

Base-Assisted Intramolecular C–N Coupling Reaction from NH 2 -Bound Cyclopalladated L -Phenylalanine to Indoline-2-carboxylic Acid

Aurélien Jacquin-Labarre, Sébastien Coufourier, Rodolphe Tamion, Alexandra Le Foll, Vincent Levacher, Carlos Afonso, Vincent Gandon, Guillaume Journot, Jean-François Brière, Christophe Hoarau

▶ **To cite this version:**

Aurélien Jacquin-Labarre, Sébastien Coufourier, Rodolphe Tamion, Alexandra Le Foll, Vincent Levacher, et al.. Base-Assisted Intramolecular C–N Coupling Reaction from NH 2 -Bound Cyclopalladated L -Phenylalanine to Indoline-2-carboxylic Acid. Organometallics, 2020, 39 (5), pp.767-773. 10.1021/acs.organomet.0c00030 . hal-02493098

HAL Id: hal-02493098

https://normandie-univ.hal.science/hal-02493098

Submitted on 21 Aug 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Base-Assisted Intramolecular C-N Coupling Reaction from NH_2-Bound Cyclopalladated L-Phenylalanine to Indoline-2-carboxylic acid

Aurélien Jacquin-Labarre,[aA] Sébastien Coufourier,[aA] Rodolphe Tamion,[b] Alexandra Le Foll,[a] Vincent Levacher,[a] Carlos Afonso,[aB] Vincent Gandon,[c,d] Guillaume Journot,*[b] Jean-François Brière*[a] and Christophe Hoarau*[a]

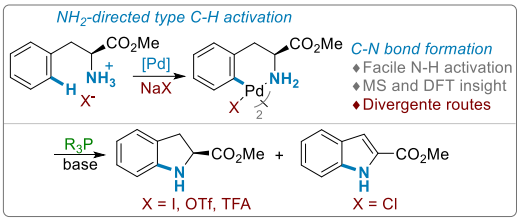
[a]Normandie Univ, UNIROUEN, INSA Rouen, CNRS, COBRA, 76000 Rouen, France.

[b]Industrial Research Centre–Oril Industrie, CS 60125, 76210 Bolbec, France.

[c]Institut de Chimie Moléculaire et des Matériaux d'Orsay, CNRS UMR 8182, Université Paris-Saclay, 91405 Orsay cedex, France.

[d]École Polytechnique, Institut Polytechnique de Paris, route de Saclay, 91128 Palaiseau cedex, France.

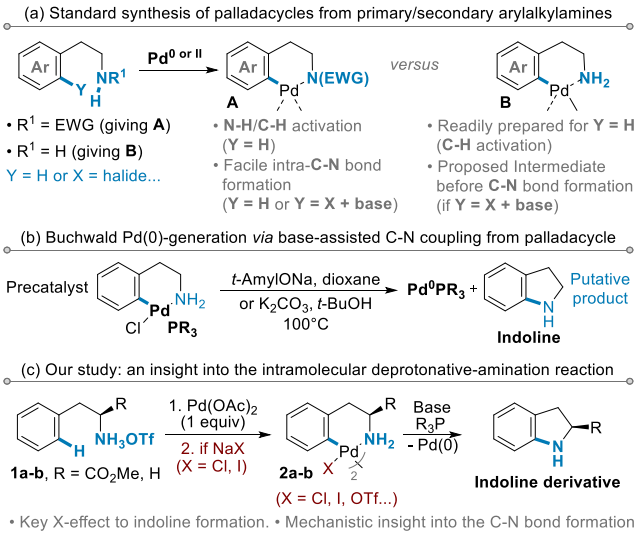
ABSTRACT: The deprotonative intramolecular-amination reaction of phenylalanine derived palladacycles has been investigated to highlight a facile carbonate-assisted N-H activation before the C-N bond formation. A major counter-ion effect led to divergent pathways whereby the SPhos-Pd-complex with iodine, triflate or trifluroacetate anions were key intermediates to afford an access to (*S*)-2-indolinecarboxylic acid derivatives.



INTRODUCTION

Due to the prevalence of nitrogen-containing heterocycles in pharmaceutical compounds and materials, the transition-metal catalyzed C-N bond formation is currently of high importance in organic synthesis.[1] In this field of research, the intramolecular N-H/C-H cross-coupling approach stands at the ideal situation among step-economy strategies. Aryl-alkylamine precursors (Scheme 1a), with an activated amine NH(EWG) (R^1 = EWG = COR, SO_2R, Y = H) have been mostly used under palladium catalysis.[2] These intramolecular C-N bond forming processes involve a Pd^{II}-catalyzed N-H activation, followed by a directed Csp^2-H intramolecular activation ended by the reductive elimination step of the transient palladacycle **A**. However, a similar palladium promoted N-H/C-H deshydrogenative amination sequence from a free and less acidic primary amine platform (R^1 = H, Y = H) remains unsolved. This strategy is often hampered by the strong complexation ability of RNH_2 precursors to Pd^{II} complexes preventing further Csp^2-H activation events.[3] Nevertheless, the *ortho*-palladation of aryl-alkyl(primary)amines by a stoichiometric amount of Pd^{II} species (R^1 = H) has been known for decades, even for more challenging 6-membered ring NH_2-bound palladacycle **B**.[4,5] As a matter of fact, the so-called Buchwald-Hartwig Pd^0-catalyzed intramolecular amination of *ortho*-halogenated phenethylamines was also applied to NH_2-derivatives (R^1 = H, Y = halide or (pseudo)halide).[6,7] The sequence was described through the proposed NH_2-palladacycle intermediates **B** (ligated by Y after the oxidative addition event) before the final base-promoted amination process. Importantly, these types of palladacycles were isolated and employed as a source of active Pd^0 catalysts under basic conditions (Scheme 1b), as demonstrated by Buchwald.[8] During this intramolecular C-N coupling reaction, the putative formation of indoline side-product was proposed but the exact mechanism remains unclear.[8] Most recent mechanistic studies provided insight into the intermolecular Buchwald-Hartwig amination, albeit a focus on intramolecular amination processes especially with primary amines remains to be achieved.[9]

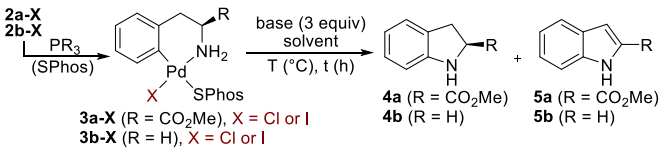
Scheme 1. Intramolecular Pd-catalyzed amination from primary amine: context and issues



We recently became interested in opening a straightforward route to (*S*)-methyl indoline-2-carboxylate, a synthetic intermediate used in the pharmaceutical industry (Scheme 1c).[10] The C-H/N-H disconnection provoked by a palladium-promoted dehydrogenative amination would afford a step-economy approach from L-phenylalanine derivative **1a**. But this novel sequence also affords a great opportunity to tackled a mechanistic and reactivity investigation.Thanks to the insightful investigations of Vicente and Saura-Llama, the isolable palladacycle intermediates **2a-X** (X = Cl, I) were readily accessible from the ammonium triflate salts **1a-OTf** via a C-H directed palladation followed by ion metathesis processes with NaX.[4d] In that context, we embarked into a reactivity study of the deprotonative intramolecular-amination event of palladium-complexes of type **2** and found a marked counter-ion effect leading to divergent pathways.[11] We are pleased to report on this intramolecular C-N bond investigation, encompassing a mechanistic insight by DFT and mass analyses, which led to primary investigations towards a racemization-free synthesis of indoline-2-carboxylic acid derivative via the palladium promoted N-H/C-H cross-coupling of a primary amine starting material.

RESULTS AND DISCUSSIONS

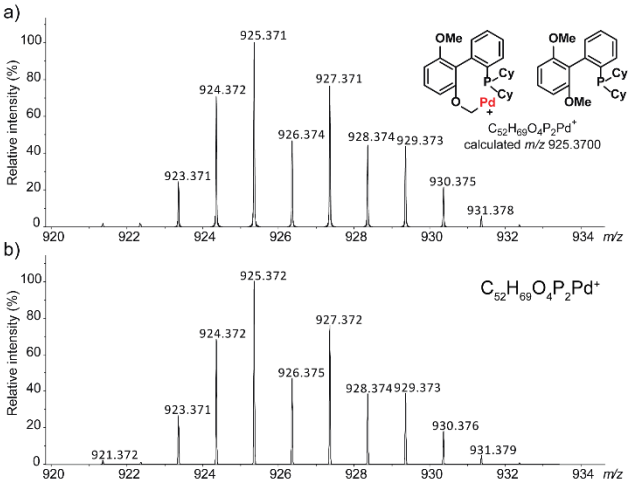
TABLE 1. Optimization of the deprotonative amination reaction of complexes 3[a]



entry	3-X	Base/solvent	T (°C) /t (h)	**4/5** yield (%)[b,d]
1	**3a-Cl**	K_2CO_3/*t*-BuOH	100/14	0/20
2	**3a-I**	K_2CO_3/*t*-BuOH	100/14	48/0
3	**3a-I**	K_2CO_3/MeCN	100/14	77/-[c]
4	**3a-I**	K_2CO_3/toluene	100/14	77/-[c]
5	**3a-I**	K_2CO_3/toluene	100/4	26/0
6	**3a-I**	K_2CO_3/toluene	100/24	45/33
7	**3a-I**	Na_2CO_3/toluene	100/14	16/10
8	**3a-I**	Cs_2CO_3/toluene	100/14	20/25
9	**3a-I**	CsF/toluene	100/14	63/37
10	**3a-I**	K_3PO_4/toluene	100/14	74/26
11	**3a-I**	DBU/toluene	100/14	-[c]
12[d]	**3a-I**	K_2CO_3/toluene	130/14	**99** (**61**)/-[c]
13[d]	**3a-Cl**	K_2CO_3/toluene	130/14	0/**46** (**46**)
14[d]	**3b-I**	K_2CO_3/toluene	130/14	**63**(**50**)/28
15[d]	**3b-Cl**	K_2CO_3/toluene	130/14	0/**41** (**38**)

[a]Reaction made with 0.1 mmol of palladacycle and 0.3 mmol of base (3 equiv) in 1 mL of solvent. [b]Yield determined by ^{1}H NMR spectroscopy with Bn_2O as an internal standard. [c]Traces of product (< 10% by ^{1}H NMR). [d]Reaction made with 0.3 mmol of palladacycle – Isolated yields in parentheses.

At the onset, a series of phosphino-palladacycles **3a-X** and **3b-X** (X = Cl or I) was prepared from the dimeric palladacycles **2-X** (Scheme 1c *versus* Table 1), according to a literature protocol.[4d] After an extensive investigation of the reaction conditions with various complexes, we successfully performed the deprotonative amination reaction (see supporting information). We found that the L-phenylalanine derived palladium complex **3a-Cl**, ligated by the Buchwald SPhos phosphine and a chloride,[8] cyclized in the presence of K_2CO_3 (3 equiv) in *t*-BuOH at 100 °C (entry 1). Unfortunately, the aromatic indole product **5a** was formed in a moderate 20% NMR yield (estimated by ^{1}H NMR with an internal standard). To our delight, we observed a major counterion-effect of this carbonate-assisted C-N bond forming step (entry 2), as iodide-complex **3a-I** furnished exclusively the indoline product **4a** with an improved 48% NMR yield in similar conditions. In spite of the reaction remaining effective both in polar and apolar solvents (see supporting information), the best results were obtained in acetonitrile and toluene, both affording **4a** in 77% yield (entries 3 and 4) in 14 h, along with the concomitant formation of trace amounts of indole **5a**. A higher proportion of indole **5a** (**4a**:**5a** = 45/33) was observed by carrying out the reaction for 24 h (entry 6). Additionally, sodium and cesium carbonates turned out to be less effective bases for the construction of the indoline product **4a** (16-20% yields, entries 7 and 8). Among non-carbonated bases, cesium fluoride and potassium phosphate provided indoline **4a** in 63% and 74% yields respectively (entries 9-10), which is in line with the result obtained with K_2CO_3 (entry 4) even though a significant amount of indole **5a** was detected (26-37%). By contrast, the reaction failed when using DBU as an organic base (entry 11).[9e] Finally, these reaction conditions executed at 130 °C led to an excellent conversion into the indoline product **4a** (99% NMR yield) and gave an isolated yield of 61% after column chromatography (entry 12). For comparison purposes, under these optimal reaction conditions, the chlorinated palladacycle **3a-Cl** was transformed into the indole **5a** in 46% yield (entry 13). A similar trend was observed with complexes **3b-I** and **3b-Cl** (R = H, entries 14-15), prepared from phenethylamine derivative **1b** and **2b** (Scheme 1 and Table 1). Nevertheless, the isolated yields of the corresponding indoline **4b** (50%) and indole **5b** (38%) were lower than those obtained from phenylalanine-derived palladacycles **3a-Cl** and **3a-I**, suggesting that the ester group slightly facilitates the base-assisted N-H activation step probably by reinforcing the N-H acidity. In any case, we could devise an overall counter-ion directed synthesis of either indole **4** or indoline **5** thanks to this carbonate assisted C-N bond forming reaction.



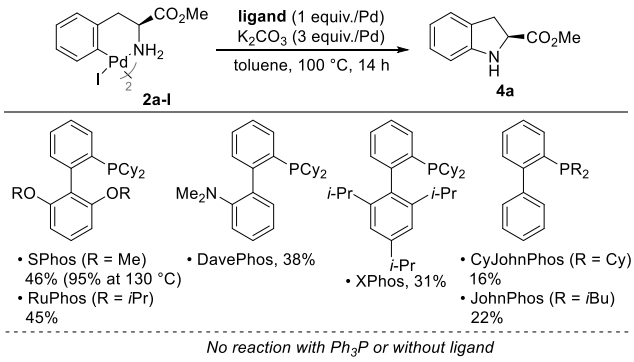
FIGURES 1. (a) Enlargement of the ESI(+)-FTICR mass spectrum of the crude reaction mixture showing the *m/z* 925.370 cationic palladium complex. (b) Theoretical isotopic pattern of the $C_{52}H_{69}O_4P_2Pd^+$ ion with a resolution of 60,000.

It is worth noticing that during silica-gel column chromatography, co-elution between indoline **4a** and a moderately stable

Pd-complex impurity was observed, which could explain the difference between the estimated NMR yield (up to 99% under optimal conditions) and the isolated yield of pure product. Among the crude reaction mixture (see supporting information), this side-product was identified by electrospray ionization – Fourier-transform ion cyclotron resonance mass spectrometry (ESI-FT-ICR, Figure 1). Thus, the cationic palladium complex with an exact *m/z* 925.3700 was detected and features one palladium atom. Accordingly, the $C_{52}H_{69}O_4P_2Pd^+$ molecular formula may account for the palladacycle depicted in Figure 1 (the palladium atom is arbitrarily located) flanked by another SPhos ligand, which could be formed from complex **3a** through an intramolecular C-H activation process.

In order to evaluate the influence of the phosphine ligand on the C-N bond formation, the *in situ* formation of palladacycles **3a-I** was undertaken by mixing the dimeric palladacycle **2a-I** with various Buchwald phosphine ligands (Scheme 2). Although no indoline **4a** formation was observed either from the dimeric Pd-complex **2a-I** or in the presence of triphenylphosphine ligand, the model SPhos ligand furnished the indoline product **4a** in 46% NMR yield. This straightforward approach gave promising results as compared to the 77% yield obtained from the phosphine-Pd-complex **3a-I** (the putative intermediate obtained from **2a-I**; see Table 1, entry 4).

Scheme 2. Screening of phosphine ligands[a]



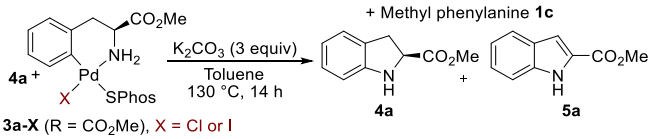
[a]Reaction made with 0.1 mmol of palladacycle in 1 mL of toluene. Yield determined by ^{1}H-NMR with Bn_2O as an internal standard.

Similar results were obtained with analogous but more sterically hindered RuPhos ligand giving 45% yield. However, in this series, XPhos as well as more electron-rich DavePhos, and less sterically hindered JohnPhos and CyJohnPhos, revealed to be slightly less effective than SPhos under these conditions (yields < 38%). These observations suggest that the decomplexation/N-H activation/reductive elimination sequence is optimal with Buchwald ligands, and the SPhos provides the best balance between steric and electronic effects. Finally, by heating the reaction at 130 °C in the presence of SPhos ligand the indoline **4a** was obtained in a high 95% NMR yield.

Having these conditions in hand, the investigation of the free energy profile was undertaken by DFT calculation as depicted in Figure 2 (see the supporting information for computational details). The amine-(SPhos)Pd^{II} complex **A** (X = Cl or I) and CO_3^{2-} were taken as energy reference. The geometry of this complex when X = I is in good agreement with the ones characterized by Vicente, Saura-Llamas *et al* by X-ray crystallography.[4d] The dissociation of the halide was achieved through $\mathbf{TS_{AB}}$ to give the cationic Pd complex **B**. With X = Cl or I, the free energy of activation is ~ 11 kcal/mol. At 373 K in MeCN, this dissociation was found exergonic by 4.2 and 8.9 kcal/mol respectively. This is notably due to the well-known ability of the SPhos moiety to act as a bidentate ligand, involving the electron-rich carbon of the biaryl core. One of the two nitrogen protons of **B** is sterically shielded by the dimethoxybenzene ring, while the other is electronically protected from the approach of CO_3^{2-} by the ester functionality. Thus, no direct deprotonation of **B** into the corresponding neutral complex **E** could be modeled. The formation of **E** could instead derive from the direct attack of CO_3^{2-} to **B** to give the palladium carbonate **C** lying at -13.7/-18.5 kcal/mol. Yet, the approach of CO_3^{2-} towards **B** did not yield a transition state. The intramolecular deprotonation could then be computed through $\mathbf{TS_{CD}}$ lying at -10.6/-15.4 kcal/mol, i.e. only ~ 3 kcal/mol above **C**. The resulting H-bonded complex **D** is formed in a slightly endergonic fashion (1.7 kcal/mol above **C** for the two halides). The C-N bond forming reductive elimination towards the Pd^0 complex **F** is markedly exergonic by ~ 13 kcal/mol from **E**, but the corresponding transition state lies quite high relatively to **D** (~ 22 kcal/mol of free energy of activation). A better option is to first dissociate HCO_3^- from **D** to give the chelate **E**, which liberates ~ 10 kcal/mol of free energy. The reductive elimination of **E** requires only ~ 14 kcal/mol of free energy of activation to reach $\mathbf{TS_{EF}}$. We also explored the direct deprotonation of **A** by CO_3^{2-} to give **G**. No transition state could be found for what seems to be a barrierless process according the scan of the surface. The resulting negatively charged amido-Pd^{II} complex **G** is more stable than **A** by 7.7/9.9 kcal/mol. Reductive elimination yields the H-bonded complex **H** at the expense of 16.8/14.0 kcal/mol of free energy of activation to reach $\mathbf{TS_{GH}}$. Alternatively, the dissociation of X to give **E** requires a lower free energy of activation 10.9/8.1 kcal/mol through $\mathbf{TS_{GE}}$. Thus, the best pathway for both halides appears to be **A** → **G** → **E** → **F**. However, this proposal does not take the cation effect into account, and does not rationalize the ion-dependence observed.

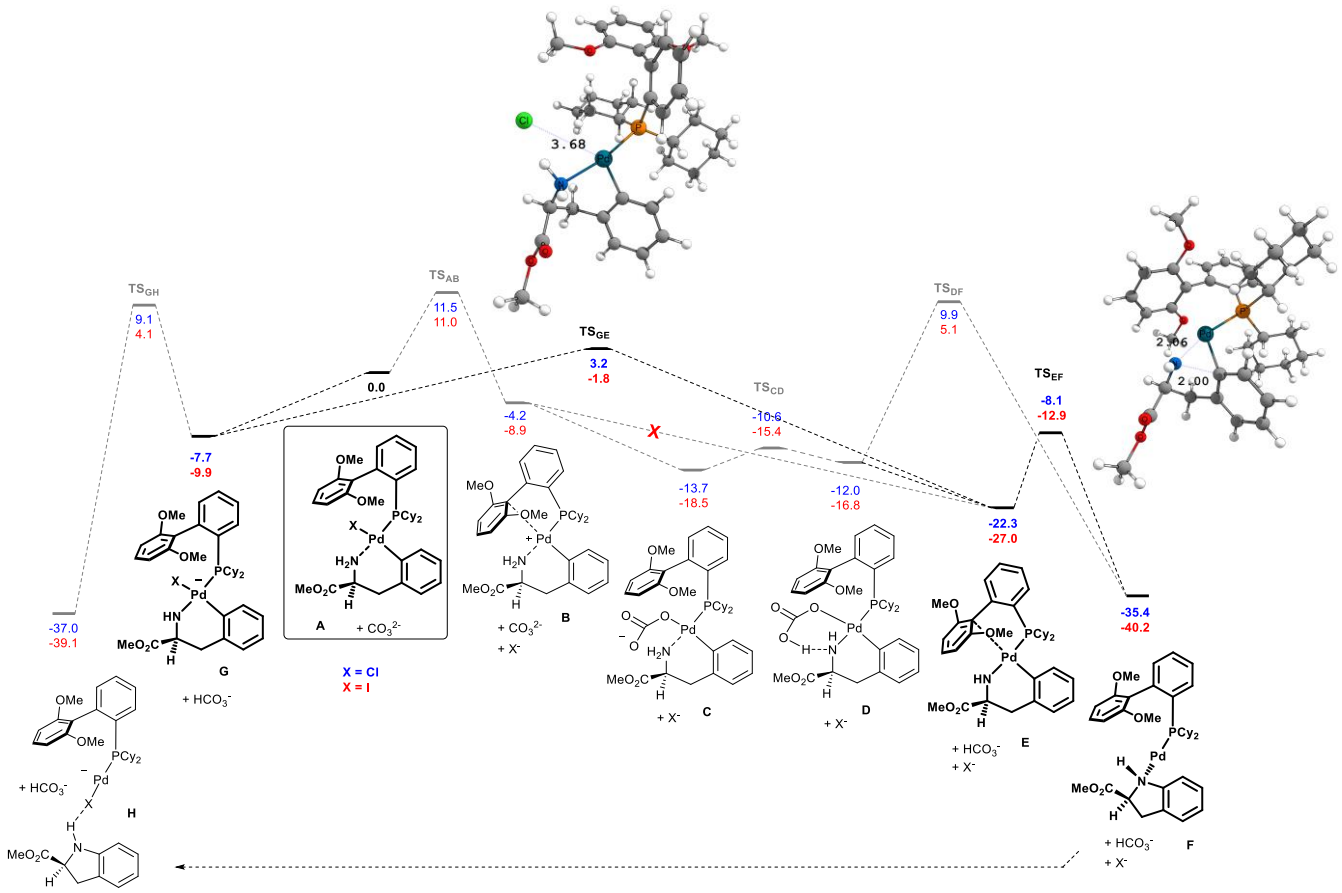
Since a clear-cut explanation accounting a divergent route towards the formation of the aromatic indole product **5a** from one of the chlorinated-palladacycles was not found, further experiments were carried out (see supporting information for further details). Heating the indoline products **4a** in the presence of the chlorinated SPhos-palladacycle **3a-Cl** led essentially to the formation of indole **5a** (Table 2, entry 1), especially in the absence of base (entry 2). Contrariwise, in the presence of the iodide-palladacycle **3a-I** and K_2CO_3 the deprotonated amination process was the favored pathway (entry 3, only 17% of **5a**) although a mixture of product was obtained.

TABLE 2. Shedding light on the formation of the indole side product 5a[a]



entry	3-X	K_2CO_3	**4a** (%)[b]	**5a** (%)[b]	1c (%)[b]
1[c]	Cl (**3a-Cl**)	yes	28	72	38
2[c]	Cl (**3a-Cl**)	no	traces	100	35
3	I (**3a-I**)	yes	107	17	38
4	I (**3a-I**)	no	70	12	33

[a]Reaction made with palladacycle **3a** (0.05 mmol), the indoline **4a** (1 equiv) and K_2CO_3 (3 equiv) in toluene at 130 °C for 14 h. [b]Yield determined by ^{1}H NMR spectroscopy with Bn_2O as an internal standard after filtration on a pad of celite. [c]Precipitation of palladium was observed.

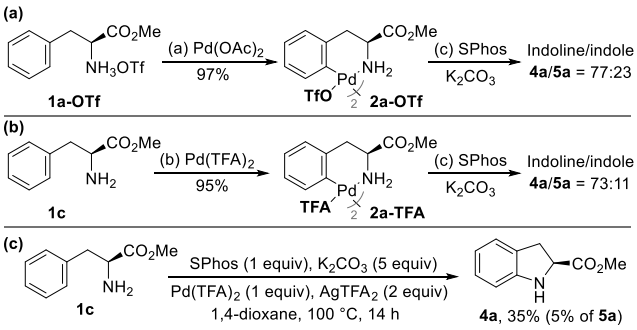


FIGURES 2. Free energy profile to form the dihydroindole product **4a** (ΔG_{373}, kcal/mol, geometries of **TS$_{GE}$** (X = Cl) and **TS$_{EF}$** with selected distances in Å)

The main product **4a** was apparently obtained with more than 100% yield due to the remaining starting material **4a**. Without any base, a small amount of indole **5a** (12%) was still observed but with no-extra formation of indoline **4a** (entry 4). Worthy of note, although a clear quantification of the other minor side products was not trivial within the reaction mixture, an estimated amount of methyl ester phenylalanine **1b** around 30% was measured. With these observations in hand, we propose that a complexation event between indoline **4a** (product of the reaction) and the chlorinated SPhos-palladacycle **3a-Cl**, or Pd^{II} species derived thereof, might initiate an N-H or a C-H insertion reaction leading eventually to indole **5a** (and phenylalanine **1c**) after the subsequent β-H elimination process. The electronic or kinetic issues underlying these counter-ion divergent processes would deserve further investigations, but already show the key role of the iodide based-complexes to secure a base promoted-amination reaction instead of an oxidative pathway.

These results prompted us to investigate other complexes with weakly coordinated counter-ions in order to investigate their influence onto these possibly divergent pathways. Thanks to the adaptation of the Vicente and Saura-Llama protocol, the palladacycle **2a-OTf** was synthesized and isolated as a solid from the corresponding ammonium triflate salts **1a-OTf** of L-phenylalanine in the presence of $Pd(OAc)_2$ (Scheme 3a). Gratifyingly, making use of the previously optimized conditions, the palladium complex **2a-OTf** in the presence of SPhos and K_2CO_3 was smoothly transformed into the corresponding indoline **4a** in 77% NMR yield as the major product along with a smaller amount of indole **5a** (23%). More importantly, a similar directed C-H activation process took place directly from the more challenging free amine **1c** as starting material by means of the electrophilic $Pd(TFA)_2$, to furnish the more stable palladacycle **2a-TFA** (Scheme 3b).

Scheme 3. Investigation towards a palladium promoted N-H/C-H cross-coupling



(a) Reaction conditions: (a) $Pd(OAc)_2$ (1 equiv), MeCN, 80 °C, 4h. (b) $Pd(TFA)_2$ (1 equiv), MeCN, 80 °C, 4 h. (c) SPhos (1 equiv./Pd), K_2CO_3 (3 equiv./Pd), MeCN, 100 °C, 14 h.

According to the ^{1}H NMR, IR spectra and mass analysis, the dimeric complexes **2a-X** (X = OTf, TFA) were likely formed. In line to palladium complex **2a-OTf**, the homologous **2a-TFA** underwent the amination sequence to lead to indoline **4a** in 73% yield, along with only 11% of indole **5a**. Worthy of note, no racemization took place under these conditions. Based on these important observations, a first screening of conditions eventually highlighted that methyl ester phenylalanine **1c** could be transformed into the corresponding indoline **4a** in moderate

albeit significant 35% yield in the presence of $Pd(TFA)_2$, SPhos, K_2CO_3 and AgOTf as additive (Scheme 3c). These results under stochiometric conditions demonstrate that complexes directly accessible from a NH_2-directed C-H amination reaction could be engaged into the subsequent deprotonated amination reaction.

CONCLUSION

In summary, this reactivity and DFT investigations of the phenylalanine derived palladacycles, obtained by NH_2 directed C*sp*^{2}-H activation, sheds light on (1) a major anion effect to achieve the intramolecular C-N bond formation towards the construction of the corresponding indoline product and (2) a facile carbonate-assisted N-H activation prior to the events leading to a reductive elimination step. We believe this study highlights key features which will be useful for further developments towards highly valuable catalytic dehydrogenative amination processes, via a C-H/N-H activation process from primary amines.

EXPERIMENTAL SECTION

Triflate-bridged ortho-palladated L-phenylalanine methylester (2a-OTf). *N.B.: for this specific experimental procedure, no precautions were taken against moisture or oxygen*. To a mixture of L-Phenylalanine methylester ammonium triflate salt **1a-OTf** (1.0 g, 3.04 mmol) and $Pd(OAc)_2$ (682 mg, 3.04 mmol) into a sealed-tube was added acetonitrile (0.1 M). The solution was stirred at 80 °C for 4 h. The reaction mixture was filtered through a pad of Celite®/Na_2CO_3 washed with MeCN. The filtrate was concentrated under reduced pressure and a mixture of Et_2O and *n*-Pentane was added. The precipitate was vigorously stirred for 10 min and the suspension was filtered under vacuum. The solid was washed with *n*-pentane and then air-dried to furnish the corresponding complex **2a-OTf** as a yellow solid (1.28 g, 97 %). Melting point 117-118 °C; IR (neat) ν_{max} 3229, 2976, 1736, 1553, 1439, 1241, 1167, 1028, 751, 638, 517, 457 cm^{-1}; δ_H (300 MHz, CD_3CN): 7.19 (d, *J* = 7.5 Hz, 1H), 7.02-6.87 (m, 3H), 4.31 (s, 1H), 3.64 (s, 3H), 3.64-3.57 (m, 1H), 3.33 (dd, *J* = 14.1, 4.5 Hz, 1H), 3.17 (dd, *J* = 14.1, 5.6 Hz, 1H) ppm (one NH signal missing); δ_C (75 MHz, CD_3CN): 172.8, 136.4, 136.1, 128.4, 126.2, 126.1, 53.5, 50.4, 45.2 ppm; δ_F (282 MHz, CD_3CN): -79.3 ppm; HRMS (ESI$^+$): calcd for $C_{12}H_{15}N_2O_2{}^{106}Pd$ [(M/2)−(CF_3SO_3)+(1xACN)]$^+$: 325.01629; found: 325.01620.

Trifluoroacetate-bridged ortho-palladated L-phenylalanine methylester (2a-TFA). *N.B.: for this specific experimental procedure, no precautions were taken against moisture or oxygen.* To a mixture of L-Phenylalanine methylester **1c** (250 mg, 1.39 mmol) and $Pd(TFA)_2$ (464 mg, 1.39 mmol) into a sealed-tube was added acetonitrile (0.1 M). The solution was stirred at 80 °C for 4 h. The reaction mixture was filtered through a pad of Celite®/Na_2CO_3 washed with MeCN. The filtrate was concentrated under reduced pressure and a mixture of Et_2O and *n*-Pentane was added. The precipitate was vigorously stirred for 10 min and the suspension was filtered under vacuum. The solid was washed with *n*-pentane and then air-dried to furnish the corresponding complex **2a-TFA** as a yellow solid (525 mg, 95 %). Remark: A similar process could be achieved from L-phenylalanine methylester ammonium trifluoroacetate salt **1a-TFA** and $Pd(OAc)_2$ to give the dimer **2a-TFA**. Melting point 132-134 °C; IR (neat) ν_{max} 3268, 2954, 1740, 1659, 1554, 1435, 1202, 850, 749, 730, 452, 406 cm^{-1}; δ_H (300 MHz, CD_3CN): 7.16 (d, *J* = 7.7 Hz, 1H), 7.95-6.80 (m, 3H), 5.32 (s, 1H), 4.49 (s, 1H), 3.58 (s, 3H), 3.55-3.49 (m, 1H), 3.30 (dd, *J* = 14.1, 4.3 Hz, 1H), 3.11 (dd, *J* = 14.1, 5.8 Hz, 1H) ppm; δ_C (75 MHz, CD_3CN): 173.0, 136.9, 136.5, 128.1, 125.9, 125.7, 53.4, 50.5, 45.5 ppm (C-Pd and TFA carbons missing); δ_F (282 MHz, CD_3CN): -75.8 ppm; $C_{26}H_{24}F_9N_2O_{10}{}^{105}Pd_2$ [M+TFA]$^-$: 904.9389; found: 904.9424.

Typical procedure A for preparation of phosphino-palladacycles 3. To a solution of the corresponding dimeric-palladacycle **2a** (1 equiv.) in CH_2Cl_2 (0.05 M) was added SPhos (1 equiv./Pd) in one portion. The resulting solution was stirred at r.t. for 30 min, concentrated under vacuum and *n*-pentane was added in one portion. The precipitate was vigorously stirred for 10 min and the suspension was filtered under vacuum. The solid was washed with *n*-pentane and then air-dried to provide the corresponding phosphino-complex **3** as a beige solid.

SPhos-chloro-ortho-palladated L-phenylalanine methylester (3a-Cl). Following the general procedure A starting from palladacycle **2a-Cl** (286 mg, 0.45 mmol),[4d] the title palladacycle **3a-Cl** was obtained as beige solid (564 mg, 87%). Melting point 162–165 °C; IR (neat) ν_{max} 3052, 2923, 2849, 1738, 1587, 1471, 1248, 1109, 728 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.35 (1H, t, *J* = 8.4 Hz), 7.25 (1H, t, *J* = 7.5 Hz), 7.22 – 7.14 (1H, m), 7.00 (1H, ddd, *J* = 7.7, 3.1, 1.0 Hz), 6.92 (1H, t, *J* = 7.7 Hz), 6.81 (1H, dd, *J* = 7.7, 4.8 Hz), 6.72 – 6.68 (2H, m), 6.64 (2H, dd, *J* = 8.4, 2.7 Hz), 6.46 – 6.39 (1H, m), 3.82 (2H, br s), 3.69 (3H, s), 3.65 (3H, s), 3.62 (3H, s), 3.22 (1H, dd, *J* = 13.0, 2.0 Hz), 2.42 (1H, br s), 2.31 – 2.13 (3H, m), 1.81 – 1.44 (12H, m), 1.34 – 1.14 (3H, m), 1.11 – 0.87 (5H, m) ppm; δ_C (75 MHz, $CDCl_3$): 179.5, 172.8, 158.1, 139.8, 138.0, 136.5, 135.4, 133.0, 129.4, 128.9, 126.7, 124.7, 124.0, 123.3, 118.9, 103.8, 103.6, 103.1, 55.4, 55.2, 52.8, 52.4, 49.9, 48.9, 47.1, 46.8, 36.5, 36.1, 34.0, 33.9, 32.2, 31.7, 31.3, 30.5, 29.1, 28.4, 27.5, 27.2, 26.9, 26.2, 26.1, 25.6 ppm (observed complexity results from C−P coupling); δ_P (121 MHz, $CDCl_3$): 46.21 ppm; HRMS (ESI$^+$): calcd for $C_{36}H_{47}NO_4P^{104}Pd$ [M−Cl]$^+$: 692.2285; found: 692.2283.

SPhos-iodo-ortho-palladated L-phenylalanine methylester (3a-I). Following the general procedure A starting from palladacycle **2a-I** (529 mg, 0.64 mmol), the title palladacycle **3a-I** was obtained as a beige solid (970 mg, 92%). Melting point 186–188 °C; δ_H (300 MHz, $CDCl_3$): 7.37 (1H, t, *J* = 8.3 Hz), 7.23 – 7.07 (2H, m), 6.92 (1H, dd, *J* = 7.4, 2.4 Hz), 6.85 (1H, br s), 6.75 – 6.60 (5H, m), 6.44 (1H, m), 3.99 – 3.75 (3H, m), 3.70 (3H, s), 3.69 (3H, s), 3.67 (3H, s), 3.55 (1H, br s) 3.21 (1H, d, *J* = 13.3 Hz), 2.52 – 2.13 (4H, m), 2.05 – 1.38 (12H, m), 1.37 – 1.13 (3H, m), 1.08 – 0.92 (3H, m) ppm; δ_C (75 MHz, $CDCl_3$) 173.1, 158.2, 139.3, 137.0, 134.7, 133.0, 132.9, 129.6, 128.7, 127.0, 125.0, 125.0, 124.7, 123.6, 119.4, 103.9, 55.4, 53.0, 49.8, 45.6, 32.2, 30.9, 30.4, 29.1, 27.7, 27.6, 27.5, 27.4, 27.2, 27.0, 26.2, 26.0 ppm (observed complexity results from C−P coupling); HRMS (ESI$^+$): calcd for $C_{36}H_{47}NO_4P^{104}Pd$ [M−I]$^+$: 692.2285; found: 692.2283. Data are in accordance with literature.[4d]

Typical procedure B for the deprotonative amination from SPhos-halogeno palladacycle 3. To a mixture of SPhos-phosphino-complex **3a** (1 equiv.) and K_2CO_3 (3 equiv.) in a flame-dried sealed tube was added toluene (0.1 M). The resulting solution was stirred at 130 °C for 14 h under nitrogen atmosphere, then cooled to r.t.. The solution was diluted with CH_2Cl_2 and filtered through a pad of Celite®. Bn_2O (0.25 equiv.) was added and the filtrate was concentrated under reduced pressure to provide crude residue. Conversion and NMR yield were monitored by ^{1}H-NMR spectroscopy. When needed the crude reaction mixture, after evaporation under reduced pressure, was purified by flash column chromatography on silica gel.

Typical procedure C for deprotonative amination from dimeric complex 2. To a mixture of dimeric-complex **2** (1 equiv.), SPhos (1 equiv./Pd) and K_2CO_3 (3 equiv./Pd) in a flame-dried sealed tube were added in the corresponding solvent (0.1 M) under nitrogen atmosphere. The resulting solution was stirred at 100 °C for 14 h, then cooled to r.t.. The solution was diluted with CH_2Cl_2 and filtered through a pad of Celite®. Bn_2O (0.25 equiv.) was added and the filtrate was concentrated under reduced pressure to provide crude residue. Conversion and NMR yield were monitored by ^{1}H-NMR spectroscopy.

Typical procedure D for *one-pot* synthesis of indoline (4a). To a mixture of L-Phenylalanine methylester **1c** (18 mg, 0.1 mmol), $Pd(TFA)_2$ (33 mg, 0.1 mmol), SPhos (41 mg, 0.1 mmol), K_2CO_3 (69 mg, 0.5 mmol) and AgTFA (44 mg, 0.2 mmol) in a flame-dried sealed tube was added 1,4-dioxane (0.05 M) under nitrogen atmosphere. The resulting solution was stirred at 100 °C for 14 h, then cooled to r.t.. The solution was diluted with CH_2Cl_2 and filtered through a pad of Celite®. Bn_2O (0.25 equiv.) was added and the filtrate was concentrated under reduced pressure to provide crude residue. Conversion was monitored by ^{1}H-NMR spectroscopy.

Methyl (S)-indoline-2-carboxylate (4a). Following the general procedure B starting from palladacycle **3a-I** (247 mg, 0.3 mmol), the title indoline **4a** was obtained a yellow oil (32 mg, 61 %) after purification by flash column chromatography on silica gel (eluent: petroleum ether/acetone [90:10]). δ_H (300 MHz, $CDCl_3$): 7.13 – 7.01 (2H, m), 6.79 – 6.69 (2H, m), 4.39 (1H, dd, *J* = 9.9, 5.7 Hz), 3.76 (3H, s), 3.47 – 3.25 (2H, m) (NH signal not observed). Data are in accordance with literature.[12]

Methyl 1*H*-indole-2-carboxylate (5a). Following the general procedure B starting from palladacycle **3a-Cl** (219 mg, 0.3 mmol), the title indole **5a** was obtained a white solid (24 mg, 46 %) after purification by flash column chromatography on silica gel (eluent: petroleum ether/acetone [95:5]). δ_H (300 MHz, $CDCl_3$): 8.90 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 1.2 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 3.95 (s, 3H) ppm. Data are in accordance with literature.[12]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental protocols, characterization data, mass spectroscopy, computational details, coordinates and energies of the computed species (PDF).

AUTHOR INFORMATION

Corresponding Author

* E-mail: christophe.hoarau@insa-rouen.fr (C.H.)
* E-mail: jean-francois.briere@insa-rouen.fr (J.-F.B.)
* E-mail: guillaume.journot@servier.com (G.J.)

ORCID

Christophe Hoarau: 0000-0001-9668-9970
Jean-François Brière: 0000-0002-1381-4535
Guillaume Journot: 0000-0002-3695-3175

Notes

[A]Contributed equally to this work.
[B]From the mass-spectroscopy department.
The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work has been partially supported by INSA Rouen, Rouen University, the Centre National de la Recherche Scientifique (CNRS), EFRD, and Labex SynOrg (ANR-11-LABX-0029), the Region Normandie (CRUNCh network) and by Oril Industrie, affiliated to "Les laboratoires Servier". This work has been realized under the aegis of the joint laboratory Cobra – Oril Industrie: "IDECHEM". VG thanks UPSaclay, CNRS and Ecole Polytechnique for financial support.

REFERENCES

1. For recent reviews, see: (a) Yuan, J.; Liu, C.; Lei, A., Construction of N-containing heterocycles via oxidative intramolecular N–H/X–H coupling. *Chem. Commun.* **2015**, *51*, 1394-1409; (b) Kim, H.; Chang, S., Transition-Metal-Mediated Direct C–H Amination of Hydrocarbons with Amine Reactants: The Most Desirable but Challenging C–N Bond-Formation Approach. *ACS Catal.* **2016**, *6*, 2341-2351; (c) Kim, H.; Chang, S., The Use of Ammonia as an Ultimate Amino Source in the Transition Metal-Catalyzed C–H Amination. *Acc. Chem. Res.* **2017**, *50*, 482-486; (d) Park, Y.; Kim, Y.; Chang, S., Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247-9301; (e) Henry, M. C.; Mostafa, M. A. B.; Sutherland, A., Recent Advances in Transition-Metal-Catalyzed, Directed Aryl C–H/N–H Cross-Coupling Reactions. *Synthesis* **2017**, *49*, 4586-4598.

2. (a) Mei, T.-S.; Wang, X.; Yu, J.-Q., Pd(II)-Catalyzed Amination of C−H Bonds Using Single-Electron or Two-electron Oxidants. *J. Am. Chem. Soc.* **2009**, *131*, 10806-10807; (b) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G., Highly Efficient Syntheses of Azetidines, Pyrrolidines, and Indolines via Palladium Catalyzed Intramolecular Amination of C(sp3)–H and C(sp2)–H Bonds at γ and δ Positions. *J. Am. Chem. Soc.* **2012**, *134*, 3-6; (c) Nadres, E. T.; Daugulis, O., Heterocycle Synthesis via Direct C–H/N–H Coupling. *J. Am. Chem. Soc.* **2012**, *134*, 7-10; (d) He, G.; Lu, C.; Zhao, Y.; Nack, W. A.; Chen, G., Improved Protocol for Indoline Synthesis via Palladium-Catalyzed Intramolecular C(sp2)–H Amination. *Org. Lett.* **2012**, *14*, 2944-2947; (e) Mei, T.-S.; Leow, D.; Xiao, H.; Laforteza, B. N.; Yu, J.-Q., Synthesis of Indolines via Pd(II)-Catalyzed Amination of C–H Bonds Using PhI(OAc)2 as the Bystanding Oxidant. *Org. Lett.* **2013**, *15*, 3058-3061; (f) Wang, C.; Chen, C.; Zhang, J.; Han, J.; Wang, Q.; Guo, K.; Liu, P.; Guan, M.; Yao, Y.; Zhao, Y., Easily Accessible Auxiliary for Palladium-Catalyzed Intramolecular Amination of C(sp2)-H and C(sp3)-H Bonds at δ- and ε-Positions. *Angew. Chem. Int. Ed.* **2014**, *53*, 9884-9888; (g) Yang, M.; Jiang, X.; Shi, Z.-J., Direct amidation of the phenylalanine moiety in short peptides via Pd-catalyzed C–H activation/C–N formation. *Org. Chem. Front.* **2015**, *2*, 51-54; (h) He, G.; Lu, G.; Guo, Z.; Liu, P.; Chen, G., Benzazetidine synthesis via palladium-catalysed intramolecular C−H amination. *Nat. Chem.* **2016**, *8*, 1131.

3. Gaunt proposed an elegant strategy based on the use of activated secondary arylamines to adress this challenging issue, see: (a) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J., Oxidative Pd(II)-Catalyzed C−H Bond Amination to Carbazole at Ambient Temperature. *J. Am. Chem. Soc.* **2008**, *130*, 16184-16186; (b) Haffemayer, B.; Gulias, M.; Gaunt, M. J., Amine directed Pd(II)-catalyzed C–H bond functionalization under ambient conditions. *Chem. Sci.* **2011**, *2*, 312-315.

4. (a) Cope, A. C.; Siekman, R. W., Formation of Covalent Bonds from Platinum or Palladium to Carbon by Direct Substitution. *J. Am. Chem. Soc.* **1965**, *87*, 3272-3273; (b) Cope, A. C.; Friedrich, E. C., Electrophilic aromatttic substitution reactions by platinum(II) and palladium(II) chlorides on N,N-dimethylbenzylamines. *J. Am. Chem. Soc.* **1968**, *90*, 909-913; (c) López, B.; Rodriguez, A.; Santos, D.; Albert, J.; Ariza, X.; Garcia, J.; Granell, J., Preparation of benzolactams by Pd(II)-catalyzed carbonylation of N-unprotected arylethylamines. *Chem. Commun.* **2011**, *47*, 1054-1056; (d) Vicente, J.; Saura-Llamas, I.; Oliva-Madrid, M.-J.; García-López, J.-A.; Bautista, D., A New Method for High-Yield Cyclopalladation of Primary and Secondary Amines. Atom-Efficient Open-to-Air Inexpensive Synthesis of Buchwald-Type Precatalysts. *Organometallics* **2011**, *30*, 4624-4631.

5. For reviews, see: (a) Dunina, V. V.; Zalevskaya, O. A.; Potapov, V. M., General Principles and Characteristics of Cyclopalladation Reactions. *Russ. Chem. Rev.* **1988**, *57*, 250-269; (b) Vicente, J.; Saura-Llamas, I., Ortho-Palladation of Primary Amines: the Myth Dispelled. *Comment Inorg. Chem.* **2007**, *28*, 39-72.

6. For selected examples, see: (a) Omar-Amrani, R.; Schneider, R.; Fort, Y., Novel Synthetic Strategy of N-Arylated Heterocycles via Sequential Palladium-Catalyzed Intra- and Inter-Arylamination Reactions. *Synthesis* **2004**, 2527-2534; (b) González-Gómez, J. C.; Medjahdi, M.; Foubelo, F.; Yus, M., Stereoselective α-Aminoallylation of Aldehydes with Chiral tert-Butanesulfinamides and Allyl Bromides. *J. Org. Chem.* **2010**, *75*, 6308-6311; (c) Harada, R.; Nishida, N.; Uchiito, S.; Onozaki, Y.; Kurono, N.; Senboku, H.; Masao, T.; Ohkuma, T.; Orito, K., Phosphane-Free Pd(0)-Catalyzed Cycloamination and Carbonylation with $Pd(OAc)_2$ and $Cu(OAc)_2$ in the Presence of K_2CO_3: Preparation of Benzocyclic Amines and Benzolactams. *Eur. J. Org. Chem.* **2012**, *2012*, 366-379; (d) Monguchi, Y.; Marumoto, T.; Takamatsu, H.; Sawama, Y.; Sajiki, H., Palladium on Carbon-Catalyzed One-Pot N-Arylindole Synthesis: Intramolecular Aromatic Amination, Aromatization, and Intermolecular Aromatic Amination. *Adv. Synth. Catal.* **2014**, *356*, 1866-1872.

7. (a) Hartwig, J. F., Transition Metal Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046-2067; (b) Dorel, R.; Grugel, C. P.; Haydl, A. M., The Buchwald–Hartwig Amination After 25 Years. *Angew. Chem. Int. Ed.* **2019**, *58*, 17118-

17129; (c) Ingoglia, B. T.; Wagen, C. C.; Buchwald, S. L., Biaryl monophosphine ligands in palladium-catalyzed C–N coupling: An updated User's guide. *Tetrahedron* **2019**, *75*, 4199-4211.

8. Biscoe, M. R.; Fors, B. P.; Buchwald, S. L., A New Class of Easily Activated Palladium Precatalysts for Facile C−N Cross-Coupling Reactions and the Low Temperature Oxidative Addition of Aryl Chlorides. *J. Am. Chem. Soc.* **2008**, *130*, 6686-6687.

9. (a) Yamashita, M.; Hartwig, J. F., Synthesis, Structure, and Reductive Elimination Chemistry of Three-Coordinate Arylpalladium Amido Complexes. *J. Am. Chem. Soc.* **2004**, *126*, 5344-5345; (b) Arrechea, P. L.; Buchwald, S. L., Biaryl Phosphine Based Pd(II) Amido Complexes: The Effect of Ligand Structure on Reductive Elimination. *J. Am. Chem. Soc.* **2016**, *138*, 12486-12493; (c) Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L., Breaking the Base Barrier: An Electron-Deficient Palladium Catalyst Enables the Use of a Common Soluble Base in C–N Coupling. *J. Am. Chem. Soc.* **2018**, *140*, 4721-4725; (d) Kim, S.-T.; Pudasaini, B.; Baik, M.-H., Mechanism of Palladium-Catalyzed C–N Coupling with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as a Base. *ACS Catal.* **2019**, *9*, 6851-6856; (e) Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L., Pd-Catalyzed C–N Coupling Reactions Facilitated by Organic Bases: Mechanistic Investigation Leads to Enhanced Reactivity in the Arylation of Weakly Binding Amines. *ACS Catal.* **2019**, *9*, 3822-3830.

10. de Lange, B.; Hyett, D. J.; Maas, P. J. D.; Mink, D.; van Assema, F. B. J.; Sereinig, N.; de Vries, A. H. M.; de Vries, J. G., Asymmetric Synthesis of (S)-2-Indolinecarboxylic Acid by Combining Biocatalysis and Homogeneous Catalysis. *ChemCatChem* **2011**, *3*, 289 and references cited therein.

11. The formation of either indole or indoline product during intramolecular Pd-catalyzed amination reaction from *ortho*-brominated precursor was already observed e.g. reference 7.

12. Jørgensen, M. R.; Olsen, C. A.; Mellor, I. R.; Usherwood, P. N. R.; Witt, M.; Franzyk, H.; Jaroszewski, J. W., The Effects of Conformational Constraints and Steric Bulk in the Amino Acid Moiety of Philanthotoxins on AMPAR Antagonism. *J. Med. Chem.* **2005**, *48*, 56-70.