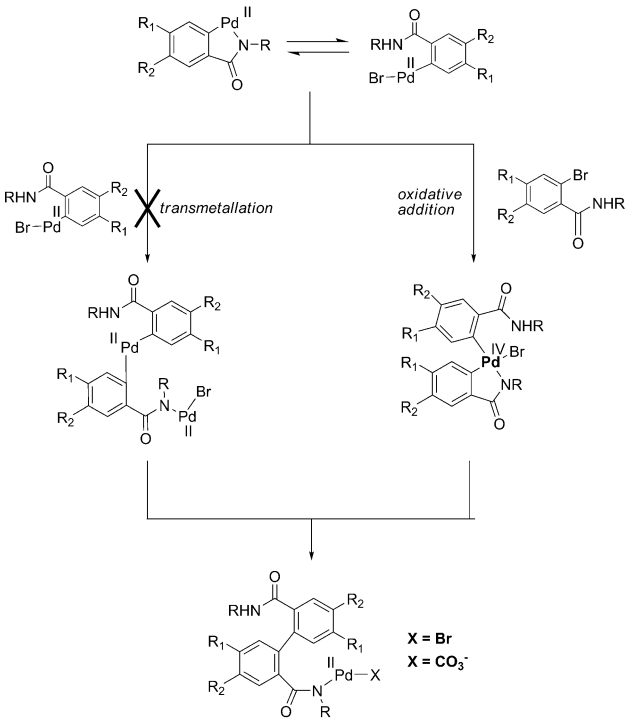


Scheme 4. Pd-mediated dehalogenation of **1f**.

This result is essential when considering the mechanism proposed in the literature for the formation of C(sp^2)–C(sp^2) biaryl bonds in related cases. A bimolecular step that involves two Pd^{II} species has been postulated.[9] However, this mechanism involves the interaction of two different organometallic species present at very low concentrations under the conditions of a catalytic reaction. In the present case, a large amount of Ar-Pd^{II}-X and Pd^{II} palladacycle was formed in the reaction medium, thereby allowing a high probability for a Pd^{II}–Pd^{II} transmetalation to occur (Scheme 5). However, this process was not observed here, which indicates that the transmetalation step between two Pd^{II} species is unlikely to be involved in the formation of the C(sp^2)–C(sp^2) bond in these domino reactions. Moreover, under the conditions of catalysis, such a step may not be fast enough to compete efficiently with the oxidative addition of an aryl halide unit into the Pd^{II} palladacycle, which is controlled by the concentration of **1**, the latter being much higher than that of the catalyst. If there is no Pd^{II}–Pd^{II} transmetalation process, the formation of a transient Pd^{IV} intermediate should be considered.[24] Nevertheless, it is not possible at this stage to specify whether insertion of a second benzamide unit occurs in a Pd^{II} palladacycle or an Ar-Pd^{II}-X species.

We next carried out the reaction with 0.2 equiv of [$PdCl_2$-(PPh_3)$_2$]. The catalyst loading was actually higher than the quantities used in the reaction (20 versus 5 mol%), yet this feature proved necessary to observe the formation of intermediates by spectroscopy. The ^{1}H NMR spectroscopic kinetic profile of the reaction is depicted in Figure 3.

Consumption of amide **1f** is correlated to the formation of tricycle **2f**. One hour after the beginning of the reaction, the ESI-MS(+) spectrum showed a cluster peak attributable to **1f** (*m*/*z* 402/404 [*M*+K]$^+$) and two characteristic cluster peaks assigned to phosphinopalladacycle **4** (*m*/*z* 690 [*M*+K]$^+$ and *m*/*z* 652 [*M*+H]$^+$) (Figure 4). Moreover, a new interesting peak was detected at *m*/*z* 607, attributable to an uncyclized biaryl derivative (*m*/*z* calcd 607 [*M*+K]$^+$). This observation also agrees with the proposed mechanism (Scheme 2). Indeed, after oxidative addition into the C(sp^2)–Br bond, the second major step of the process is the formation of the C(sp^2)–C(sp^2) bond. Unfortunately, the corresponding biaryl–Pd^{II} intermediate **6** was not observed by ESI-MS.[25] This is probably due to the sensitivity of the N–Pd^{II} bond of this intermediate, which precludes its detection. Thus only the organic fragment at *m*/*z* 607 appears. After 6 h, the ^{1}H NMR spectrum clearly indicated that tricycle **2f** was accumulating in the suspension, in correlation with the consumption of the



Scheme 5. Transmetalation versus oxidative addition pathways.

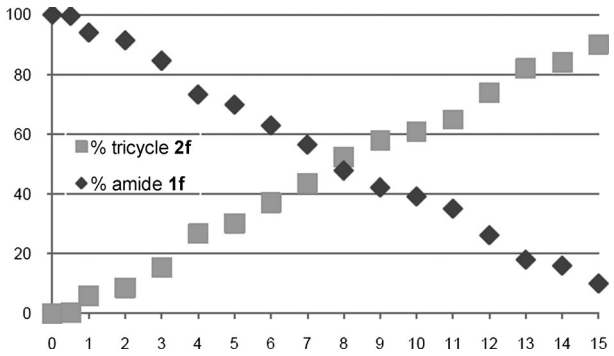


Figure 3. Reaction in [D_7]DMF (^{1}H monitoring).

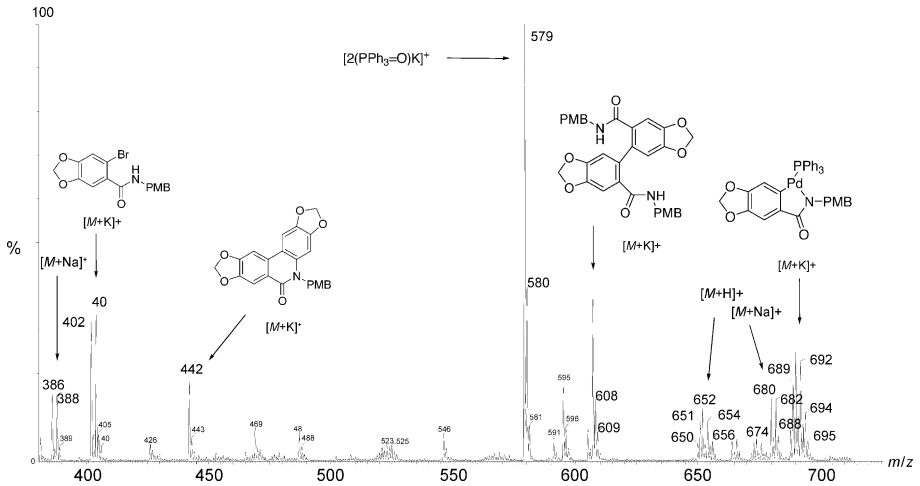


Figure 4. ESI-MS (+) spectrum after one hour ([D_7]DMF).

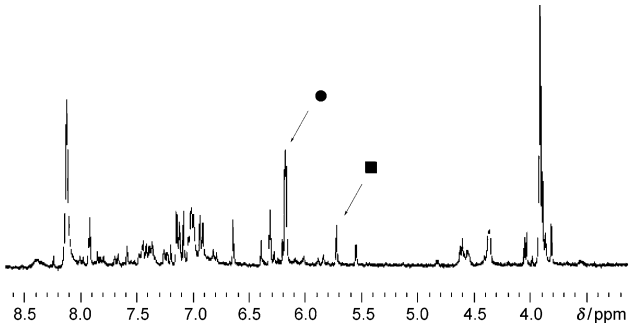


Figure 5. ^{1}H NMR spectrum after 6 h ([D_7]DMF): PMB-CH_2 (■) and methylenedioxy (●) signals of phenanthridinone **2f**.

starting amide **1f** (Figure 5).[26] In ESI-MS(−) a cluster peak attributable to an $ArPd^{II}Br$ intermediate was observed (*m*/*z* 470). In ESI-MS(+) the cluster peak that corresponded to **2c** (*m*/*z* 442 [*M*+K^+]) was clearly detected accompanied by the signal of the biaryl intermediate (*m*/*z* 607 [*M*+K^+]) and traces of the palladacycle **4** (*m*/*z* 690 [*M*+K^+]) (Figure 6).

From these experimental results, it can be deduced that after initial oxidative insertion into the C(sp^2)–Br bond, the formation of the biaryl intermediate constitutes the second major step of this catalytic process. Tricycle **2f** is the end product of the reaction.

Reaction in [D_8]1,4-dioxane: The reaction was carried out with 0.2 equiv of [$PdCl_2(PPh_3)_2$]. The same type of kinetic profile was observed (see the Supporting Information). As previously noted, the reaction started immediately after introduction of the alkaline agent. After one hour, ^{1}H NMR spectroscopic signals that correspond to phenanthridinone **3f** were observed, thus indicating that the reaction had started (Figure 7). In ESI-MS(+) four species were detected after 6 h: amide **1f** (*m*/*z* 386, 388 and 402, 404, [*M*+$Na]^+$ and [*M*+$K]^+$, respectively); palladacycle **4**; the previously observed uncyclized biaryl ligand of **6** (*m*/*z* 591 and *m*/*z* 607, [*M*+$Na]^+$ and [*M*+$K]^+$, respectively); and tricycle **3f** (*m*/*z* 389 and *m*/*z* 605, [*M*+$Na]^+$ and [*M*+$K]^+$, respectively) (Figure 8). Moreover ESI-MS(−) spectrum provided evidence for the formation of $ArPd^{II}X$ species (see the Supporting Information).

Because the same intermediates are formed in both [D_7]DMF and [D_8]1,4-dioxane, the initial hypothesis of two overlapped catalytic cycles seems plausible. From the results presented in Table 2, the discrimination between one pathway over the other relies on the participation of the carbonate base in the reaction

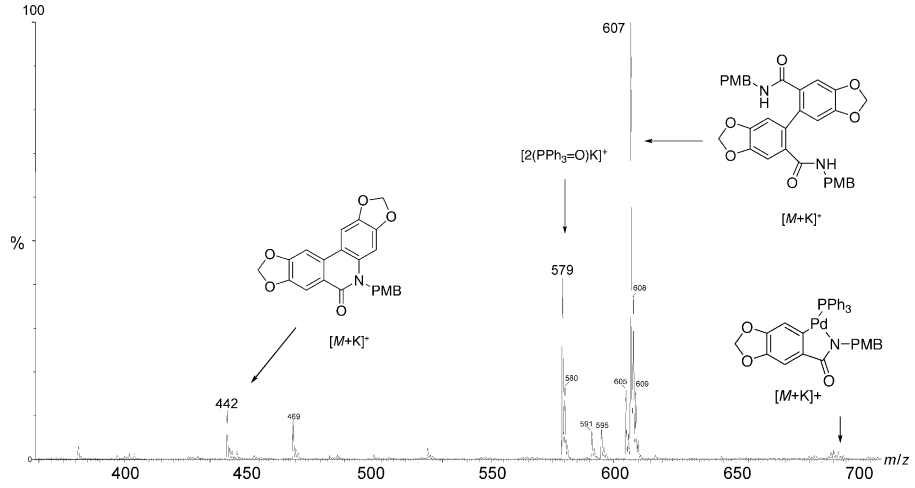


Figure 6. ESI-MS(+) spectrum after 6 h ([D_7]DMF).

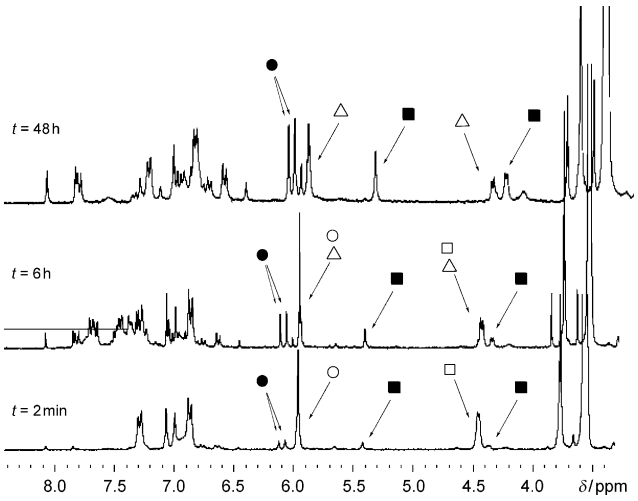


Figure 7. ^{1}H NMR spectra in [D_8]1,4-dioxane: Evolution of the PMB-CH_2 (■, □) and methylenedioxy (●, ○) signals: amide **1f** (full symbols), 1-carboxamide phenanthridinone **3f** (empty symbols), intermediate △.

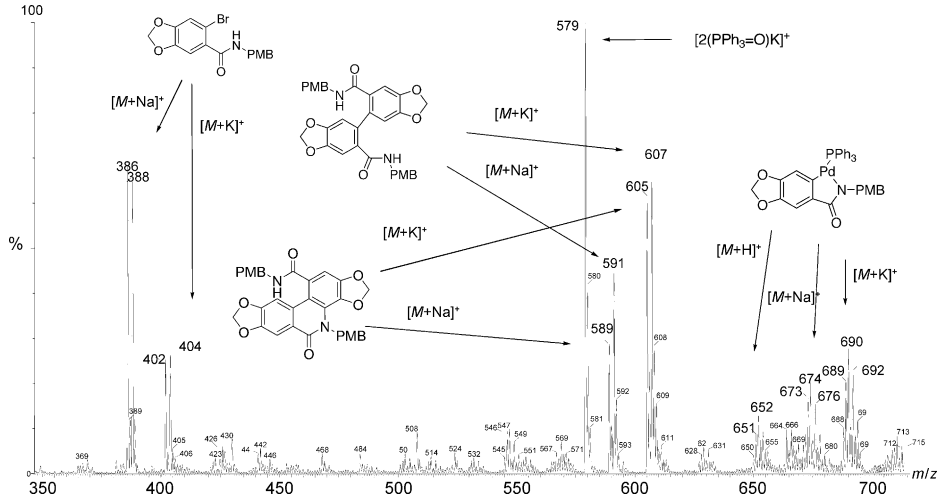
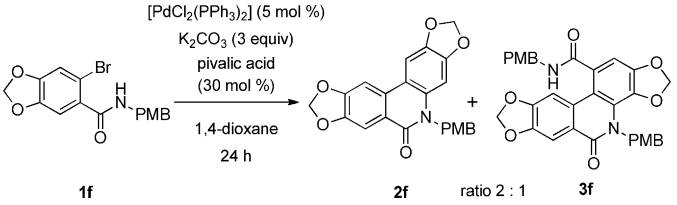


Figure 8. ESI-MS(+) spectrum after 6 h ([D_8]1,4-dioxane).

mechanism. Our initial hypothesis was based on a Br–carbonate exchange on the biaryl intermediate **6**; such an exchange could only be hypothesized in a dissociating medium in which sufficient amount of carbonate base is dissolved. The presumed role of the base is then to stabilize the biaryl intermediate in such a conformation that the two carboxamide functionalities are close enough to react. The *ipso* substitution could then occur to furnish the corresponding phenanthridinone **2**. To validate this hypothesis, two complementary experiments were carried out.

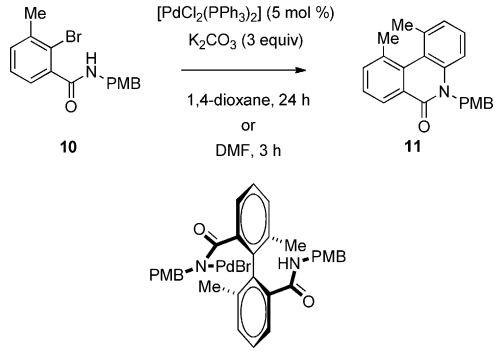
Additional experiments on the role of the carbonate base: In some direct arylation reactions, the dramatic influence of the carbonate base was rationalized by the concerted metalation–deprotonation pathway (CMD pathway).[27] However, studies aimed at determining the solubility in the medium indicated that very little carbonate base was actually dissolved.[11] To increase the amount of dissolved base, the influence of the addition of several carboxylic acids was studied. After optimization, the best yields were reached upon addition of 30 mol% of pivalic acid.[28] Therefore, it was decided to submit amide **1c** to the Pd-catalyzed reaction conditions in 1,4-dioxane in the presence of this additive. The replacement of the carbonate by a more soluble carboxylate should allow, in a weakly dissociating medium, the coexistence of the two reaction pathways as previously observed in moderately polar THF (Table 2, entry 3). As expected, whereas a total selectivity was observed in 1,4-dioxane (Table 2, entry 3), the addition of pivalic acid led to a mixture of the two tricycles **2f** and **3f** (Scheme 6). The selectivity observed in this case is in favor of **2f**. As expected, this result confirms the crucial role of the carboxylate moiety in the reaction pathway for the formation of **2f**.

If the biaryl–Pd intermediate conformation could be blocked in such a way that the two carboxamide functions are close enough to react together and furnish phenanthridinones **2**, then we could confirm our mechanistic hypothesis. *N*-PMB-3-methyl-2-bromobenzamide **10** was selected for this purpose. The steric hindrance



Scheme 6. Addition of soluble carboxylate in a weakly polar solvent.

of the methyl group should stabilize the biaryl intermediate by slowing down or preventing the rotation around the C-(sp^2)–C(sp^2) biaryl bond. Moreover, since the 3-position is occupied by a methyl group, the formation of the 1-carboxamide phenanthridinone structure should not be possible in 1,4-dioxane and the reaction should stop at the biaryl intermediate stage or follow the pathway observed in a dissociating medium. The reaction was carried out in DMF and 1,4-dioxane (Scheme 7). In both cases, the selectivity was total



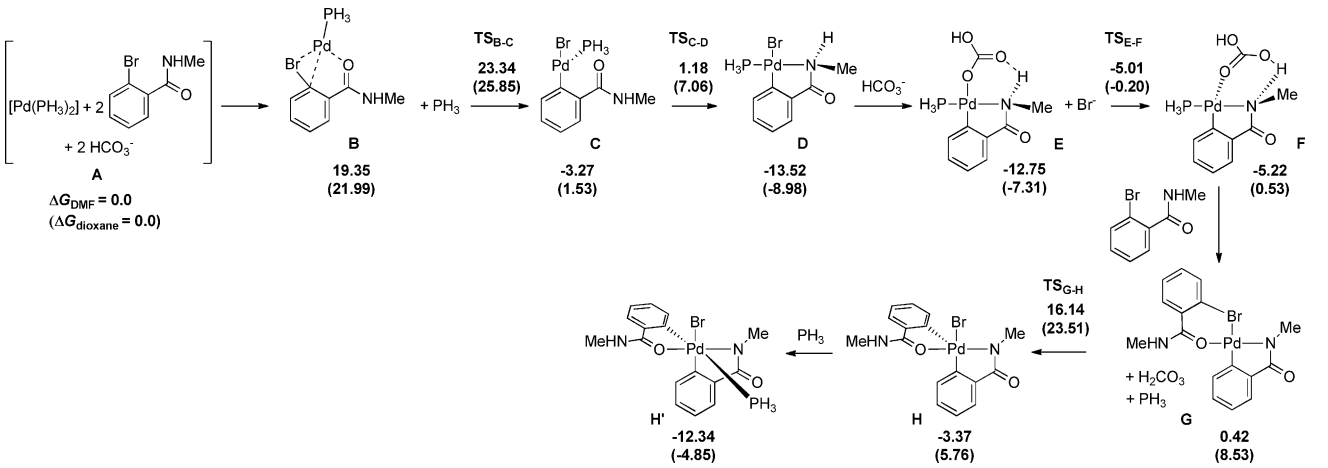
Scheme 7. Sterically controlled reversal of selectivity.

and phenanthridinone **11** was isolated as the sole product. This observation indicates that the selectivity in 1,4-dioxane is reversed with bulky substituents and confirms the role of the carbonate base in the stabilization of the biaryl–Pd intermediate in a dissociating medium.

DFT computations: To support some of the mechanistic conclusions reached so far, DFT computations were carried out. All calculations were performed with the Gaussian series of programs.[29] The geometry optimizations and thermodynamic corrections were carried out with hybrid density functional theory (B3LYP) with the 6-31G(d) (N, O, P, C, H) and LANL2DZ+ECP basis sets (Pd, Br). Solvation corrections for DMF and 1,4-dioxane were computed by the polarizable continuum model (PCM) method as implemented in Gaussian 09 with single points at the SDD(Pd)/6-311+G** (other elements) level. All relative energies presented in this paper are free energies (ΔG_{DMF}; $\Delta G_{dioxane}$) in kilocalories per mole. To save computer time, PH_3 and HCO_3^- were used instead of PPh_3 and CO_3^{2-}.[27b] 2-Bromo-*N*-methylbenzamide was chosen as model benzamide. This compound was actually tested experimentally (compound **1i**; see Table 1). $Pd(PH_3)_2$ was used as active species instead of $Pd(PPh_3)_2$. This simplification proved acceptable in many cases.[30] Even after this truncation, because of the size of the starting system (57 atoms with PH_3, 117 with PPh_3), we did not attempt to address all mechanistic issues. In particular, the role of the cation in M_2CO_3 (M = Na, K, Cs) was not studied. We rather focused on the implication of the anion within the catalytic cycle, and on the potential intervention of Pd^{IV} species.

We first computed the oxidative addition steps (Scheme 8). Among various options, the lowest-lying transition state that could be found was $\mathbf{TS_{B-C}}$, which connects the T-shaped $ArPd^{II}Br$ species **C** with the Pd^0 complex **B** in which the $(PH_3)Pd$ fragment is coordinated to the C–Br bond and the carbonyl functionality of the starting benzamide. As expected for reactions that require elevated temperatures, the free energies of activation of this process are quite high, 23–25 kcal mol^{-1} depending on the solvent, and, as shown later, represent the highest computed values of the catalytic cycle.

Rotation of the pendant amide moiety to form the square-planar Pd^{II} palladacycle **D** is kinetically facile and appreciably exothermic in both solvents.[31] Elimination of HBr could be modeled, yet at a high energetic cost of about



Scheme 8. Oxidative addition steps leading to a Pd^{IV} intermediate.

40 kcal mol^{-1} from **D**. Therefore, Br^- was exchanged by HCO_3^- prior to deprotonation.[32] Although the substitution had little impact on the relative free energy of the system, it had a dramatic influence on the deprotonation barrier to become around 7 kcal mol^{-1} from **E**. In the resulting intermediate **F**, H_2CO_3 remains hydrogen-bonded to the nitrogen atom and O-coordinated to palladium.

To reach a Pd^{IV} intermediate, a second equivalent of benzamide was introduced in the coordination sphere of the metal. For that matter, PH_3 and H_2CO_3 were removed before optimization. Various square-planar isomers such as **G** in which Br and one heteroatom of the amide fragment coordinates palladium converged. Complex **G**, in which the carbonyl group is *trans* to N (O-Pd-N arrangement), was found thermodynamically favored over the others. Besides, oxidative addition into the C–Br bond proved also kinetically more attainable from **G**.[33] The resulting pentacoordinated Pd^{IV} complex **H** (Figure 9) is also the most stable of the possible isomers. Overall, the formation of the Pd^{IV} species **H** from the starting system is moderately exothermic in DMF, and moderately endothermic in 1,4-dioxane. It is made through accessible transition states, provided a ligand exchange between Br^- and HCO_3^- takes place. Saturation of the coordination sphere of the metal using PH_3 to give the octahedral species **H′** is exothermic by approximately

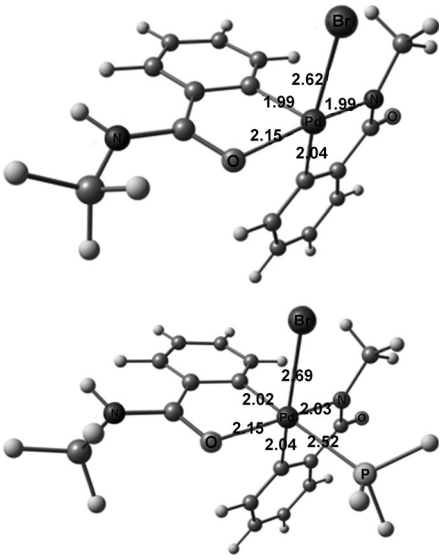
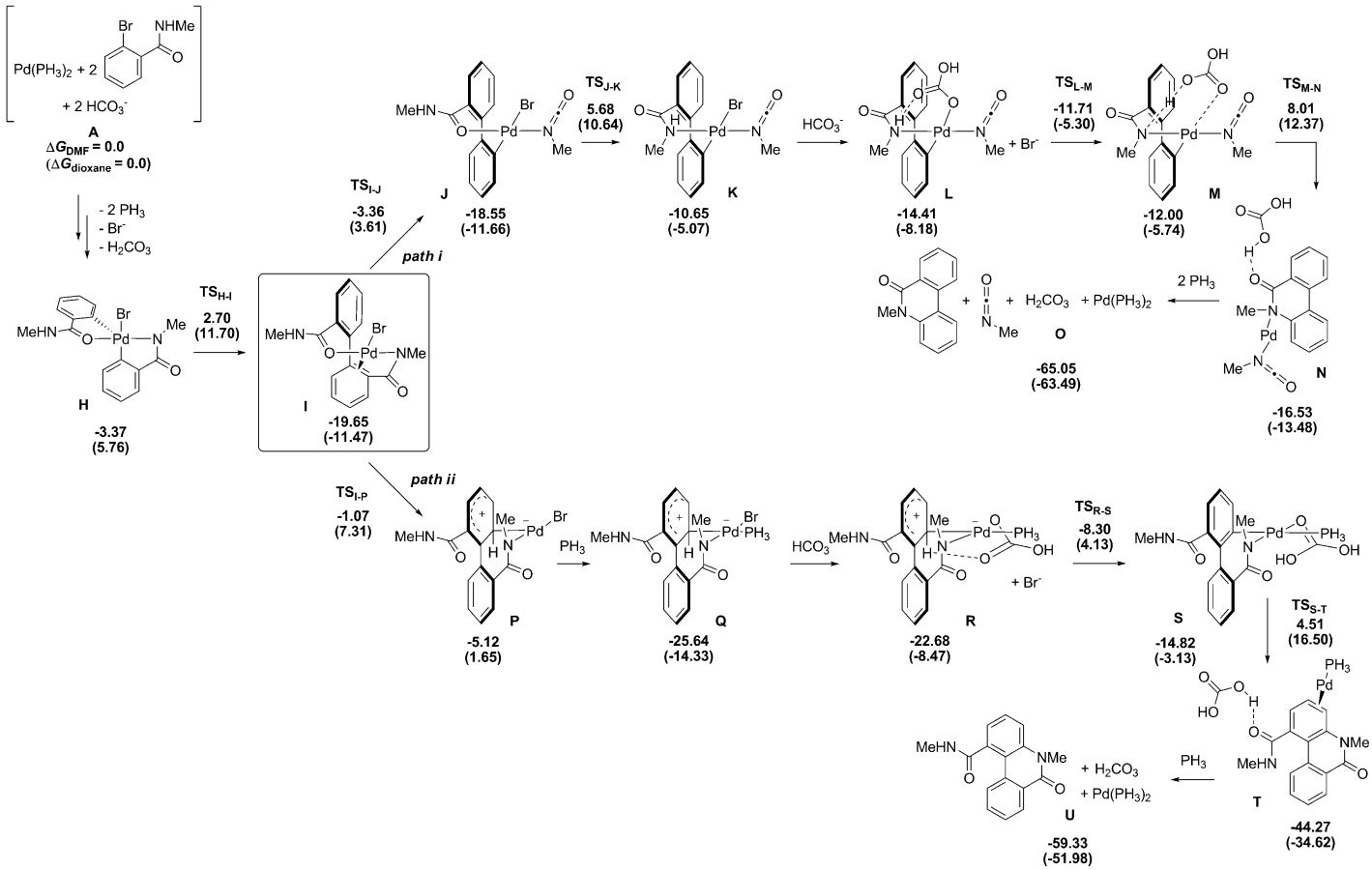


Figure 9. Optimized molecular structures for complexes **H** (top) and **H′** (bottom); selected bond lengths in Å.

9 kcal mol^{-1}. The reductive elimination pathway that constructs the biaryl unit was investigated next (Scheme 9). It could not be modeled from **H′** but rather from **H**, which is



Scheme 9. Divergent pathways to 5-methylphenanthridin-6(5*H*)-one or *N*,5-dimethyl-6-oxo-5,6-dihydrophenanthridine-1-carboxamide.

consistent with the literature.[34] It requires around 5 kcal mol^{-1} of free energy of activation and leads, with the liberation of around 15 kcal mol^{-1}, to the η^2-arene Pd^{II} complex **I**, cornerstone of the two overlapped catalytic cycles postulated in Scheme 2. Elimination of methylisocyanate converts **I** into the $ArPd^{II}Br$ species **J** (path i in Scheme 9) by means of a quite easily accessible transition state and with little influence on the relative energy of the system. On the other hand, rotation of the amide fragment to reach the 14-electron $\mathbf{TS_{J-K}}$ requires more than 20 kcal mol^{-1} and provides the less stable intermediate **K** with a *trans* N-Pd-N arrangement. Again, prior to deprotonation, Br^- was substituted by HCO_3^-, thereby resulting in the more stable complex **L** from which H_2CO_3 elimination was found kinetically straightforward ($\approx$3 kcal mol^{-1} of free energy of activation).[32] Reductive elimination to give the phenanthridinone framework could be modeled through the quite high-lying $\mathbf{TS_{M-N}}$ (18–20 kcal mol^{-1} of free energy of activation). Finally, regeneration of the active species $Pd(PH_3)_2$ gives the final product in a strongly exothermic fashion, more than 60 kcal mol^{-1} lower than the starting system. Thus, from a Pd^{IV} intermediate, it was possible to compute a pathway that led to the phenanthridinone core. The highest-lying transition states of this sequence correspond to the reductive elimination that forms the C–N bond. The ligand exchange between nitrogen and oxygen by rotation of the amide moiety is also difficult to achieve, yet those barriers are not inaccessible under thermal conditions. We then sought a pathway to 1-carboxamide phenanthridinones from **I** (path ii in Scheme 9). An electrophilic aromatic substitution (S_EAr) mechanism could be computed. This implied first a quite slow and endothermic ligand exchange between the carbonyl functionality and one aromatic ring to give the η^1-benzene complex **P**, to which PH_3 was added to complete to coordination sphere of palladium. In the end, the resulting Wheland intermediate **Q** is more stable than **I** by 3–5 kcal mol^{-1}. To achieve the subsequent hydrogen elimination, the substitution of Br^- by HCO_3^- to give **R** was found to be more accessible prior to deprotonation and reductive elimination that creates the C–N bond.[35] The transition state that corresponds to the latter elementary step is the highest-lying one of path ii in both solvents ($\approx$20 kcal mol^{-1} of energy of activation), yet this transformation is strongly exothermic by approximately 30 kcal mol^{-1}. Overall, after regeneration of the active species of the catalytic cycle, liberation of 52–59 kcal mol^{-1} relative to the starting system is calculated.

Thus, as in path i, although the transition states that correspond to the ligand exchange and the reductive elimination are quite high-lying, they should nevertheless be accessible under the experimental conditions used. The computations of a viable pathway toward 1-carboxamide phenanthridinones from **I**, and therefore from the Pd^{IV} intermediate **H**, supports the mechanistic rationale depicted in Scheme 2 that involves two overlapped catalytic cycles that share **4**, **5**, and **6** (i.e., **F**, **H**, and **I**). We realize, however, that the computed energies do not reproduce the clear experimental switchover between DMF and 1,4-dioxane. We attribute this discrepancy between the experimental and computational studies to the fact that the exact nature of the medium, including the presence of alkali metals, was not fully taken into account. Geometry optimizations in solution could solve this problem but we were unable to carry them out.

Summary of the mechanistic data and proposed catalytic cycle: From these results, a new catalytic cycle can be proposed to explain the selective formation of **2** and **3**. The first steps are common and involve two successive oxidative additions of an *o*-bromobenzamide unit into a Pd species. A Pd^{II} intermediate is generated by oxidative addition into the $C(sp^2)$–Br bond. This complex is in equilibrium between an Ar-Pd^{II}-Br form and a palladacyclic form. Then oxidative addition of a second *o*-bromobenzamide unit occurs to give a transient Pd^{IV} intermediate complex, which leads to a biaryl-Pd^{II}-Br species after reductive elimination. Then depending on the solvent polarity, two intramolecular pathways occur. In a dissociating medium (DMF), Br–CO_3 exchange allows the rotation and the stabilization of subunit A. Then elimination of isocyanate RNCO (or RNH_2+CO_2) gives complex **7**, which releases tricycle **2** after reductive elimination. In a weakly dissociating medium, no carbonate–bromide exchange occurs. A Pd^{II} direct *N*-arylation can proceed to give compound **3** by means of an S_EAr-type process. The S_EAr pathway is favored in this latter step because the base is not involved in the cyclization, which rules out the CMD pathway.

Conclusion

In summary, we have described here simple and efficient reaction conditions to access selectively two differently substituted phenanthridinone frameworks, **2** and **3**, from a common *o*-bromobenzamide precursor in a Pd-catalyzed one-step sequence. The outcome of these domino processes is strongly influenced by the nature of the substituents on the aromatic core, and the best yields are reached in the presence of electron-donating groups. Studies on the reaction parameters highlight the dramatic influence of the carbonate base/solvent alliance in the selective formation of **2** or **3**. Thus, in a weakly dissociating medium 1-carboxamide phenanthridinones **3** are preferentially formed, and conversely, formation of phenanthridinones **2** is favored in a dissociating medium. Addition of a soluble carboxylate or the use of a benzamide that bears bulky substituents leads to a reversal of the selectivity observed in a weakly dissociating medium, thus outlining the crucial role of the alkaline agent in the formation of **3**. Mechanistic studies allowed to characterize, by ESI-MS, the Pd^{II} palladacycle **4** and biaryl species as common intermediates for these two domino processes. Furthermore, the experimental data strongly support the C-(sp^2)–$C(sp^2)$ bond formation by generation of a transient Pd^{IV} intermediate, this rationale being also corroborated by DFT calculations. A general catalytic cycle is proposed to account for these observations. Overall, we believe that the

formation of aryl–aryl bonds from aryl halides by means of Pd^{IV} intermediates should also be considered in other related Pd-catalyzed processes.

Experimental Section

General procedure for the domino reaction: K_2CO_3 (3 equiv) and [Pd(PPh_3)$_2Cl_2$] (0.05 equiv) were successively added to a solution of the amide (1 equiv) in anhydrous DMF or 1,4-dioxane (20 mL). The resulting suspension was purged three times with argon then heated at reflux in a preheated oil bath at 155 °C for 3 h (DMF) or at 105 °C for 24 h (1,4-dioxane). The reaction mixture was then cooled to RT, and the solvent was removed in vacuo. H_2O was added to the residue and extracted with CH_2Cl_2 (3 times). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica gel to afford the corresponding phenanthridinone.

2-Bromo-3-methyl-*para*-methoxybenzylamide (10): According to the general procedure, **10** (451 mg, 1.35 mmol, 58 % yield) was obtained from 2-bromo-3-methylbenzoic acid (500 mg, 2.33 mmol) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, J = 8.6 Hz, 2H; PMB), 7.28–7.18 (m, 3H; H^4, H^5 and H^6), 6.88 (d, J = 8.6 Hz, 2H; PMB), 6.17 (br s, 1H; NH), 4.56 (d, J = 5.6 Hz, 2H; CH_2, PMB), 3.81 (s, 3H; $2OCH_3$), 3.43 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4 (C, C=O), 159.1 (C, PMB), 139.3 (C, C^3), 139.0 (C, C^1), 131.8 (CH, C^4), 129.8 (C, PMB), 129.4 (2CH, PMB), 127.3 (CH, C^5), 126.3 (CH, C^6), 121.7 (C, C^2), 114.1 (2CH, PMB), 56.3 (CH_3, OCH_3, PMB), 43.6 (CH_2, PMB), 23.6 ppm (CH_3); MS (ESI): m/z calcd: 356 $[M+Na]^+$; found: 358; HRMS (ESI): m/z calcd for $C_{16}H_{16}BrNNaO_2$: 356.0262 $[M+Na]^+$; found: 356.0271.

5-Methylphenanthridin-6(5*H*)-one-1-methylcarboxamide (3i): According to the general procedure, **3i** (16 mg, 0.06 mmol, 76 % yield) was obtained from **1i** (59 mg, 0.19 mmol) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19–8.17 (m, 2H; H^7 and H^4), 8.07 (d, J = 8.1 Hz, 1H; H^{10}), 7.76 (td, J = 7.5 and 1.2 Hz, 1H; H^9), 7.57 (td, J = 7.5, 1.2 Hz, 1H; H^8), 7.48 (t, J = 7.3 Hz, 2H; H^2 and H^3), 6.62 (s, 1H; NH), 3.72 (s, 3H; N^5–CH_3), 3.07 ppm (d, J = 4.8 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7 (C, C^1C=O), 162.8 (C, C^6=O), 133.1 (C), 132.6 (CH, C^9), 130.3 (CH, C^2), 129.5 (C), 128.3 (CH, C^7), 128.3 (CH, C^8), 127.0 (C), 124.9 (C), 124.6 (CH, C^4), 122.3 (CH, C^3), 121.7 (CH, C^{10}), 121.0 (C), 36.0 (CH_3, N^5–CH_3), 27.1 ppm (CH_3, N–CH_3); IR (NaCl, film): $\tilde{\nu}$ = 3292, 3072, 1650, 1637, 1592, 1550, 1467, 1431, 1408, 1316, 1259, 1173, 1122, 1048, 970, 765, 729, 666 cm^{-1}; UV/Vis (MeOH): λ_{max} ($\log\varepsilon$) = 218 (4.7), 228 (4.5), 263 nm (3.2); MS (ESI): m/z calcd: 291 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{16}H_{14}N_2NaO_2$: 289.0953 $[M+Na]^+$; found: 289.0962.

Reaction in the presence of PivOH: K_2CO_3 (42 mg, 0.306 mmol, 3 equiv), [Pd(PPh_3)$_2Cl_2$] (3.6 mg, 5.1 mmol, 0.05 equiv), and pivalic acid (3 mg, 0.031 mmol, 0.3 equiv) were successively added to a solution of amide **1f** (36 mg, 0.102 mmol, 1 equiv) in 1,4-dioxane (20 mL). The resulting suspension was purged three times under argon then heated to reflux at 105 °C for 24 h. The reaction mixture was cooled to RT, and 1,4-dioxane was removed in vacuo. After addition of H_2O, the solution was extracted with CH_2Cl_2 (3 times). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (20–45 μm, cyclohexane/EtOAc 7:3 to 1:1) to afford the corresponding tricycles **2f** (4.5 mg, 0.011 mmol, 22 %) and **3f** (3.3 mg, 0.006 mmol, 11.5 %).

5-*para*-Methoxybenzyl-2,10-dimethylphenanthridin-6(5*H*)-one (11): Reaction in DMF: According to the general procedure, **11** (47 mg, 0.137 mmol, 92 % yield) was obtained from **10** (100 mg, 0.299 mmol) as a colorless oil. Reaction in 1,4-dioxane: According to the general procedure, **11** (31 mg, 0.090 mmol, 60 % yield) was obtained from **10** (100 mg, 0.299 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (d, J = 7.5 and 1.1 Hz, 1H; H^7), 7.60 (td, J = 7.5 and 1.1 Hz, 1H; H^8), 7.54 (t, J = 7.5 Hz, 1H; H^9), 7.28 (t, J = 6.8 Hz, 1H; H^3), 7.23 (d, J = 8.7 Hz, 2H; PMB), 7.19–7.11 (m, 2H; H^4 and H^2), 5.66 (d, J = 15.1 Hz, 1H; CH_2, PMB), 5.33 (d, J = 15.1 Hz, 1H; CH_2, PMB), 3.77 (s, 3H; OCH_3, PMB), 2.49 (s, 3H; CH_3), 2.47 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (C, C=O), 158.6 (C, PMB), 137.8 (C, C^1), 136.5 (C, C^{4a}), 135.3 (C, C^{10}), 134.4 (CH, C^9), 133.8 (C, C^{10a}), 129.0 (C, C^{6a}), 128.4 (C, PMB), 127.9 (2CH, PMB), 127.9 (CH, C^3), 127.1 (CH, C^8), 125.7 (CH, C^7), 124.9 (CH, C^4), 119.9 (C, C^{10b}), 114.1 (2CH, PMB), 112.0 (CH, C^2), 55.3 (CH_3, OCH_3), 46.1 (CH_2, PMB), 22.2 (CH_3, C^1), 21.8 ppm (CH_3, C_{10}); MS (ESI): m/z calcd: 366 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{23}H_{21}NNaO_2$: 366.1470 $[M+Na]^+$; found: 366.1474.

^{1}H NMR spectroscopy and mass spectrometry (ESI-MS) monitoring: In an NMR spectroscopy tube, **1f** (10 mg, 0,028 mmol, 1 equiv) and [Pd(PPh_3)$_2Cl_2$] (1.2 or 0.2 equiv) were successively introduced. The tube was sealed by an appropriate septum and purged with argon (3 times). Then [D_7]DMF or [D_8]1,4-dioxane (0.7 mL) was added, and the resulting solution was degassed. The tube was introduced into the spectrometer and the probe was warmed at 120 °C ([D_7]DMF) or 90 °C ([D_8]1,4-dioxane). Then a first FID acquisition was carried out. The solution was cooled to RT, and K_2CO_3 (12 mg, 3 equiv) was introduced. The resulting mixture was homogenized and an aliquot was analyzed by ESI-MS (t = 0). The tube was then placed into the NMR spectrometer and heated at 120 or 90 °C. FID acquisitions were achieved every 30 min. When a significant modification was observed by ^{1}H NMR spectroscopy, an aliquot of the reaction mixture was analyzed by ESI-MS. The ^{1}H NMR spectroscopic monitoring is reported in Tables 1 and 2 for [D_7]DMF and [D_8]1,4-dioxane, respectively, as the percentage composition of amide **1f** and tricycles **2f** or **3f** based on the methylenedioxy moieties and PMB CH_2-group signals. ESI mass spectra were performed in both positive and negative modes at 30 and 60 V from the aliquot taken beforehand and diluted in acetonitrile.

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[1] a) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347; b) According to the MDL Drug Data Report, the most widespread heterocycles in pharmaceutically active compounds are pyridine (out of 15000 structures), imidazole (out of 11000), indole (out of 6700), and pyrimidine (out of 4500); see: V. Bonnet, F. Mongin, F. Trécourt, G. Breton, F. Marsais, P. Knochel, G. Quéguiner, *Synlett* **2002**, 1008–1010; c) G. Quéguiner, F. Marsais, V. Snieckus, J. Epsztajn, *Adv. Heterocycl. Chem.* **1991**, *52*, 187–304; d) R. W. Friesen, C. Brideau, C. C. Chan, S. Charleson, D. Deschênes, D. Dubé, D. Ethier, R. Fortin, J. Y. Gauthier, Y. Girard, R. Gordon, G. M. Greig, D. Riendeau, C. Savoie, Z. Wang, E. Wong, D. Visco, L. J. Xu, R. N. Young, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2777–2782; e) J. Quirk, M. Thornton, P. Kirkpatrick, *Nat. Rev. Drug Discovery* **2003**, *2*, 769–770; f) G. Chelucci, G. Orrù, G. A. Pinna, *Tetrahedron* **2003**, *59*, 9471–9515.

[2] a) F. Diederich, P. J. Stang, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, New York, **1998**; b) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1469.

[3] The advantages of direct carbon–hydrogen bond functionalization were recognized some time ago. For a recent review on the topic of C–H activation, see: *Topics in Current Chemistry, Vol. 292, C–H Activation* (Eds.: J.-Q. Yu, Z. Shi), Springer, Berlin, **2010**.

[4] a) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; c) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

[5] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; b) G. Dyker, *Angew. Chem.* **1992**, *104*, 1079–1081; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1023–1025.

[6] L. Donati, S. Michel, F. Tillequin, F.-H. Porée, *Org. Lett.* **2010**, *12*, 156–158.

[7] a) R. Ferraccioli, D. Carenzi, E. Motti, M. Catellani, *J. Am. Chem. Soc.* **2006**, *128*, 722–723; b) T. Furuta, Y. Kitamura, A. Hashimoto, S. Fujii, K. Tanaka, T. Kan, *Org. Lett.* **2007**, *9*, 183–186. For the first example of this reaction, see: S. Caddick, W. Kofie, *Tetrahedron Lett.* **2002**, *43*, 9347–9350. See also: P. Thansandote, D. G. Hulcoop, M. Langer, M. Lautens, *J. Org. Chem.* **2009**, *74*, 1673–1678.

[8] a) D. V. Ferraris, *J. Med. Chem.* **2010**, *53*, 4561–4584; b) J.-H. Li, L. Serdyuk, D. V. Ferraris, G. Xiao, K. L. Tays, P. W. Kletzly, W. Li, S. Lautar, J. Zhang, V. J. Kalish, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1687–1690.

[9] a) D. J. Cárdenas, B. Martín-Matute, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 5033–5040. For an experimental evidence of a Pd^{II}–Pd^{II} transmetalation (intramolecular version), see: b) Y. Suzaki, K. Osakada, *Organometallics* **2003**, *22*, 2193–2195.

[10] Pd^{II}-mediated isomerization of heteroatom–allyl is known, see: E.-I. Negishi in *Handbook of Organopalladium Chemistry for Organic Synthesis* (Eds.: E.-I. Negishi, A. de Meijeire), Wiley, New York, **2002**, p. 2783.

[11] See the Supporting Information.

[12] A comparative solubility study of some carbonate bases has been performed by Chemetall GmbH and is available at Chemetall.com (released on February 16, **2011**). For a discussion on the solubility of carbonate bases in organic solvents, see also L. C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581–590.

[13] M. Catellani, E. Motti, N. della Ca, R. Ferraccioli, *Eur. J. Org. Chem.* **2007**, 4153–4165.

[14] For a discussion on palladacycle and Pd nanoparticles see: V. Farina, *Adv. Synth. Catal.* **2004**, *346*, 1553; J. G. deVries, *Dalton Trans.* **2006**, 421. See also ref. [23].

[15] Oxidative addition of organic halides into Pd^{II} species to generate Pd^{IV} complexes is well known. See: a) A. J. Canty, *Acc. Chem. Res.* **1992**, *25*, 83–90; b) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev.* **2010**, *110*, 824–889, and references cited therein; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169, and references cited therein.

[16] Formation of such Pd^{IV} species has been proposed by Catellani and Dyker but no intermediate was isolated nor characterized. See Refs. [5b], [6a] and see also: a) M. Catellani, *Synlett* **2003**, 0298–0313; b) G. Dyker, *Angew. Chem.* **1992**, *104*, 1079–1081; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1023–1025.

[17] J. Hassan, V. Penalva, L. Lavenot, C. Gozzi, M. Lemaire, *Tetrahedron* **1998**, *54*, 13793–13804.

[18] A. J. Mota, A. Dedieu, C. Bour, J. Suffert, *J. Am. Chem. Soc.* **2005**, *127*, 7171–7182.

[19] a) D. C. Powers, M. A. L. Geibel, J. E. M. N. Klein, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 17050–17051; b) D. C. Powers, D. Benitez, E. Tkatchouk, W. A. Goddard III, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 14092–14103.

[20] To the best of our knowledge, there is no report, to date, that relates the formation of a $C(sp^2)$–$C(sp^2)$ biaryl bond through a Pd^{III} intermediate (monomeric or bimetallic species).

[21] See the Supporting Information for details on the experimental procedure.

[22] The reaction time was longer than that observed when the reactions were carried out in an oil bath with magnetic stirring.

[23] Review on palladacycles and their role in catalysis: J. Dupont, C. S. Consorti, J. Spencer, *Chem. Rev.* **2005**, *105*, 2527–2571.

[24] Hypothesis for the formation of a Pd^{III} intermediate is difficult to envisage here. In most cases, bimetallic Pd^{III} is generated in the presence of a strong oxidant from a dimeric Pd^{II} species, this latter being stabilized by acetate ligands. See Ref. [19] and the work of M. Sanford in Ref. [13c].

[25] A biaryl intermediate was prepared by Catellani's group from *N*-phenyl-2-bromobenzamide and treated with $[PdCl_2(MeCN)_2]$. A small but significant amount of the corresponding phenanthridinone was obtained, see: Ref. [7a].

[26] Under these conditions, debrominated compound **9** was not observed.

[27] a) D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067; b) D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886; c) M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756.

[28] M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497.

[29] Gaussian 09, Revision A.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.

[30] See inter alia Refs. [9a] and [27b].

[31] The O-bonded isomer is 1.5 kcal mol^{-1} less stable than **D**.

[32] Manifold efforts failed to locate an assisted intermolecular deprotonation pathway, as described in Ref. [27b].

[33] PH_3 can be kept in the oxidative addition transition state, yet it lies 9 kcal mol^{-1} higher than $\mathbf{TS_{G-H}}$.

[34] It is noteworthy that although hexacoordinated Pd^{IV} complexes are more common that pentacoordinated ones, the latter are more likely to give reductive elimination products, see: a) T. Furuya, T. Ritter, *J. Am. Chem. Soc.* **2008**, *130*, 10060–10061; b) P. K. Byers, A. J. Canty, M. Crespo, R. J. Puddephat, J. D. Scott, *Organometallics* **1988**, *7*, 1363–1367.

[35] An unassisted S_EAr mechanism would involve HBr elimination without intervention of the base. The computed free energy of activation of such a process is prohibitively high ($\approx$40 kcal mol^{-1}).

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