DOI: 10.1002/adsc.201000512

"On Water" Direct and Site-Selective Pd-Catalysed C–H Arylation of (NH)-Indoles

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Received: June 30, 2010; Revised: September 22, 2010; Published online: November 17, 2010

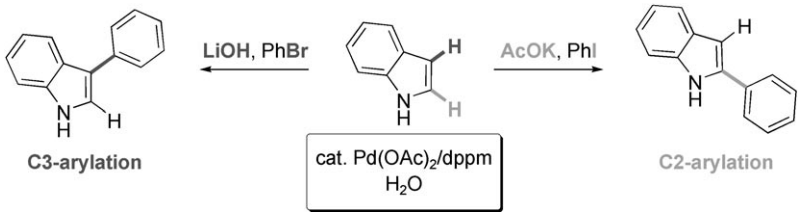
Dedicated to the memory of Professor Keith Fagnou.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000512.

Abstract: This communication describes the development of a versatile catalytic system based on palladium(II) acetate/bis(diphenylphosphino)methane [$Pd(OAc)_2$/dppm] that works "on water" giving site-selective C–H arylation of (NH)-indoles without protecting or directing groups. Remarkably, the control of regioselectivity was achieved by small changes in the "extra-catalytic" base/halide partners. These innovative methodologies allow a high-yielding access to both C2 and C3-arylindoles, as well as 2,3-diarylindoles, and display high chemo/regioselectivities and structural versatility with regard to either indole or aryl moieties.

Keywords: C–H arylation; indoles; palladium; regioselectivity; water

"Direct arylation"[1] has emerged over the past few years as an outstanding alternative to traditional cross-coupling reactions[2] in the preparation of biaryl molecules because this strategy partially avoids the need of stoichiometric organometallic activating groups. Since the indole nucleus is ubiquitous in materials science, pharmaceutical and natural products,[3] major improvements have been achieved in the direct and site-selective arylation of (NH)-indoles through either Pd-, Rh- or Cu-catalyzed methodologies.[4] Nevertheless, to the best of our knowledge no report focuses on complementary C2-[5] and C3-arylation[6] procedures by means of a unique catalytic system.[7] Moreover, several drawbacks remain associated with these methodologies such as the often required nitrogen protecting groups or the need of high-boiling, toxic solvents. Recently, substantial "green-oriented" efforts have been achieved in the field of C–H activation[8] through the development of "on water" transition metal-catalyzed reactions[9] which afford economical, environmental and safety advantages. Unfortunately, accounts dealing with direct C–H arylation of heterocycles on water are scarce. Greaney et al. disclosed an arylation reaction of five-membered heterocycles under mild reaction conditions,[10] but a bimetallic system was needed including the expensive Ag_2CO_3 base. Herein, we describe an innovative "on water" palladium-catalyzed C–H arylation of (NH)-indoles that is site-selective and base/halide-controlled using cheap reagents.[11] This methodology allows the preparation of either C2- or C3-arylindoles (Scheme 1).



Scheme 1. Tunable functionalization of (NH)-indoles through [base/halide]-controlled regioselective Pd-catalyzed C–H arylation.

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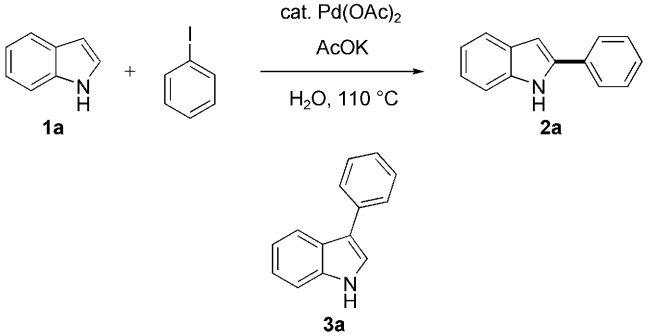
Initially, we examined the coupling between indole (**1a**) and iodobenzene (Table 1) using 5 mol% of $Pd(OAc)_2$ and AcOK as base, a catalytic system inspired by the work of Sames. Under these conditions, 2-phenylindole (**2a**) was obtained as the major regioisomer albeit with a low 20% yield (entry 1). Further optimization toward a selective C2-arylation protocol featured the crucial role of arylphosphine ligands in order to achieve a better catalytic performance. As shown in Table 1, such easy-to-handle mono- or bidentate phosphines (i.e., PPh_3, BINAP) with a [Pd]/phosphine ratio of 1/2 (see Supporting Information, Figure S1), as well as commonly employed complexes [e.g., Herrmann-Beller's palladacycle, $PdCl_2(PPh_3)_2$], allowed enhanced conversions (50–60%) and selectivities (up to 20:1). On the other hand, either electron rich phosphines such as PCy_3 and $P(OEt)_3$ (entries 4 and 5) or hydrosoluble ones like TPPTS and TPPMS (entries 7 and 8) were found unsuitable to perform such arylation. Remarkably, $PdCl_2(dppm)\cdot CH_2Cl_2$ (entry 10) and especially $Pd(OAc)_2$/dppm (entry 13) exhibited both higher activities (75% yield within 18 h) and selectivities (>20/1) toward 2-phenylindole.

Table 1. Optimization studies for indole C2-arylation: phosphine screening.[a]



Entry	Phosphine (mol%)	Selectivity[b]	Yield [%][c]
1	–	11:1	20
2	PPh_3 (5)	14:1	54
3	PPh_3 (10)	17:1	60
4	PCy_3 (10)	–	28
5	$P(OEt)_3$ (10)	–	9
6	$P(o\text{-Tol})_3$ (10)	16:1	31
7	TPPTS (10)	–	20
8	TPPMS (10)	–	31
9	HBP (1.0)	7.5:1	57
10	***$PdCl_2(dppm)\cdot CH_2Cl_2$ (5)***	***>20:1***	***68 (82)***[d]
11	$PdCl_2(PPh_3)_2$ (5)	19:1	48
12	BINAP (5)	>20:1	54
13	***dppm (5)***	***>20:1***	***75 (90)***[d]
14	dppm (10)	>20:1	58
15	dppm (5)	–	34[e]

[a] *Reaction conditions:* **1a** (1.0 mmol), iodobenzene (1.2 mmol), AcOK (3.0 mmol), [Pd] (5 mol%), H_2O (2 mL), 110 °C, 18 h. TPPTS = tris(3-sulfonatophenyl)-phosphine sodium salt; TPPMS = diphenylphosphinobenzenesulfonic acid sodium salt; dppm = bis(diphenylphosphino)methane; HBP = Herrmann–Beller palladacycle.

[b] **2a**:**3a** selectivity determined by GC.

[c] The yield was determined by GC.

[d] 48 h at 110 °C.

[e] $PdCl_2$ (5 mol%) was used as palladium source.

The scope of the reaction was then examined for several aryl iodides and indole derivatives (Table 2). This methodology was found to be general, providing the desired C2-arylindoles in useful to good yields (48–79%); disappointingly, the use of 7-azaindole (**2k**) resulted in no arylation. High regioselectivities (*ca.* 20:1) were generally obtained except when *ortho*-substituted derivatives were used. Furthermore, these reaction conditions featured a full chemoselectivity with either 5-bromoindole (**2j**) or 4-bromoiodobenzene (**2f**), the arylation occurring selectively on the C–I bond. The procedure is tolerant for both electron-donating and electron-withdrawing groups including OMe (**2d**, **2i**), Ac (**2c**), naphthyl (**2g**) and CO_2Me (**2l**). Especially noteworthy are substrates bearing a Cl (**2b**, **2e**, **2h**) or a Br (**2f**, **2j**) substituent, which allow further functionalization through cross-coupling reactions.[12] Comparatively, the use of Larrosa's conditions[5m] [i.e., 5 mol% $Pd(OAc)_2$, 1.5 equiv. *o*-nitrobenzoic acid, 0.75 equiv. Ag_2O, H_2O, 110 °C] furnished **2j** in a slightly improved 59% yield and **2l** in a poor 12% yield despite full conversions, which suggests a high rate of degradation of the starting material when silver salts are used.[13]

We next turned our attention to the development of a selective C3-arylation procedure since a profound base effect was uncovered during optimization of the C2 protocol. Remarkably, extensive screening[14] revealed that $LiOH\cdot H_2O$ resulted in a 3.6:1 ratio of **3a**:**2a** and a full conversion within 18 h. To our delight, when iodobenzene was replaced by bromobenzene, an enhanced and synthetically useful 6.5:1 regioselectivity (Table 3, entry 1) was achieved. By these means, **3a** was obtained in 74% yield together with a small amount of **2a** (13%).

The scope of the reaction with aryl bromides is outlined in Table 3. Gratifyingly, good to high yields (69–91%) were achieved independent of the electron donating or withdrawing nature of substituents (OMe, Cl, CF_3 groups, entries 4–6) and the substitution pattern of both indole (4-, 5- and 6-positions) and aryl moieties, including *ortho*-substituted bromoarenes. Furthermore, 2-phenylindole **2a** was fully converted under such conditions and furnished 2,3-diphenylindole **3j** [Scheme 2, Eq. (1)] in a nearly quantitative yield. Thus, the synthesis of 2,3-diarylindoles can be envisioned *via* the sequential C2- then C3-arylation of the parent indole core in two steps.[5h,15] Ester groups resulted in a complete degradation of the starting material as hydrolysis might be expected in the presence

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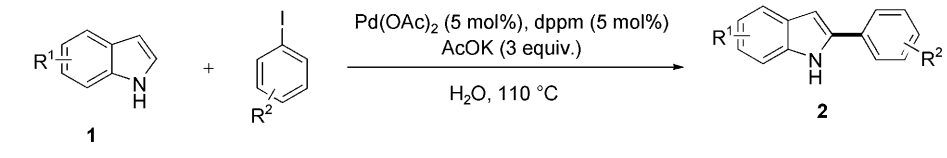
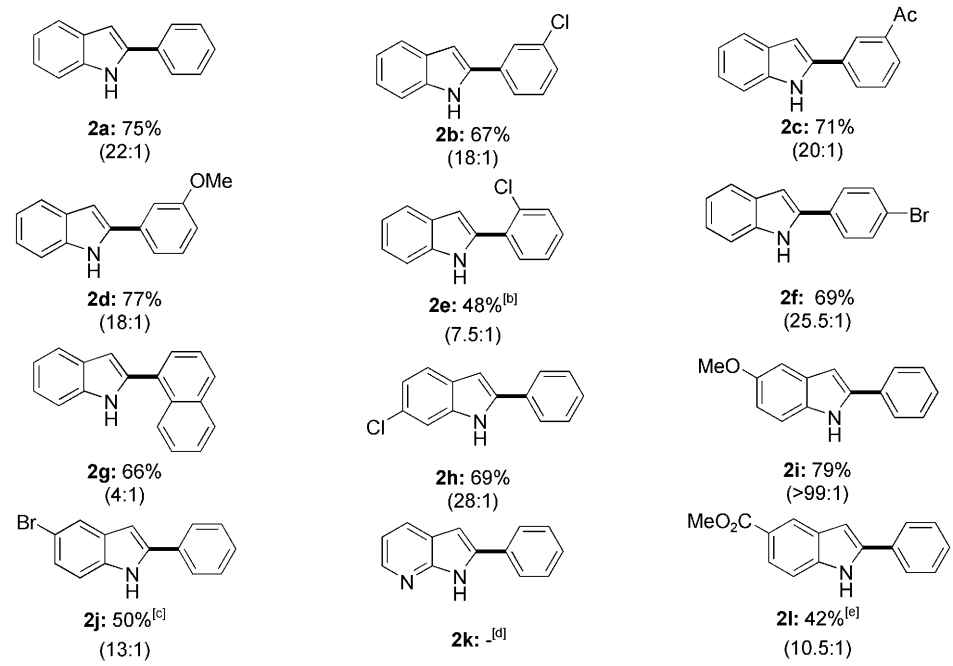
Table 2. Regioselective C2-arylation of indoles.[a]





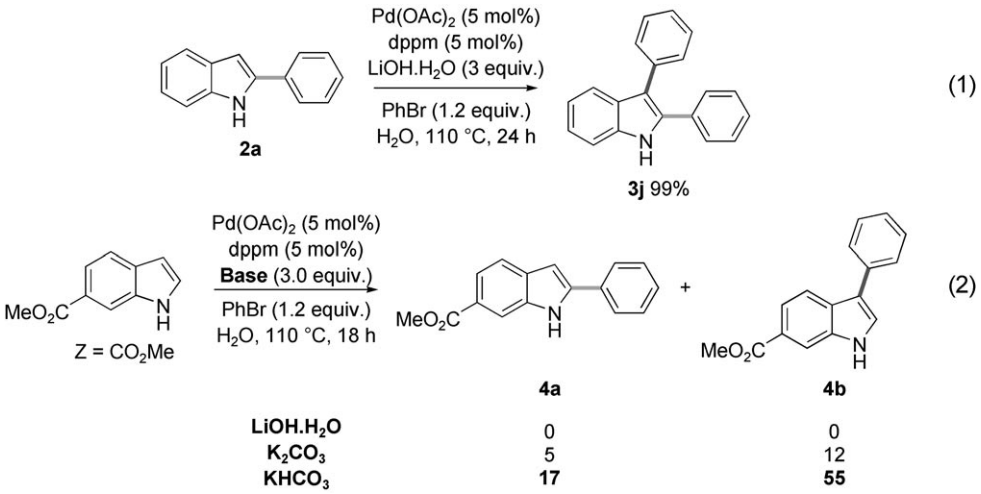
[a] *Reaction conditions:* **1** (1.0 mmol), aryl iodide (1.2 mmol), AcOK (3.0 mmol), Pd(OAc)$_2$ (5 mol%), dppm (5 mol%), H_2O (2 mL), 110 °C, 24 h. Isolated yields of pure C2-isomers after flash column chromatography over silica are reported. Values in brackets refer to **2**:**3** selectivity of crude material determined by GC.

[b] 24% of starting material recovered.

[c] 40% of starting material recovered.

[d] Traces of 2-phenyl-7-azaindole detected by GC/MS.

[e] 53% of starting material recovered.



Scheme 2. Sequential synthesis of 2,3-diphenylindole [Eq. (1)] and special behaviour of methyl ester derivative [Eq. (2)].

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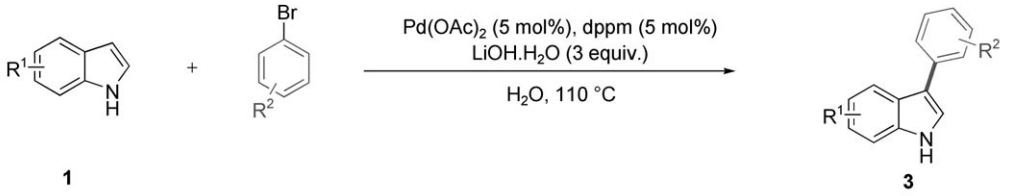
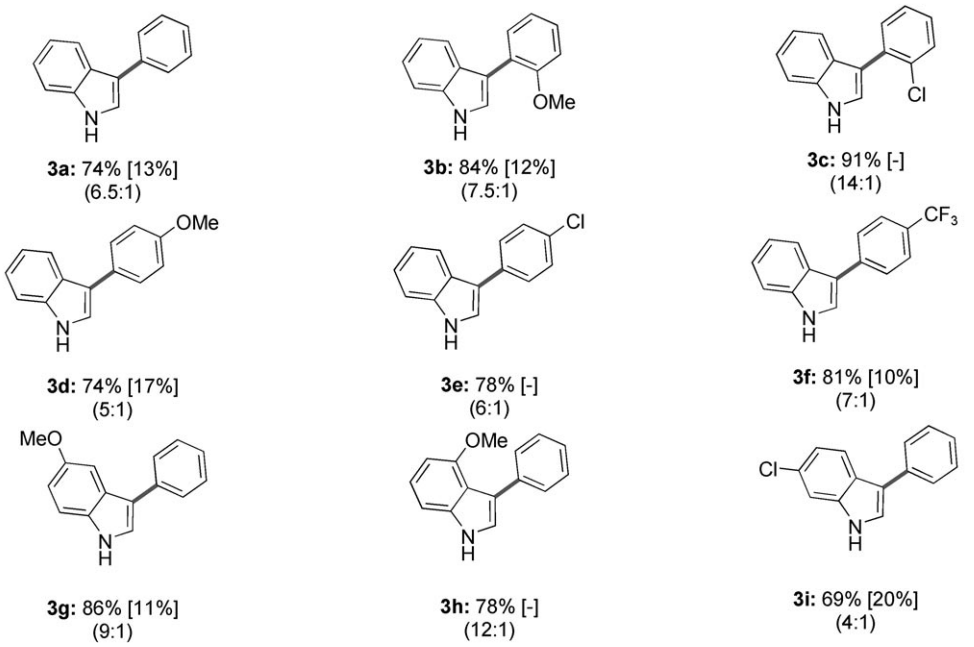
Table 3. Regioselective C3-arylation of indoles.[a]





[a] *Reaction conditions:* **1** (1.0 mmol), aryl bromide (1.2 mmol), $LiOH{\cdot}H_2O$ (3.0 mmol), $Pd(OAc)_2$ (5 mol%), dppm (5 mol%), H_2O (2 mL), 110 °C, 18 h. **3:2** selectivity of crude material determined by GC in brackets. In some cases, small amounts (< 5%) of 2,3-diarylindoles were also detected. Isolated yield of pure C3-isomer (C2-isomer in square brackets) after flash column chromatography over silica.

of such a strong base [Scheme 2, Eq. (2)]. K_2CO_3 furnished the targeted arylindoles in 17% overall yield despite a full conversion. To our delight, the use of the weaker base $KHCO_3$ prevented saponification and successfully provided the C3-regioisomer (**4b**) in a useful 55% yield (72% with combined C2- and C3-regioisomers).[16]

Obviously, the use of the appropriate base/halide partners is the key element in the catalyst design to control C2- *versus* C3-arylation. Particularly, the presence of bromide anions significantly controls the outcome of this palladium-catalyzed C–H arylation, both in terms of selectivity and activity (Table 4).[17] Accordingly, superior selectivities and/or catalytic activities were observed with respect to LiOH/ArBr partners (entries 3/5 *versus* 2/4). It's noteworthy that the addition of LiBr featured an improved C3-selectivity when LiOH/PhI partners are used (entry 8 *versus* 2). In contrast, AcOK/Br association suppressed either C2- or C3-arylation (entry 7 *versus* entries 6/1), a profound bromide effect supported by a weakened reactivity of AcOK/I partners toward C2-arylation when LiBr is added to the reaction mixture (entry 9 *versus* 7). Nevertheless, almost full conversions and good C3-selectivities were achieved with NaOH or KOH whether aryl bromides or iodides are used (entries 10–13). These results support an electrophilic palladation at the C3 position of the indole nucleus[6a] and suggest that two kinds of active palladium species are involved (Scheme 3). Indeed, the highly electrophilic cationic Pd complex **A**[18] is expected to easily undergo a C3-palladation while the activation of the neutral complex **B** requires the action of a stronger base than AcOK, probably through *in situ* deprotonation of the indole nitrogen. Therefore, the key intermediate **C** is expected to follow two pathways: a) a C3→C2 migration of the palladium center favored in the presence of the weak base AcOK, affording the complex **D** which leads to the C2-regioisomer; b) a rearomatization privileged with stronger bases such as

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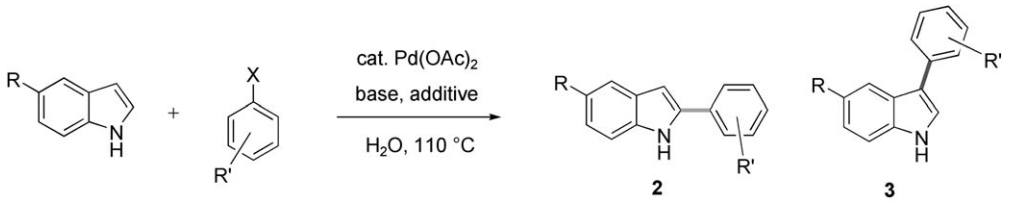
Table 4. Connecting base and halide effects to regioselectivity.[a]



Entry	R	R′	Additive	Base/Halide	Selectivity	Conversion [%]
1	H	H	–	AcOK/I	>20:1	>95
2	H	H	–	LiOH/I	1:3.6	100
3	H	H	–	LiOH/Br	1:6.5	100
4	H	4-OMe	–	LiOH/I	1.3:1	60
5	H	4-OMe	–	LiOH/Br	1:5	100
6	Br	H	–	AcOK/I	13:1	60
7	H *or* Br	H	–	AcOK/Br	–	0
8	H	H	LiBr	LiOH/I	1:4.5	100
9	Br	H	LiBr	AcOK/I	3:1	20
10	H	H	–	NaOH/Br	1:5.9	100
11	H	H	–	NaOH/I	1:5.5	100
12	H	H	–	KOH/Br	1:6.5	100
13	H	H	–	KOH/I	1:5.7	100

[a] *Reaction conditions:* indole (1.0 mmol), aryl halide (1.2 mmol), base (3.0 mmol), $Pd(OAc)_2$ (5 mol%), dppm (5 mol%), H_2O (2 mL), 110 °C, 18-24 h. LiBr (1.0 mmol) was added when indicated. Conversions and **2:3** selectivities were determined by GC.

CO_3^{2-} or OH^- affording the σ-Pd complex **E**, precursor of the C3-regioisomer after reductive elimination of Pd(0). Notably, such a rearomatization could be elsewhere promoted by the presence of the more nucleophilic bromide anions compared to the iodide ones. Thus, such mechanisms rationalize the reversed C3/C2 selectivity obtained with LiOH/PhI partners and the C3-selectivity enhancement when either bromides are added in the reaction media – *via* a **A**→**B** Pd species displacement – or a more nucleophilic base (i.e., NaOH or KOH) is employed. However, we cannot rule out the co-existence of the so-called "concerted metallation-deprotonation" pathway when AcOK/ArI partners are used.[19]

In summary, we have developed a versatile catalytic system allowing an innovative "on water" direct and site-selective arylation of (NH)-indoles. This palladium-catalyzed C–H functionalization reaction highlighted a [base/halide]-controlled regioselectivity, so that the arylation can be directed to either the 2- or the 3-position of (NH)-indoles. By these means, a straightforward two-step synthesis of 2,3-diarylindoles can be envisioned. These procedures exhibit good to high regio- and chemoselectivity, displaying high structural versatility with regard to both indole and aryl moieties. Current studies are directed towards mechanistic investigations and application of these methodologies to other heterocyclic scaffolds.

Experimental Section

General Procedures for the Direct Arylation of (NH)-Indoles

General procedure for C2 arylation: In a screw-cap vial under air, a mixture of $Pd(OAc)_2$ (11.3 mg, 0.05 mmol, 5 mol%), dppm (19.2 mg, 0.05 mmol, 5 mol%), AcOK (294 mg, 3.00 mmol, 3.0 equiv.), iodobenzene (244 mg, 1.20 mmol, 1.2 equiv.), and indole **1a** (117 mg, 1.0 mmol, 1.0 equiv.) in degassed H_2O (2 mL) was vigorously stirred at 110 °C. After 24 h the reaction mixture was cooled to room temperature and partitioned between 1N HCl (5 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was further extracted with 2×10 mL ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO_2, petroleum ether/EtOAc 9/1) afforded 2-phenylindole **2a** as a white solid; yield: 145 mg (0.75 mmol, 75%).

General procedure for C3 arylation: In a screw-cap vial under air, a mixture of $Pd(OAc)_2$ (11.3 mg, 0.05 mmol, 5 mol%), dppm (19.2 mg, 0.05 mmol, 5 mol%), $LiOH{\cdot}H_2O$ (126 mg, 3.00 mmol, 3.0 equiv.), bromobenzene (188 mg, 1.20 mmol, 1.2 equiv.), and indole **1a** (117 mg, 1.0 mmol, 1 equiv.) in degassed H_2O (2 mL) was vigorously stirred at 110 °C. After 18 h the reaction mixture was cooled to room temperature and partitioned between 1N HCl (5 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was further extracted with 2×10 mL ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO_2,

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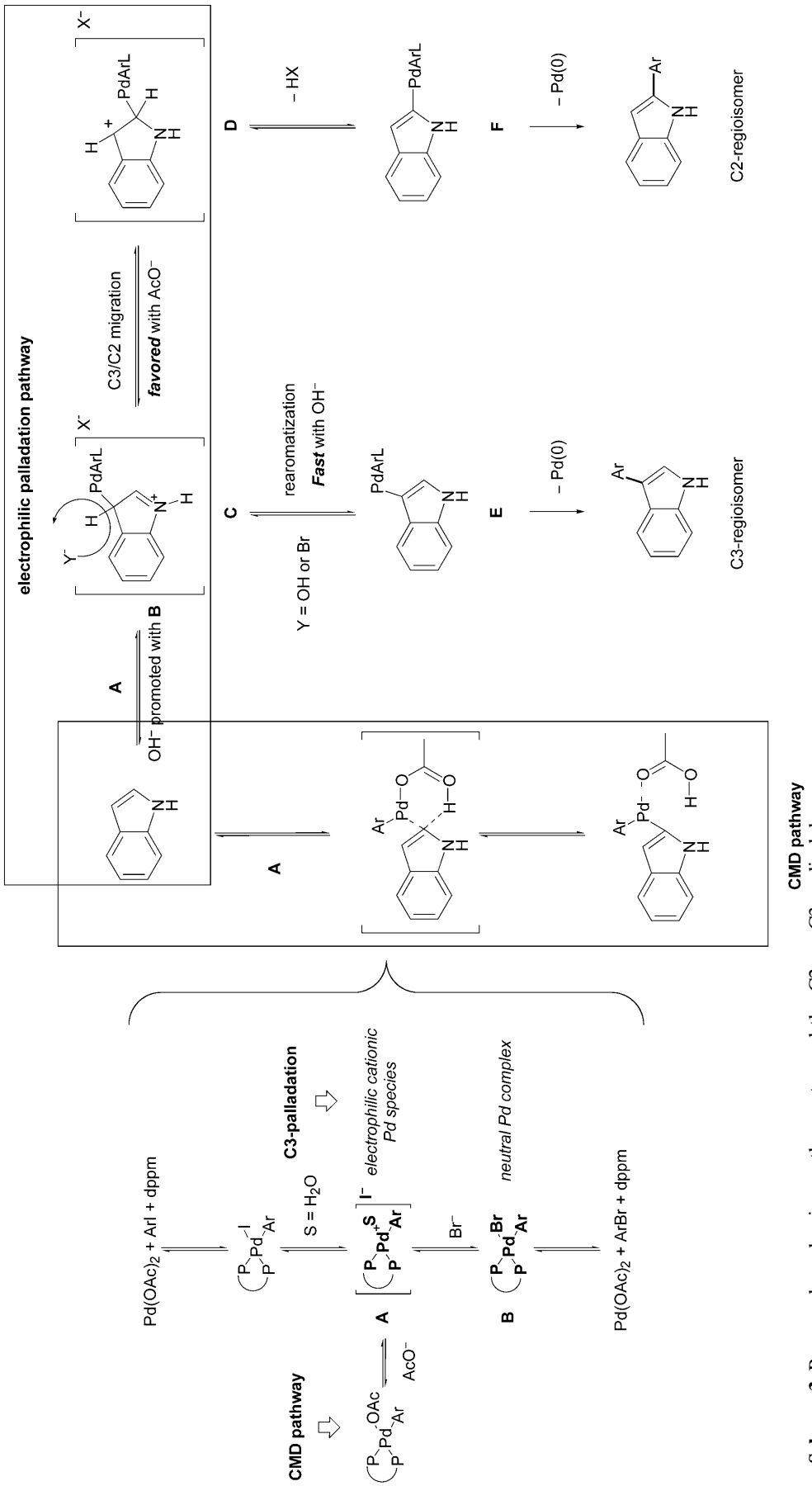

Scheme 3. Proposed mechanism pathways toward the C2- or C3-arylindoles.

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petroleum ether/EtOAc 9/1) afforded 3-phenylindole **3a** as a pale yellow solid; yield: 143 mg (0.74 mmol, 74%) and 2-phenylindole **2a**; yield: 25 mg (0.13 mmol, 13%).

Acknowledgements

The authors thank Prof. Piet W. N M. van Leeuwen for proof-reading and correction of the manuscript. We gratefully acknowledge the Région Rhône-Alpes Programme CIBLE-2007 (Contract number 07 016376 01/02/03) and the National Agency of Research (No. ANR-07-BLAN-0167-01/02) for funding.

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[7] a) For a pioneering work, see ref.[6a] Recently, Gaunt and co-workers disclosed a regioselective copper-catalyzed C–H arylation of indoles controlled however by the nature of the nitrogen protecting group, see ref.[5o] In a previous work, they developed a [solvent/oxidant]-controlled regioselective palladium-catalyzed C–H alkenylation of (NH)-indoles, see: N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem.* **2005**, *117*, 3185; *Angew. Chem. Int. Ed.* **2005**, *44*, 3125. b) During the preparation of this manuscript, Su and co-workers have reported a site-selective arylation of indoles, protected however with Ac of Piv groups, using a versatile $Pd(TFA)_2/Ag_2CO_3/EtCO_2H$ catalyst through a decarboxylative cross-coupling, see: J. Zhou, P. Hu, M. Zhang, S. Huang, M. Wang, W. Su, *Chem. Eur. J.* **2010**, *16*, 5876.

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