

# Synthesis of Isoquinolin-4-ols by Palladium-Catalysed Intramolecular Nucleophilic Addition of Aryl Iodides to Aldehydes

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**Abstract.** A palladium-catalysed intramolecular nucleophilic addition of aryl iodides to aldehydes leading to tetrahydroisoquinolin-4-ols is reported. A variety of products were isolated in good to excellent yields. The joint experimental-computational study shows that although two competitive reaction pathways can be promoted by Pd(0) starting from  $\alpha$ -(2-iodobenzylamino)-aldehydes, the selectivity of the process can be controlled by the proper selection of the base. While the nucleophilic addition of the aryl-Pd(II) intermediate to the carbonyl group is selectively promoted by using the base Et<sub>3</sub>N, the C–H bond activation at the formyl group competes with the nucleophilic addition only when the base is replaced by Cs<sub>2</sub>CO<sub>3</sub>.

**Keywords:** catalysis; palladium; cyclization; nucleophilic addition; DFT calculations

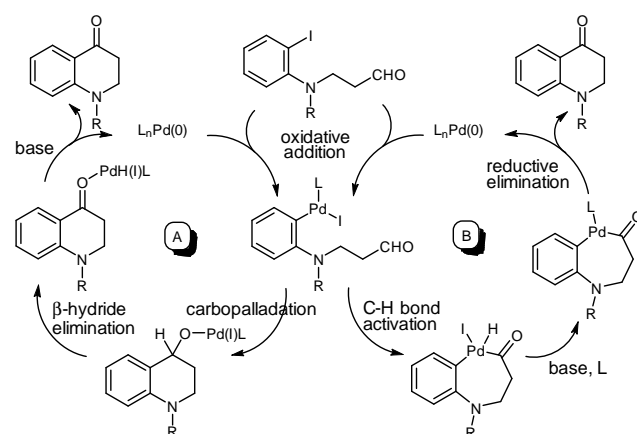
catalysis.<sup>[4,5]</sup> On the other hand, the intramolecular Pd-catalysed direct acylation of aryl halides with aldehydes, though scarcely explored, has been successfully used for the preparation of benzocyclobutenones<sup>[6]</sup> and for the synthesis of a variety of azaheterocycles starting from 2-iodoanilines.<sup>[7]</sup>

Two mechanistic scenarios (Scheme 1) have been proposed for these intramolecular processes: (1) carbopalladation of the aryl-Pd(II) moiety across the C=O bond,<sup>[8,9,10]</sup> followed by  $\beta$ -hydride elimination would afford the ketone and regenerate the Pd(0) catalyst (mechanism A),<sup>[7a]</sup> or (2) C–H bond activation, loss of HX from the resulting Pd(IV) intermediate, and reductive elimination from the acyl-Pd complex would also form the ketone and regenerate the catalyst (mechanism B).<sup>[6a]</sup>

## Introduction

Aldehydes are probably the most versatile synthon in organic chemistry. Consequently, it is not surprising that, in the last years, several alternative C–C bond forming methods have appeared based on the insertion of aldehydes into late transition metal-carbon bonds.<sup>[1]</sup> Among the variety of available synthetic methodologies, the Pd-catalysed cross-coupling reactions of arylborons and aryl halides with aldehydes have been attracting increasing interest in the last decade. Thus, the intermolecular Pd-catalysed nucleophilic addition of arylborons to aldehydes currently constitutes a powerful methodology for the synthesis of diarylmethanols.<sup>[2]</sup>

In contrast, there are only a few reported examples of the reaction between aryl halides and aldehydes, a transformation that always affords the corresponding acylation product (i.e. arylketone). The intermolecular version of this process requires bimetallic systems<sup>[3]</sup> or occurs via a Heck-type mechanism by means of Pd-amine cooperative

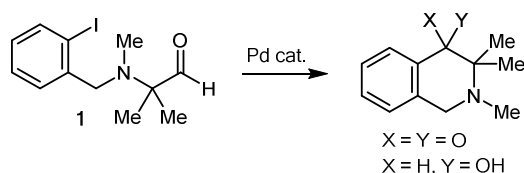


**Scheme 1.** Proposed catalytic cycles for the intramolecular acylation of aryl halides with aldehydes.

Our DFT calculations have shown that in the reaction of (2-iodoanilino)-aldehydes the carbopalladation of the C=O group is kinetically and thermodynamically favoured over the C–H bond

oxidative insertion. This preference may be ascribed to the high nucleophilicity of the carbon atom directly attached to the transition metal because of the  $\pi$ -donor effect of the *ortho*-nitrogen atom.<sup>[7a]</sup>

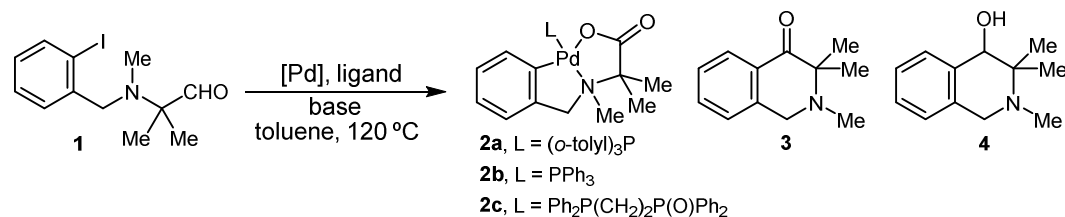
Continuing with our interest in these processes, we decided to study the Pd-catalysed reaction of  $\alpha$ -(2-iodobenzylamino)-aldehydes (Scheme 2) as a methodology for the synthesis of functionalised tetrahydroisoquinolines, which are important scaffolds present in a number of natural products.<sup>[11]</sup>



**Scheme 2.** Synthesis of tetrahydroisoquinolines.

Moreover, the process is not only interesting from a synthetic point of view but also from a mechanistic point of view, because in aldehyde **1** the nitrogen atom has been separated from the aryl ring to avoid the delocalisation of its LP into the aryl  $\pi$ -system.

**Table 1.** Optimization of the reaction conditions.<sup>[a]</sup>



Entry	[Pd] (mol%)/Ligand (mol%)	Base	Time	Products (Yield [%]) <sup>[b]</sup>
1	Pd <sub>2</sub> (dba) <sub>3</sub> (5)/dtpf (10)	Cs <sub>2</sub> CO <sub>3</sub> /Et <sub>3</sub> N	24 h	<b>1</b> (99%)
2	Pd <sub>2</sub> (dba) <sub>3</sub> (10)/( <sup>t</sup> Bu) <sub>3</sub> PH·BF <sub>4</sub> (20)	Cs <sub>2</sub> CO <sub>3</sub> /Et <sub>3</sub> N	24 h	<b>1</b> (46%)
3	Pd <sub>2</sub> (dba) <sub>3</sub> (10)/( <i>o</i> -tolyl) <sub>3</sub> P (20)	Cs <sub>2</sub> CO <sub>3</sub> /Et <sub>3</sub> N	48 h	<b>1</b> (not quantified) <sup>[c]</sup>
4	Pd(OAc) <sub>2</sub> (10)/rac-BINAP (15)	Cs <sub>2</sub> CO <sub>3</sub>	24 h <sup>[d]</sup>	<b>1</b> (not quantified)
5	Pd <sub>2</sub> (dba) <sub>3</sub> (55)/( <i>o</i> -tolyl) <sub>3</sub> P (120)	Cs <sub>2</sub> CO <sub>3</sub>	24 h	<b>2a</b> (45%), <b>3</b> (10%)
6	Pd <sub>2</sub> (dba) <sub>3</sub> (10)/PPh <sub>3</sub> (25)	Cs <sub>2</sub> CO <sub>3</sub>	72 h	<b>1</b> (not quantified) <sup>[e]</sup>
7	Pd <sub>2</sub> (dba) <sub>3</sub> (55)/PPh <sub>3</sub> (120)	Cs <sub>2</sub> CO <sub>3</sub>	24 h	<b>2b</b> (27%), <b>3</b> (26%), <b>4</b> (25%)
8	Pd(OAc) <sub>2</sub> (20)/dppe (25)	Cs <sub>2</sub> CO <sub>3</sub>	72 h	<b>1</b> (not quantified) <sup>[f]</sup>
9	Pd(OAc) <sub>2</sub> (100)/dppe (110)	Cs <sub>2</sub> CO <sub>3</sub>	15 h	<b>1</b> (10%), <b>2c</b> (42%) <sup>[g]</sup>
10	Pd <sub>2</sub> (dba) <sub>3</sub> (10)/PPh <sub>3</sub> (25)	Et <sub>3</sub> N	72 h	<b>4</b> (97%)
11	Pd(PPh <sub>3</sub> ) <sub>4</sub> (20)	Et <sub>3</sub> N	72 h	<b>4</b> (86%)
12	Pd(OAc) <sub>2</sub> (20)/dppe (25)	Et <sub>3</sub> N	72 h	<b>4</b> (93%)
13	Pd(OAc) <sub>2</sub> (20)/rac-BINAP (25)	Et <sub>3</sub> N	48 h	<b>4</b> (76%)
14	Pd <sub>2</sub> (dba) <sub>3</sub> (5)/PPh <sub>3</sub> (11)	Et <sub>3</sub> N	24 h	<b>4</b> (83%)

<sup>[a]</sup> Reaction conditions: **1** (0.2 mmol), [Pd] and ligand (see table), and Cs<sub>2</sub>CO<sub>3</sub> (3.0 equiv.) and/or Et<sub>3</sub>N (6.0 equiv.) in toluene at 120 °C in a sealed tube.

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup> Minor amounts of **2a** were observed in the reaction mixture.

<sup>[d]</sup> Either THF or toluene was used as the solvent.

<sup>[e]</sup> Minor amounts of **2b** and **3** ( $\approx$  10%, 2:1 ratio) were observed in the reaction mixture.

<sup>[f]</sup> Minor amounts of **2c** were observed in the reaction mixture.

<sup>[g]</sup> Minor amounts of **3** and **4** ( $\approx$  5%, 1:1 ratio) were observed in the reaction mixture.

Similar behaviour was observed when PPh<sub>3</sub> and dppe were used as the ligand. Thus, the use of catalytic amounts of a Pd source and ligand resulted

Thus, we hypothesised that the consequent decrease in the nucleophilicity of the corresponding aryl-Pd(II) intermediate could overcome the nucleophilic attack at the carbonyl group and perhaps favour the C–H bond activation pathway commented above.

## Results and Discussion

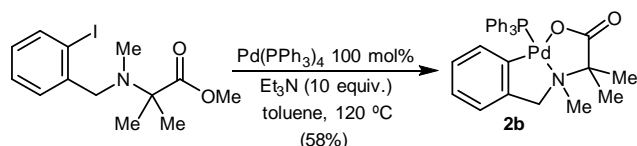
The reactivity of aldehyde **1** with several Pd precatalysts, ligands, and bases was first studied. The most representative results are summarised in Table 1.

The reaction conditions previously employed for the acylation of (2-iodoanilino)-aldehydes<sup>[7]</sup> failed to promote the reaction from (2-iodobenzyl)amine **1** (entries 1-3). Nor was acylation observed under the conditions used for the synthesis of benzocyclobutenones (entry 4).<sup>[6a]</sup> Nevertheless, since we observed the formation of small amounts of what seemed to be an aryl-Pd complex when using (*o*-tolyl)<sub>3</sub>P as the ligand (entry 3), we decided to modify the reaction conditions by using equimolar amounts of Pd(0) and ligand, which led to the isolation of complex **2a** (45%) and the ketone **3** (10%) (entry 5).

mainly in the recovery of the aldehyde and the formation of minor amounts of the corresponding Pd complexes **2b** (entry 6) and **2c** (entry 8). On the other

hand, equimolar amounts of both Pd and PPh<sub>3</sub> led to complex **2b** (27%), ketone **3** (26%), and alcohol **4** (25%) (entry 7), while the use of equimolar amounts of Pd and dppe resulted mainly in the formation of the Pd complex **2c** (42%) (entry 9).

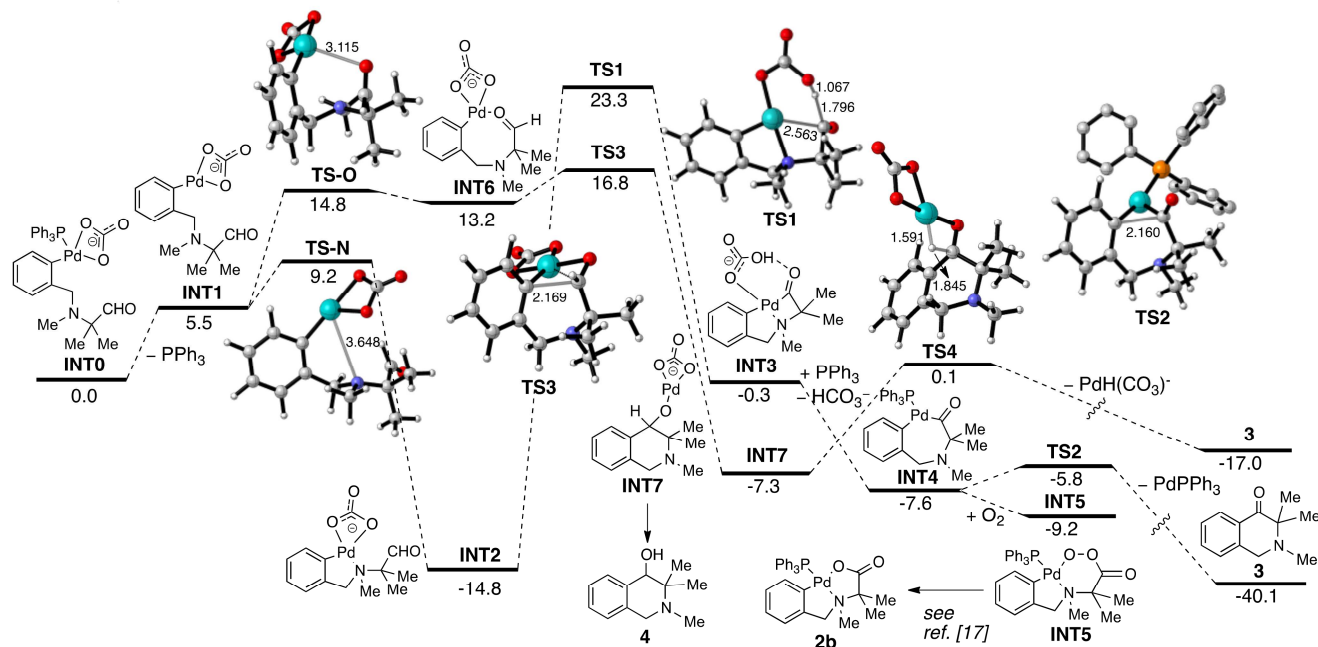
The structures of complexes **2a-c** were unambiguously assigned from their spectroscopic data.<sup>[12]</sup> Moreover, tridentate [C,N,O] Pd(II) complex **2b** was prepared independently starting from the corresponding methyl ester.<sup>[13]</sup>



**Scheme 3.** Alternative synthesis of tridentate [C,N,O] Pd(II) complex **2b**.

Density Functional Theory (DFT) calculations were carried out at the PCM-B3LYP/def2-TZVP//B3LYP/def2-SVP level<sup>[14]</sup> to gain more insight into the mechanism of the above Pd-promoted reactions of **1**, which led to the completely unexpected formation of Pd complexes **2a-c**. The computed reaction profile starting from intermediate **INT0**, readily formed from the initial oxidative addition of **1** upon iodide ligand exchange by the CO<sub>3</sub><sup>2-</sup>, is showed in Figure 1, which gathers the corresponding computed free energies ( $\Delta G_{393}$ , at 393.15 K) in toluene as solvent.

All our attempts to locate a transition state associated with the direct C–H activation reaction leading to a Pd(IV) intermediate similar to that depicted in Scheme 1 met with no success. Fortunately, we found an alternative concerted metalation-deprotonation (CMD) process which is mediated by CO<sub>3</sub><sup>2-</sup> (Figure 1). Thus, intermediate **INT0** evolves to **INT1** by initial loss of PPh<sub>3</sub>. Intramolecular saturation of its coordination vacant by the nitrogen atom lone-pair occurs then to produce **INT2** via transition state **TS-N** in a highly exergonic transformation ( $\Delta G_{393} = -20.3$  kcal/mol). This species is transformed into the Pd(II) intermediate **INT3** via the transition state **TS1**. This saddle point is associated with the concerted hydrogen migration from the aldehyde to the carbonate ligand and Pd–C(=O) bond formation. In this sense, this process is analogous to the palladium-catalysed C–H arylation reactions which is assisted by acetate<sup>[15]</sup> or carbonate.<sup>[16]</sup> Indeed, the computed activation barrier for this process ( $\Delta G^\ddagger = 38.1$  kcal/mol, at 120 °C) is also similar to that found for AcO-assisted CMD arylation reactions.<sup>[15]</sup> Then, **INT3** is transformed into **INT4** by releasing of the HCO<sub>3</sub><sup>-</sup> ligand and coordination of PPh<sub>3</sub> in an exergonic process ( $\Delta G_{393} = -7.3$  kcal/mol). Species **INT4** is finally converted into the observed complex **2b** very likely via reaction with O<sub>2</sub> leading to the peroxy-complex **INT5**, as previously described in the literature for related acyl-palladium systems.<sup>[17]</sup> Alternatively, **INT4** can produce ketone **3** via **TS2**, a saddle point associated with the reductive elimination forming the new C(aryl)–C(=O) bond.



**Figure 1.** Computed reaction profile starting from **INT0**. Free energy values ( $\Delta G_{393}$ , computed at 120 °C) and bond distances are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM(toluene)-B3LYP/def2-TZVP//B3LYP/def2-SVP level.

In addition, ketone **3** and alcohol **4** can be also produced from an alternative reaction pathway

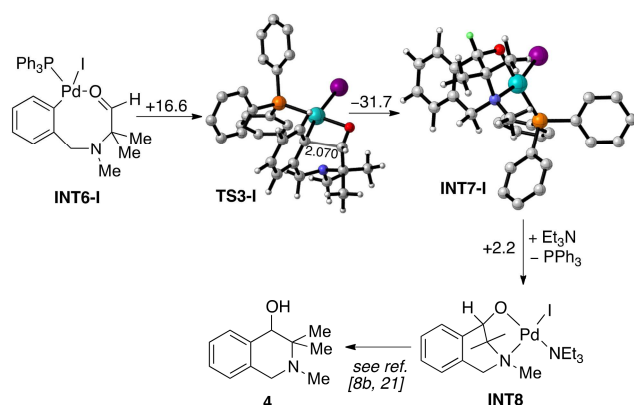
starting from the same intermediate **INT1**. Indeed, our calculations indicate that this species can be

converted into **INT6** via **TS-O**, a transition state associated with the intramolecular coordination of the carbonyl oxygen atom. This process is endergonic and proceeds with a higher activation barrier than the analogous process involving **TS-N** ( $\Delta\Delta G^\ddagger = 5.6$  kcal/mol). Despite that, the formed **INT6** readily evolves to **INT7** in a highly exergonic nucleophilic addition reaction ( $\Delta G_{393} = -20.5$  kcal/mol) with a very low activation barrier of only 3.6 kcal/mol. Therefore, although the formation of **INT2** is kinetically and thermodynamically favoured over **INT6**, the high barrier of the process involving **TS1** makes the pathway involving **TS3** competitive. From **INT7**, ketone **3** is formed through a  $\beta$ -hydride elimination reaction via **TS4** (computed barrier of 7.4 kcal/mol), whereas alcohol **4** is alternatively produced in a Cs(I)-assisted reaction.<sup>[18]</sup>

The above computational data show that, although ketone **3** could be derived from both reaction pathways, the formation of complexes **2a-c** can only be explained by a bias towards the C–H bond activation process. The formation of the quite stable Pd complexes **2**, which is due to the adventitious presence of O<sub>2</sub> in the reaction mixture,<sup>[19]</sup> would divert the metal from the productive cycle leading to ketone **3**, thus explaining why the acylation reaction is not really catalytic when using Cs<sub>2</sub>CO<sub>3</sub> as the base.

Moreover, the above computational data also suggest that the C–H activation process needs CO<sub>3</sub><sup>2-</sup> to take place. Therefore, in the absence of Cs<sub>2</sub>CO<sub>3</sub>, the reaction pathway should switch from C–H activation to nucleophilic addition, allowing us to develop a catalytic coupling process. Indeed, to our delight, this is exactly what occurred when the base Cs<sub>2</sub>CO<sub>3</sub> was changed to Et<sub>3</sub>N. Thus, when **1** was treated with a catalytic amount of Pd<sub>2</sub>(dba)<sub>3</sub> and PPh<sub>3</sub>, in the presence of Et<sub>3</sub>N, tetrahydroisoquinolin-4-ol **4** was isolated in 97% yield (entry 10, Table 1). Similar results were obtained when using either Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd(OAc)<sub>2</sub>/dppe or Pd(OAc)<sub>2</sub>/rac-BINAP as the catalyst (entries 11-13). Both the amount of catalyst and reaction time were successfully reduced (entry 14).

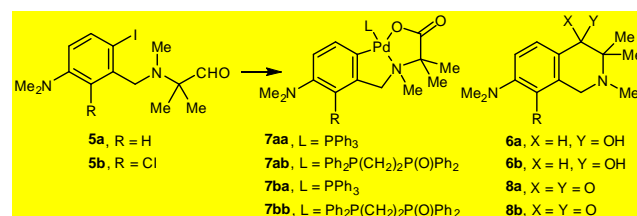
As proposed above, our DFT calculations confirm that the formation of alcohol **4** in the presence of Et<sub>3</sub>N also derives from a nucleophilic addition reaction (Figure 2). Thus, intermediate **INT6-I**, formed through the initial oxidative addition step and subsequent coordination of the carbonyl group, evolves to **INT7-I** via **TS3-I**, a transition state analogous to **TS3**, with a computed activation barrier of  $\Delta G^\ddagger = 16.6$  kcal/mol in a highly exergonic transformation ( $\Delta G_{393} = -15.1$  kcal/mol). As clearly seen in Figure 2, the coordination of the nitrogen atom to the transition metal in **INT7-I** hinders the cisoid conformation essential to  $\beta$ -hydride elimination,<sup>[20]</sup> which explains the non-formation of ketone **3**. As a consequence, **INT7-I** exclusively evolves to alcohol **4** via a Et<sub>3</sub>N-mediated reductive protonation process through **INT8**.<sup>[8b,21]</sup>



**Figure 2.** Computed nucleophilic addition reaction. Energy values are given in kcal/mol. See Figure 1 for additional caption details.

As shown, the results obtained during the optimisation studies with aldehyde **1** (Table 1) and the DFT calculations clearly indicate a competition between the nucleophilic addition and the C–H bond activation processes in the Pd-mediated reactions when using Cs<sub>2</sub>CO<sub>3</sub> as the base. In order to check the effect of the aromatic ring substituents on the balance between both processes, the Pd-promoted reactions of aldehydes **5a,b** in the presence of Cs<sub>2</sub>CO<sub>3</sub> were also explored (Table 2).

**Table 2.** Reactions of aldehydes **5a-b** using Cs<sub>2</sub>CO<sub>3</sub> as the base.<sup>[a]</sup>



Entry	Aldehyde	[Pd] (mol%)/ Ligand (mol%)	Products (Yield [%]) <sup>[b]</sup>
1	<b>5a</b>	Pd <sub>2</sub> (dba) <sub>3</sub> (55)/ PPh <sub>3</sub> (120)	<b>6a</b> (19%) <b>7aa</b> (12%) <b>8a</b> (24%)
2	<b>5a</b>	Pd(OAc) <sub>2</sub> (100)/ dppe (100)	<b>6a</b> (33%) <b>7ab</b> (26%) <b>8a</b> (30%)
3	<b>5b</b>	Pd <sub>2</sub> (dba) <sub>3</sub> (55)/ PPh <sub>3</sub> (120) <sup>[c]</sup>	<b>7ba</b> (32%) <b>6b</b> (10%) <b>8b</b> (35%)
4	<b>5b</b>	Pd(OAc) <sub>2</sub> (100)/ dppe (100)	<b>7bb</b> (47%) <b>8b</b> (9%)

<sup>[a]</sup> Reaction conditions: **5** (0.2 mmol), [Pd] and ligand (see table), and Cs<sub>2</sub>CO<sub>3</sub> (3.0 equiv.) in toluene at 120 °C in a sealed tube for 15 h.

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup> 24 h.

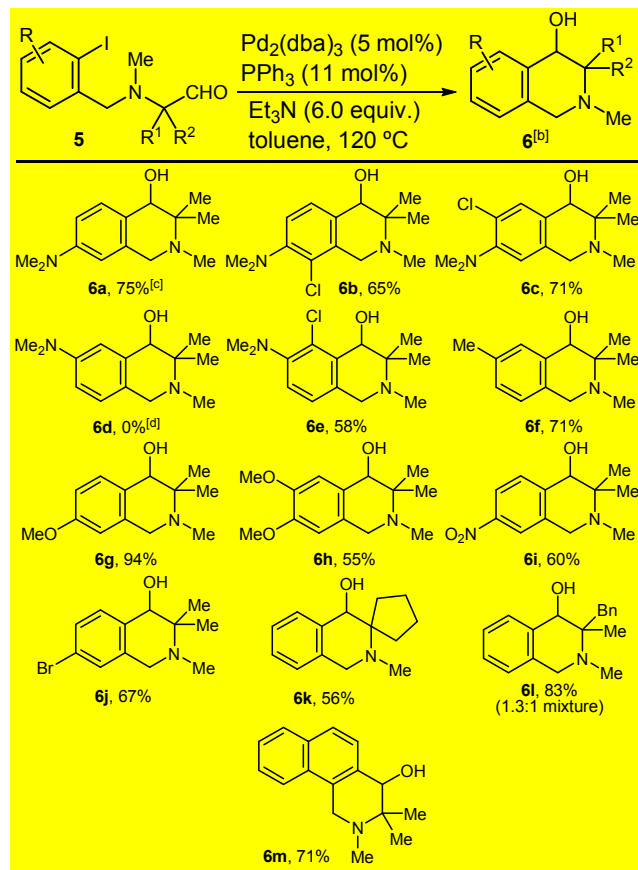
When starting from **5a**, which bears a strong electron-donating dimethylamino group on the

aromatic ring, an increase in the nucleophilic addition alcohol-to-Pd-complex ratio was observed (compare entries 7 and 9 of Table 1 with entries 1 and 2 of Table 2, respectively). Interestingly, the  $\pi$ -donor effect of the dimethylamino group was almost completely neutralised by the introduction of an additional Cl substituent at the aryl group. Thus, the use of PPh<sub>3</sub> as the ligand (entry 3, table 2) gave an alcohol-to-Pd-complex ratio similar to that obtained when starting from **1** under similar conditions. On the other hand, when starting from aldehyde **5b** and using dppe as the ligand, the formation of the Pd-complex became, once again, the predominant reaction pathway (entry 4, table 2).

These results confirm that the nucleophilic addition is strongly related to the electron density on the C(aryl) atom, as suggested previously by us.<sup>[7a]</sup> Indeed, the lower nucleophilicity of this carbon atom in **INT6** (measured by the corresponding NBO-charge of  $q = -0.176$ ) compared to the analogous Pd-intermediate derived from a 2-iodoaniline ( $q = -0.245$ )<sup>[10a]</sup> would also explain why the competition between C–H bond activation and nucleophilic addition is observed in (2-iodobenzylamino)-aldehydes but not in (2-iodoanilino)-aldehydes.<sup>[7a]</sup>

Finally, with the optimised conditions for the intramolecular Pd-catalysed nucleophilic addition in hand, we examined the scope of the reaction for the synthesis of diversely functionalised tetrahydroisoquinolin-4-ols (Table 3).

**Table 3.** Synthesis of tetrahydroisoquinolin-4-ols.<sup>[a]</sup>



<sup>[a]</sup> Reaction conditions: **5** (0.2 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (5 mol%), PPh<sub>3</sub> (11 mol%), and Et<sub>3</sub>N (6.0 equiv.) in toluene at 120 °C in a sealed tube for 24 h.

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup> **6a** (73%) and **5a** (20%) were obtained when using Pd(OAc)<sub>2</sub> (20 mol%) and dppe (25 mol%) as the catalyst.

<sup>[d]</sup> 4-[(*N,N*-Diethylamino)methyl]-*N,N*-dimethylaniline was isolated from the reaction mixture (24%).

The examples presented in Table 3 demonstrate the generality and functional group tolerance of the reaction. Overall, the introduction of substituents on the aromatic ring had little effect on the success of the reaction. Thus, aldehydes bearing electron-donating or electron-withdrawing groups, as well as a combination of both, on the aromatic ring afforded the corresponding nucleophilic addition alcohols in good yields. It is important to note that the failure to prepare **6d** was mainly a consequence of the instability of the 4-(*N,N*-dimethylamino)benzylamino moiety at the starting aldehyde, which underwent fragmentation under the reaction conditions. On the other hand, the bromo-substituted aldehyde **5j** selectively underwent the cyclisation reaction to give **6j**, which would allow further synthetic transformations by transition metal-catalysed coupling reactions. Spirocyclic and naphtho-fused heterocycles were also smoothly prepared.

In summary, we have developed an efficient protocol for the synthesis of tetrahydroisoquinolin-4-ols by means of the Pd-catalysed intramolecular nucleophilic addition of aryl halides to aldehydes. The use of Et<sub>3</sub>N as the base was found to be essential for the formation of isoquinolin-4-ols. In contrast, competition between a CO<sub>3</sub><sup>2-</sup>-mediated concerted metalation-deprotonation process and nucleophilic addition to the carbonyl group was observed when using the base Cs<sub>2</sub>CO<sub>3</sub>, which generated mixtures of the acylation product (i.e. tetrahydroisoquinolin-4-one) and stable tridentate [C,N,O] Pd(II) complexes. The outcome of these reactions provides new insight into the nucleophilic addition versus C–H bond activation dichotomy in Pd-catalysed reactions of amino-tethered aryl iodides and aldehydes. Further exploration to expand the scope of the nucleophilic addition reaction to other heterocyclic systems, as well as to develop an enantioselective process, is underway in our laboratories and will be reported in due course.

## Experimental Section

### Typical Procedure for the Pd(0)-Catalysed Reactions (Table 1, Entry 10)

A mixture of aldehyde **1** (70 mg, 0.22 mmol), Et<sub>3</sub>N (0.18 mL, 1.32 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (20 mg, 0.022 mmol), and PPh<sub>3</sub> (14.5 mg, 0.055 mmol) in toluene (8 mL) was stirred at 120 °C in a sealed tube for 72 h. The reaction mixture was partitioned between saturated NaHCO<sub>3</sub> aqueous solution and Et<sub>2</sub>O. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by

chromatography (from CH<sub>2</sub>Cl<sub>2</sub> to CH<sub>2</sub>Cl<sub>2</sub>-MeOH 8%) to give **4** (41 mg, 97%).

### Supporting Information

Detailed experimental data, characterization and copies of NMR-spectra of new compounds, and computational details.

### Acknowledgements

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