

# Investigation of the aqueous transmetalation of $\pi$ -allylpalladium with indium salt: the use of the Pd(OAc)<sub>2</sub>–TPPTS catalyst

Gianfranco Fontana,<sup>†</sup> André Lubineau and Marie-Christine Scherrmann\*

Laboratoire de Chimie Organique Multifonctionnelle, UMR 8164, ICMMO, Bâtiment 420, Université de Paris-Sud, 91405, Orsay Cedex, France. E-mail: mcscherr@icmo.u-psud.fr; Fax: +33 1 69154715; Tel: +33 1 69154719

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$\pi$ -Allylpalladium complexes could be generated in water by the palladium(0) water soluble catalyst prepared *in situ* from palladium acetate and TPPTS. These complexes were transmetalated with indium to react with benzaldehyde. The aqueous solution of Pd(0)(TPPTS)<sub>n</sub> could be reused without deterioration of the catalyst in the first and second recycling. The system proved to be efficient with primary and secondary allylic substrates. The stereochemical outcome of the allylation through umpolung of allylpalladium, was also studied using models with a restraint conformation.

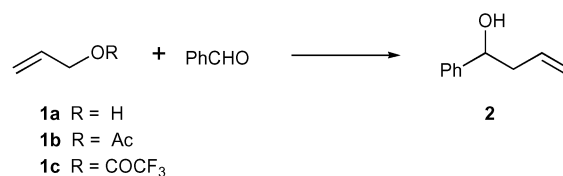
## Introduction

Since the pioneering work of Li and Chan<sup>1</sup> in 1991, indium promoted reactions leading to the formation of carbon–carbon bonds has been the subject of great interest and several reviews have been devoted to this topic.<sup>2</sup> Among these reactions, the condensation of allyl indium species and carbonyl compounds in water has been widely studied from a mechanistic point of view<sup>3</sup> and has also been used for various synthetic applications. In particular, higher carbon sugars have been synthesised by using this reaction as a key step,<sup>4</sup> as well as C-disaccharides as illustrated by recent works from this laboratory.<sup>5</sup> The organoindium species used in the above cited works were generated from allylic halides and indium powder or indium halides. Interestingly, Marshall and Grant showed that allenylindium halides can be generated through transmetalation of a transient allenylpalladium complex with InI.<sup>6</sup> This concept was extended to the preparation of allylindium reagents by Araki and coworkers.<sup>7</sup> They reported the preparation of allylic indium reagents by reductive transmetalation of  $\pi$ -allylpalladium(II) complexes obtained from a large variety of allylic substrates with indium salts in various solvents. Later on, this umpolung methodology was also applied to vinyloxiranes,<sup>8</sup> vinylaziridines,<sup>9</sup> acylnitroso-derived hetero Diels–Alder cycloadducts,<sup>10</sup> or  $\pi$ -allylpalladium species obtained from aryl iodides and allene in the presence of Pd.<sup>11</sup> Recently, a paper from the group of Kim described the Pd-catalyzed allylation of carbonyl compounds with allylic derivatives using In–InCl<sub>3</sub> in aqueous media.<sup>12</sup> On the other hand, a palladium(0) water soluble catalyst prepared from palladium acetate and the sulfonated triphenylphosphine TPPTS<sup>13</sup> has proven to be very efficient in many applications<sup>14</sup> including industrial hydrodimerisation, hydrogenation, C–C bond formation and hydroformylation.<sup>15</sup> This prompted us to examine the use of this catalyst in the umpolung process with water as the solvent.

## Results and discussion

### Reaction of primary allylic compounds

We first addressed the issue of condensation of allylic derivatives **1** and benzaldehyde in a Barbier-type procedure with indium bromide in the presence of palladium(II) acetate and TPPTS (Scheme 1, Table 1). Reactions were also carried out without TPPTS as a comparison.



Scheme 1 Reagents and conditions: see Table 1.

Table 1 Yields and reaction times for the coupling between allylic substrates and benzaldehyde in water at rt. [InBr] : [1] : [PhCHO] : 0.2 : 0.2 : 0.1 M and Pd(OAc)<sub>2</sub> 0.01 M–TPPTS 0.05 M

Entry	Substrate	Time/h	Yield (%) <sup>a</sup>
1	<b>1a</b>	4.5	100 (0) <sup>b</sup>
2	<b>1b</b>	0.5	100 (2) <sup>b</sup>
3	<b>1c</b>	0.4	100 <sup>c</sup> (38) <sup>b</sup>

<sup>a</sup> Yields were determined by RP-HPLC with anisole as internal standard.

<sup>b</sup> Yield obtained without TPPTS after 24 h. <sup>c</sup> Isolated yield.

All the allylic derivatives gave the homoallylic alcohol in quantitative yields. As expected, the time needed for the reaction to go to completion was in good agreement with the leaving group power of OR on the substrate **1**. The influence of this leaving group was even more important in the reactions conducted without TPPTS as the palladium ligand since, after 24 h, 38% of **2** was observed with allyltrifluoroacetate whereas no product was formed starting from the corresponding alcohol, and only 2% when the acetate derivative was the substrate. Furthermore, the result obtained with the acetate confirmed the power of the Pd–TPPTS catalyst in this process since the reaction was completed in 30 min and needed 5 h when tetrakis(triphenylphosphine)palladium(0) was used.<sup>7</sup> This reaction rate enhancement is presumably due to the easier formation of the  $\pi$ -allylpalladium intermediate when a water-soluble catalyst is used. The three substrates were also tested in the same reaction with indium powder as the reductant (Table 2).

Once again, the trifluoroacetate allylic derivatives proved to be the more reactive in this system since the reaction was complete after 1.7 h and the corresponding acetate gave only 11% of the product after 24 h, whereas no product was detected starting from the alcohol. When zero-valent indium was generated *in situ* by aluminium reduction of indium(III) chloride, the reaction time was longer (Table 2, entry 3b) compared to the same allylation carried out using indium powder (Table 2, entry 3a).

<sup>†</sup> Visiting researcher from University of Palermo, Italy.

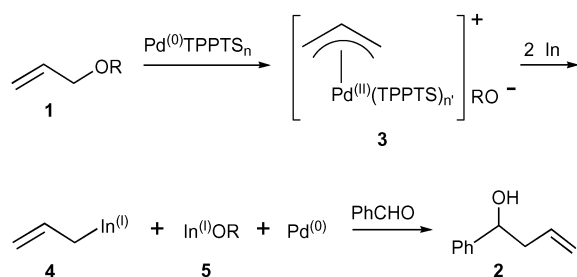
**Table 2** Yields and reaction times for the coupling between allylic substrates and benzaldehyde in water at rt. [In] : [I] : [PhCHO]: 0.2 : 0.2 : 0.1 M and Pd(OAc)<sub>2</sub> 0.01 M–TPPTS 0.05 M

Entry	Substrate	Time/h	Yield (%) <sup>a</sup>
1	<b>1a</b>	24	0 (0) <sup>b</sup>
2	<b>1b</b>	24	11 (1) <sup>b</sup>
3a	<b>1c</b>	1.7	100 <sup>c</sup> (6) <sup>b</sup>
3b <sup>d</sup>	<b>1c</b>	24	100

<sup>a</sup> Yields were determined by RP-HPLC with anisole as internal standard.

<sup>b</sup> Yield obtained without TPPTS after 24 h. <sup>c</sup> Isolated yield. <sup>d</sup> InCl<sub>3</sub> : Al 1 : 10.

Furthermore, we have shown that only one electron is given by one indium atom and therefore, two equiv. of In are needed to reduce one equiv. of allylpalladium **3** into the allylindium(I) **4** (Scheme 2).



**Scheme 2** Formation of **2** through the transmetalation process.

In fact, the conversion of the reaction conducted with one equiv. of allyltrifluoroacetate and one equiv. of indium, with respect to benzaldehyde, did not exceed 50%, even after 48 h (Table 3, entry 1) whereas a 70% yield was obtained with 2 equiv. of indium (Table 3, entry 2). Indeed, whereas the reaction using In(I) salts leads to the formation of allylindium(III) species<sup>7</sup> so that only one equiv. of indium salt is required to reduce Pd(II) intermediate, the coupling with In(0) in water should involve allylindium(I). Actually, Chan and Yang demonstrated<sup>3a</sup> the formation of indium(I) instead of indium(III) compounds in the reactions of indium metal with allyl bromide. We have also observed that the reaction was faster and the yield higher when an excess of allyltrifluoroacetate (Table 2, entry 3) or indium (Table 3, entry 3) was used. The reaction rate dependence of the indium amount in the reaction could be an indication that the limiting step of the process is the Pd–In transmetalation. Furthermore, the In(I) species **5** formed during the second step together with allylindium(I) **4** should be unreactive (Scheme 2).

We then focussed our attention upon the recycling of the catalyst. Indeed, since the homoallylic alcohol was soluble in organic solvents, it could be easily extracted and the aqueous phase containing, amongst other products, Pd(0)(TPPTS)<sub>n</sub>, could be reused for another cycle of reaction. Repeated use of the aqueous layer has proved to be valuable in hydroformylation of olefins or hydrogenation. In the case of palladium(0)–TPPTS catalysed reactions of allylic substrates with nucleophiles, a decrease in the activity of the aqueous phase has been observed from the third recycling, certainly due to the accumulation of side-products in the aqueous phase.<sup>16</sup> We have tested this

**Table 3** Isolated yields and reaction times for the coupling between **1c** and benzaldehyde in water at rt in the presence of In and Pd(OAc)<sub>2</sub> 0.01 M–TPPTS 0.05 M

Entry	<b>1c</b> (equiv.)	In (equiv.)	Time/h	Yield (%)
1	1	1	48	50
2	1	2	24	70
3	2	4	1	100

**Table 4** Yields and reaction times for the recycling in Pd(0)–TPPTS [InBr] : [Ic] : [PhCHO]: 0.2 : 0.2 : 0.1 M

Entry <sup>a</sup>	Pd(OAc) <sub>2</sub> /TPPTS <sup>b</sup> (mol%)	Time/h	Isolated yield (%)
1	5	0.5	100
1a		2.8	60
1b		3.2	52
1c		3.5	41
1d		10	22
2	10	0.5	100
2a		0.5	100
2b		0.7	100
2c		1	82
2d		4	78

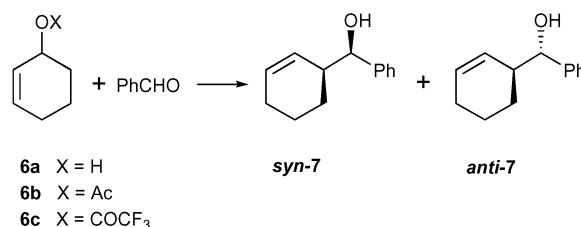
<sup>a</sup> Entries a, b, c, and d are the first, second, third, and fourth recycling. <sup>b</sup> 1 : 5 Ratio.

procedure in the coupling between allyltrifluoroacetate and benzaldehyde with InBr and TPPTS–Pd(OAc)<sub>2</sub> (Table 4).

Two set of experiments were carried out with 5 and 10% Pd(OAc)<sub>2</sub>–TPPTS (1 : 5) (Table 4). At the end of each cycle, the homoallylic alcohol and the remaining allyltrifluoroacetate were extracted with Et<sub>2</sub>O and the aqueous phase was reused by adding the substrates and InBr. With 5% Pd(OAc)<sub>2</sub>–TPPTS (1 : 5) (Table 4, entries 1–1d), the yield decreased significantly and the reaction times increased from the second run. With 10% Pd(OAc)<sub>2</sub>–TPPTS (1 : 5) (Table 4, entries 2–2d) the reaction time increased from the second recycling. The yield remained quantitative for the second recycling but decreased in the two following cycles (82 and 78%, respectively). In both cases (5 or 10% catalyst), the extraction became difficult due to precipitates from the third run so that a filtration (over Celite) was necessary and therefore, some catalyst may be lost during this operation.

#### Reaction of secondary allylic compounds

We then studied the reaction involving a secondary allylic derivative and chose cyclohexyl derivatives **6a–c** as models (Scheme 3).



**Scheme 3** Reagents and conditions: see Table 5.

In the case of the alcohol **6a**, no product was observed even after 72 h whatever the conditions. With the acetate **6b**,<sup>17</sup> a 40% isolated yield was obtained after 17 h with 10% Pd(OAc)<sub>2</sub> and In as the metal (Table 5, entry 3). The ratio of *syn* and *anti* isomers was 95 : 5 as judged by <sup>1</sup>H NMR. This selectivity is comparable to that obtained by Khan and Prabhudas for the indium-mediated coupling between 3-bromocyclohexene and benzaldehyde.<sup>18</sup> This diastereoselectivity is explained satisfactorily considering the currently accepted six-membered cycling transition state between the carbonyl compound and the allylindium cyclohexyl moiety with the phenyl group in an equatorial position. The trifluoroacetate **6c**<sup>19</sup> only gave hydrolysis so that **6a** was obtained in all the conditions we tried (Table 5, entries 7 and 8). Use of a co-solvent was then tested in the condensation reaction involving **6b**. This reaction was carried out in a 2 : 1 H<sub>2</sub>O–EtOH mixture. Compound **7**<sup>18</sup> was obtained with a 88 : 12 diastereoselectivity in 70% or 87% isolated yield after 20 h at rt or 50 °C, respectively (Table 5, entries 5 and 6).

Aiming to determine if the transmetalation was also the limiting step in the case of secondary substrates, we have carried

**Table 5** Conditions, isolated yields and reaction times for the coupling between **6** and benzaldehyde in the presence of Pd(OAc)<sub>2</sub> 0.01 M–TPPTS 0.05 M [InBr] or [In] : [6] : [PhCHO]: 0.2 : 0.2 : 0.1 M

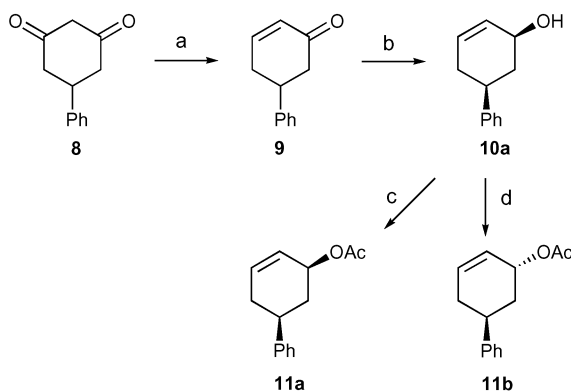
Entry	Substrate	Metal	Conditions	Time/h	Isolated yield (%) ( <i>syn</i> : <i>anti</i> )
1	<b>6a</b>	In	H <sub>2</sub> O, rt	72	0
2	<b>6a</b>	InBr	H <sub>2</sub> O, rt	72	0
3	<b>6b</b>	In	H <sub>2</sub> O, rt	17	40 (95 : 5)
4	<b>6b</b>	InBr	H <sub>2</sub> O, rt	24	25 (90 : 10)
5	<b>6b</b>	In	H <sub>2</sub> O : EtOH, (2 : 1), rt	20	70 (88 : 12)
6	<b>6b</b>	In	H <sub>2</sub> O : EtOH (2 : 1), 50 °C	20	87 (88 : 12)
7	<b>6c</b>	In	H <sub>2</sub> O, rt	24	0
8	<b>6c</b>	InBr	H <sub>2</sub> O, rt	24	0

**Table 6** Isolated yields for the coupling between **6c** and benzaldehyde in H<sub>2</sub>O–EtOH (2 : 1) at 50 °C after 15 h in the presence of In and Pd(OAc)<sub>2</sub> 0.01 M–TPPTS 0.05 M

Entry	In (equiv.)	<b>7</b> (Yield %)	Other isolated products (%)
1	2	70	PhCHO (20)
2	3	86	—
3	4	40	PhCH <sub>2</sub> OH (20)

out experiments using 2, 3, and 4 equiv. of indium (Table 6). The reaction was faster using 3 equiv. since, in this case, 86% of the alcohol **7** was isolated after 15 h while, in the same time, when 2 equiv. of indium were used **7** was obtained in 70% yield and 20% unreacted benzaldehyde was recovered. In the presence of 4 equiv. of indium we obtained only 40% of the coupling product **7** and 20% of benzylic alcohol. We checked that the reduction of benzaldehyde took place only when both palladium acetate and indium were present but we did not investigate further this side-reaction. Since the reaction rate dependence on the amount of indium is not as significant as in the case of the primary substrate **1c**, it is difficult to establish if the limiting step is the formation of the allylpalladium intermediate or the transmetalation.

In order to study the stereochemical outcome of the allylation through umpolung of allylpalladium, we have prepared **11a**<sup>20</sup> and **11b**,<sup>21</sup> models with a restraint conformation (Scheme 4).

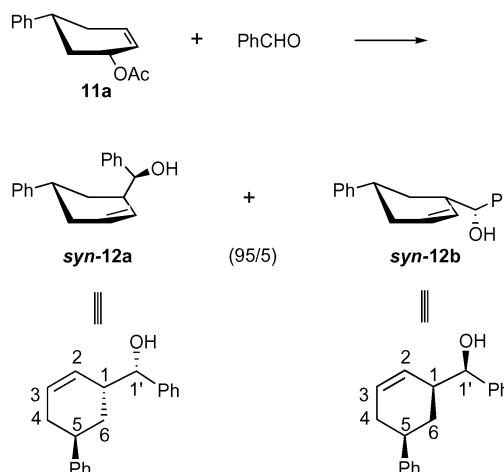


**Scheme 4** Reagents and conditions: (a) i) 2-methyl-1-propanol, APTS, benzene, Dean–Stark apparatus, ii) LiAlH<sub>4</sub>·Et<sub>2</sub>O, iii) aq. HCl; (b) CeCl<sub>3</sub>·7H<sub>2</sub>O, NaBH<sub>4</sub>, MeOH; (c) Ac<sub>2</sub>O, pyridine; (d) PPh<sub>3</sub>, DIAD, AcOH, THF.

Phenylidione **8** was transformed into enone **9**<sup>22</sup> using a method described for the methyl or *tert*-butylidione.<sup>23</sup> Luche reduction of **9** afforded the racemic *cis*-allylic alcohol **10a**<sup>24</sup> with an 86% yield and a very high diastereoselection (*de* > 99%) as judged by <sup>1</sup>H NMR. Acetylation of the *cis*-alcohol **10a** with pyridine and acetic anhydride afforded quantitatively the *cis*-acetate **11a**. Reacting **10a** in the Mitsunobu conditions afforded the *trans*-acetate **11b** as described.<sup>21</sup>

When **11a** was allowed to react with benzaldehyde in the umpolung process under the conditions giving the best results for cyclohexyl derivative **6b** (EtOH–H<sub>2</sub>O 2 : 1, In, 50 °C), the

coupling products *syn*-**12a** and *syn*-**12b** were obtained after 24 h in a 95 : 5 ratio in 58% overall yield (Scheme 5).



**Scheme 5** Reagents and conditions: Pd(OAc)<sub>2</sub> 0.01 M–TPPTS 0.05 M, [In] : [**11a**] : [PhCHO]: 0.2 : 0.2 : 0.1 M, EtOH–H<sub>2</sub>O 2 : 1, 50 °C, 24 h.

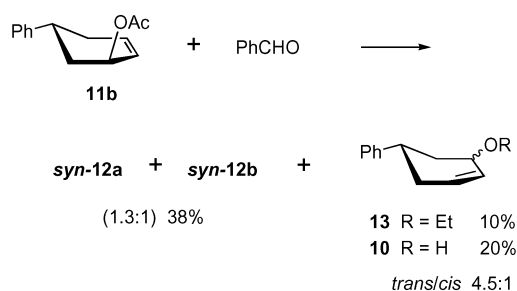
In comparison, the *cis* acetate **11a** (2 equiv.) was also allowed to react with benzaldehyde in THF with Pd(PPh<sub>3</sub>)<sub>4</sub> (10%) and InBr (2 equiv.). After 24 h *syn*-**12a** and *syn*-**12b** were obtained in a 90 : 10 ratio in only 20% yield showing that the reaction is much faster in aqueous medium using a water-soluble catalyst, the selectivity being comparable.

The relative *syn* orientation of the C1'–OH and C1–C6 bonds in *syn* **12a** and *syn*-**12b** was deduced from comparison of <sup>1</sup>H NMR spectra with those reported in the literature for **7**.<sup>18</sup> The *trans* orientation of the two cyclohexenyl substituents (phenyl and 1'-hydroxybenzyl) in *syn*-**12a** was also established on the basis of <sup>1</sup>H NMR data. In fact, the axial H6 ( $\delta$  1.84 ppm) exhibits a large coupling constant of 11.5 Hz with H5 and a small coupling constant of 6.0 Hz with H1, in addition to the large *gem*-coupling (17.5 Hz) with equatorial H6. This deduction was confirmed by the observation of a NOE between H1' and H5. In the spectrum of *syn*-**12b**, the signal of axial H6 ( $\delta$  1.70 ppm) is a ddd with three large identical coupling constants of 12.0 Hz consistent with an equatorial and quasi-equatorial position for the 5-phenyl and the 1-(1'-hydroxybenzyl) respectively.

In the same conditions, the *trans* isomer **11b** afforded a mixture of the coupling products **12a** and **12b** in a 1.3 : 1 ratio with 38% yield, together with ethoxy and hydroxy-allylic compounds **13**<sup>25</sup> and **10** as 4.5 : 1 *trans* : *cis* mixtures in **10** and 20% yield, respectively (Scheme 6).

When the reaction was carried out in THF with Pd(PPh<sub>3</sub>)<sub>4</sub> and InBr, no product was formed and the *trans* acetate **11b** was recovered without epimerisation suggesting that the  $\pi$ -allylpalladium was not formed in these conditions.

The most plausible explanation for the results obtained in aqueous medium comes from the examination of the transition states of the involved reactions (Scheme 7). In the first step, the  $\pi$ -allylpalladium(II) **15a** and **15b** are formed through a transition state resembling **14a** and **14b**. The transition state **14b** should



**Scheme 6** Reagents and conditions: Pd(OAc)<sub>2</sub> 0.01 M–TPPTS 0.05 M, [In] : [11b] : [PhCHO]: 0.2 : 0.2 : 0.1 M, EtOH–H<sub>2</sub>O, 50 °C, 24 h.

be of lower energy than **14a** because of steric repulsions in **14a** where both the acetate leaving group and the phenyl group are in an axial position.<sup>26</sup> Transmetalation of **15a** or **15b** with In(0) gave allyl indium(i) **16a** or **16b** with retention of configuration as observed for transmetalation with other metals.<sup>27</sup> From the two possible six-membered transition states in each case, those with the phenyl group from benzaldehyde in the equatorial position is more favourable, thus *syn*-**12a** is obtained from **18a** and *syn*-**12b** is obtained from **18b**. Considering the transition states **18a** and **18b**, it becomes clear that the reaction with the aldehyde is easier in the case of the *cis*-acetate **11a** since in **18a**, the phenyl group, substituent from the cyclohexene, is in an equatorial position, while it is in an axial position in **18b** formed through multiple steps from the *trans*-acetate **11b**.

The formation of *syn*-**12a** from **11b** can be explained by an isomerisation of the starting acetate **11b** into **11a**. In fact, when we isolated unreacted **11** from an incomplete reaction of **11b** (after 7 h), we obtained a mixture of *cis* and *trans* acetates **11a** and **11b** in a 1 : 1 ratio as judged by <sup>1</sup>H NMR. Such an isomerisation of cyclohexenyl derivatives in a palladium-catalysed reaction has already been described.<sup>28</sup> Since **13** was obtained, in majority, with retention of configuration at C-1, we hypothesised that it was the result of a Tsuji–Trost reaction between **15b** and the nucleophilic solvent EtOH. This product

**Table 7** Yields for the reaction of *cis*-**11a** and *trans*-**11b** with Pd(OAc)<sub>2</sub> 0.01 M–TPPTS 0.05 M in H<sub>2</sub>O–EtOH (2 : 1) at 50 °C

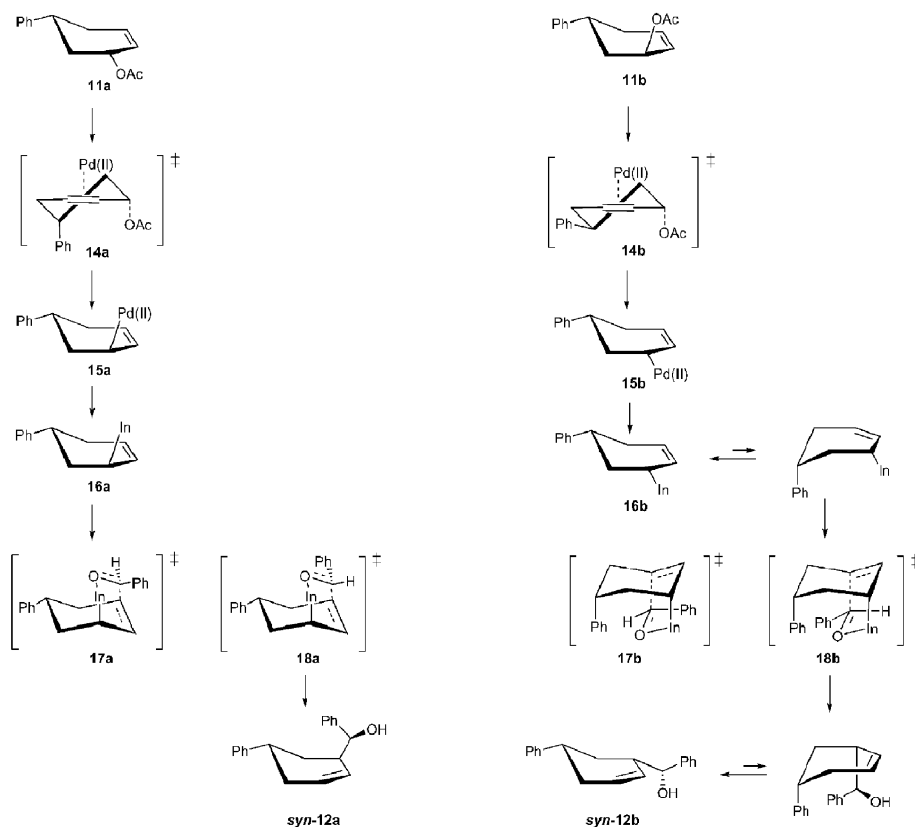
Substrate	<b>13</b>		<b>10</b>	
	Yield%	<i>trans</i> : <i>cis</i>	Yield (%)	<i>trans</i> : <i>cis</i>
<i>cis</i> - <b>11a</b>	28	1.2 : 1	55	1 : 1
<i>trans</i> - <b>11b</b>	34	3.2 : 1	51	2.5 : 1

was obtained in 4.5 : 1 *trans* : *cis* mixture showing that the Tsuji–Trost reaction is faster than the isomerisation of **11b**. The formation of the alcohol **10** can be the result of the hydrolysis of the starting acetate. In fact, while **11a** or **11b** were stable in EtOH–H<sub>2</sub>O at 50 °C for 48 h, in the presence of TPPTS, 10% of alcohol **10** was obtained without epimerisation in both cases. We have also treated the two acetates with the Pd–TPPTS catalyst in the same conditions (EtOH–H<sub>2</sub>O 2 : 1, 50 °C) and isolated, after 72 h, compounds **13** and **10** with 28 and 55% yield respectively, without *cis* : *trans* selectivity from the *cis*-substrate **11a**, whereas the *trans* isomer **11b** afforded **13** and **10** in 34 and 51% yield with an excess of the *trans*-alkoxy or hydroxy product (Table 7).

The lack of selectivity in the case of the *cis*-substrate **11a** could be explained by the isomerisation of **11a** into **11b** through the allylpalladium intermediate **15a**, the rate of the isomerisation being faster than both the Tsuji–Trost reaction and the hydrolysis, whereas the Tsuji–Trost reaction and the hydrolysis are slightly faster than the isomerisation of **11b** into **11a**. Furthermore, as no alkoxy or hydroxy products were observed from **11a** in the reaction with benzaldehyde it should be deduced that the transmetalation Pd–In is faster in the case of **15a** than the Tsuji–Trost reaction and the hydrolysis and thus than the isomerisation.

## Conclusion

We have shown that π-allylpalladium complexes could be favourably generated in water by the palladium(0) water



**Scheme 7** Rationalisation of the formation of *syn*-**12a** and *syn*-**12b**.

soluble catalyst prepared *in situ* from palladium acetate and TPPTS. These complexes were transmetalated with indium to react with benzaldehyde. Best results were obtained with InBr as the source of indium and trifluoroacetate as the leaving group in the case of primary substrate whereas acetate leaving group gave the best yields in the case of secondary substrates. Furthermore, when using 10% of the catalyst, the aqueous layer containing Pd(0)(TPPTS)<sub>n</sub> could be reused for two more cycles of reaction without decrease of the yield or increase of the reaction time. Studies of the stereochemical outcome of the reaction showed that the indium species are formed with a global inversion of configuration. When steric effects disfavour the overall process, a complex mixture was obtained, coming from the starting material isomerisation, a Tsuji–Trost reaction with the nucleophilic solvent, and an hydrolysis of the ester.

## Experimental

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. All solvents were dried over standard drying agents and were freshly distilled prior to use. Flash column chromatography was performed on silica gel 60A C.C. (6–35 μ). Reactions were monitored by TLC on silica gel 60 F<sub>254</sub> with detection by charring with phosphomolybdic acid.

### General procedure for the reactions between benzaldehyde and primary allylic substrates 1 followed by HPLC analysis

A mixture of Pd(OAc)<sub>2</sub> (11.2 mg, 0.05 mmol) and TPPTS (142 mg, 0.25 mmol) in 5 mL of water was stirred for 30 min. To 1 mL of this solution were added benzaldehyde (10.6 mg, 0.10 mmol), allylic substrate (0.20 mmol) and In (22.9 mg, 0.20 mmol) or InBr (38.9, 0.20 mmol). The resulting mixture was stirred vigorously for the time indicated in the Tables. A solution of anisole in CH<sub>3</sub>CN (1.2 mg mL<sup>-1</sup>, 2 mL) was added as well as 2 mL of MeOH. The mixture was centrifuged (15,000 tr min<sup>-1</sup> for 5 min), 0.5 mL of the supernatant was diluted with 0.5 mL of CH<sub>3</sub>CN and the solution was filtered through a 0.45 μm syringe filter. A 20 μL aliquot of the solution was analysed by HPLC (Hypersil C18, 125 × 4.6 mm, 5 μm; mobile phase: CH<sub>3</sub>CN–H<sub>2</sub>O 65 : 35 at 1 mL min<sup>-1</sup>). The chromatograms were integrated at 220 nm and the yields were deduced by comparison with a standard curve obtained from dilutions of **2** (retention time 9.2 min) and anisole (retention time 17.7 min).

### General procedure for the reactions between benzaldehyde and primary allylic substrates 1 or secondary allylic substrate 6 followed by isolation of 2 or 7

The reaction mixture was prepared as indicated above in water or water–EtOH (2 : 1) in the case of **6**, generally on a 1 mmol allylic substrate scale. After the time indicated in the Tables, the reaction mixture was filtrated over a short pad of Celite, extracted three times with ether (5 mL), the organic layer was washed with aq. saturated NaHCO<sub>3</sub> (10 mL) and brine (10 mL), dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography (petroleum ether–EtOAc 7 : 1) to give **2** from **1** or **7** from **6**.

### General procedure for the recycling experiments

A mixture of Pd(OAc)<sub>2</sub> (11.2 mg, 0.05 mmol or 22.4 mg, 0.10 mmol) and TPPTS (142 mg, 0.25 mmol or 284 mg, 0.50 mmol) in 5 mL of water–EtOH (2 : 1) was stirred for 30 min. To this solution were added benzaldehyde (53 mg, 0.50 mmol), allyltrifluoroacetate (154 mg, 1.00 mmol) and InBr (194 mg, 1.00 mmol). The resulting mixture was stirred vigorously for the time indicated in Table 4 and filtered over a short pad of Celite, extracted three times with ether (5 mL), the organic layer was treated as described above. The aqueous phase was reused by

adding benzaldehyde, allyltrifluoroacetate and InBr as described above.

**5-Phenyl-2-cyclohexenone**<sup>22</sup> (**9**). A solution of 5-phenyl-cyclohexane-1,3-dione (5.00 g, 26.50 mmol) *p*-toluenesulfonic acid monohydrate (68 mg, 0.35 mmol) and 2-methyl-1-propanol (60 mL) in benzene (60 mL) was refluxed overnight into a Dean–Stark apparatus. The resulting red solution was cooled to rt and concentrated under reduced pressure to a volume of 40 mL to which ethyl acetate (40 mL) was added. The solution was washed three times with aq 10% NaOH (20 mL), and then with brine (20 mL). The organic layer was dried (MgSO<sub>4</sub>) and concentrated to give a yellow oil, which was solubilised in diethyl ether (150 mL). LiAlH<sub>4</sub> (780 mg, 20.50 mmol) was added to this solution at 0 °C and the reacting mixture was stirred for 2 h at rt and then poured into iced water and neutralized with aq. 10% HCl. The mixture was stirred at rt for 0.5 h and the organic layer was separated. The aqueous layer was extracted twice with ether (100 mL). The combined organic layers were washed with sat. NaHCO<sub>3</sub> (50 mL) and brine (50 mL), dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography (petroleum ether–EtOAc from 7 : 1 to 6 : 1) to give compound **9** (4.10 g, 90%) as a colourless oil whose spectral properties were in accordance with those previously reported.<sup>22</sup>

**cis-5-Phenyl-2-cyclohexen-1-ol**<sup>24</sup> (**10a**). To a solution of **9** (500 mg, 2.91 mmol) and CeCl<sub>3</sub>·7 H<sub>2</sub>O (1.10 g, 2.91 mmol) in methanol (30 mL) at 0 °C was added NaBH<sub>4</sub> (120 mg, 2.91 mmol). The solution was stirred at 0 °C for 2.5 h, then the solvent was removed under reduced pressure and the residue was partitioned between water and EtOAc, the organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography (petroleum ether–EtOAc 7 : 1) to give known<sup>24</sup> **10a** (436 mg, 86%) as a white solid.

**cis-5-Phenyl-2-cyclohexen-1-yl acetate**<sup>20</sup> (**11a**). A solution of **10a** (100 mg, 0.57 mmol), pyridine (2 mL) and acetic anhydride (1 mL) was kept at rt overnight, then concentrated. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and iced aq. 5% HCl. The organic phase was washed with water, dried (MgSO<sub>4</sub>) and concentrated to afford known<sup>20</sup> **11a** (124 mg, 100%).

**trans-5-Phenyl-2-cyclohexen-1-yl acetate**<sup>21</sup> (**11b**). To a solution of **10a** (100 mg, 0.57 mmol), triphenylphosphine (228 mg, 0.86 mmol) and glacial acetic acid (42 μL, 0.75 mmol) in THF (2 mL) was added dropwise DIAD (150 μL, 0.75 mmol) at 0 °C. After 5 min, the solution was concentrated and the residue was purified by flash chromatography (petroleum ether–EtOAc 9 : 1) to give known<sup>21</sup> **11b** (111 mg, 90%).

### Procedure for the reaction between benzaldehyde and 11a

A mixture of Pd(OAc)<sub>2</sub> (22.4 mg, 0.10 mmol) and TPPTS (284 mg, 0.50 mmol) in a 2 : 1 water–EtOH mixture (10 mL) was stirred for 30 min. To this solution were added benzaldehyde (106 mg, 1.00 mmol), **11a** (432 mg, 2.00 mmol) and In (684 mg, 2.00 mmol). The resulting mixture was stirred vigorously at 50 °C for 24 h. The reaction mixture was filtered over a short pad of Celite, extracted three times with ether (10 mL), the organic layer was washed with aq. saturated NaHCO<sub>3</sub> (20 mL) and brine (20 mL), dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography (petroleum ether–EtOAc from 10 : 1 to 6 : 1) to give first *syn*-**12a** (145 mg, 55%).

IR  $\nu_{\max}$  cm<sup>-1</sup>, NaCl: 3404, 3061, 3026, 2915, 1601, 1493, 1431, 1020, 948, 910, 765, 699. EIMS 70 eV, *m/z* (%): 246 (11, M – H<sub>2</sub>O), 172 (3), 158 (19), 155(19), 129 (6), 115 (8), 107 (100), 104 (31), 91 (18), 79 (17), 77 (11), 68 (3).  $\delta_{\text{H}}$  (250 MHz, CDCl<sub>3</sub>) 1.84 (1 H, ddd,  $J_{6\text{ax},6\text{eq}}$  17.5,  $J_{6\text{ax},5}$  11.5,  $J_{6\text{ax},1}$  6.0 Hz, H6 axial), 1.91 (1 H, d,  $J_{1',\text{OH}}$  2.5 Hz, OH), 2.10–2.25 (2 H, m, H6 equatorial, H4 axial), 2.36 (dddd,  $J_{4\text{ax},4\text{eq}}$  18.0 Hz,  $J_{4\text{eq},3} = J_{4\text{eq},5}$  5.0,  $J_{4\text{eq},2}$  1.5 Hz, H4 equatorial), 2.50–2.62 (1 H, m, H1), 2.99 (1 H, dddd,  $J_{4\text{ax},5}$  9.0,  $J_{4\text{eq},5}$  5.0 Hz H-5), 4.68 (1 H, dd,  $J_{1,1'}$  7.5 Hz, H1'), 5.34–5.42

(m, 1 H, H2), 5.92 (1 H, dddd,  $J_{2,3}$  10.0,  $J_{3,4ax}$  2.5,  $J_{1,3}$  2.0 Hz, H3), 7.18–7.41 (10 H, m, Ar).  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 30.6 (C6), 32.7 (C4), 36.0 (C1), 42.0 (C5), 76.8 (C1'), 126.0–129.9 (C2, C3, Ar); elemental analysis found C 86.46, H 7.66, C<sub>19</sub>H<sub>20</sub>O requires C 86.32, H 7.63%.

Eluted second was *syn*-**12b** contaminated by 5% of *syn*-**12a** (8 mg, 3%).

$\delta_H$  (250 MHz, CDCl<sub>3</sub>) 1.70 (ddd, 1 H,  $J_{6ax,6eq} = J_{6ax,5} = J_{6ax,1} = 12.0$  Hz, H6 axial), 1.85–2.05 (m, 2 H, H4a and H6 equatorial), 2.12–2.40 (m, 2 H, H1 and H4b), 2.72–2.90 (m, 2 H, H5 and OH), 4.72 (d, 1 H,  $J_{1,1'}$  5.5 Hz), 5.55–5.65 (m, 1 H, H2), 5.90–6.00 (m, 1 H, H3), 7.20–7.40 (m, 20 H, Ar).  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 29.7 (C6), 32.3 (C4), 36.2 (C1), 45.0 (C5), 77.3 (C1'), 126.0–130.0 (C2, C3, Ar).

#### Procedure for the reaction between benzaldehyde and **11b**

Benzaldehyde (106 mg, 1 mmol) was coupled with **11b** (432 mg, 2 mmol) as described for **11a**. The residue was purified by flash chromatography (petroleum ether–EtOAc from 20 : 1 to 6 : 1) to give first **13<sup>25</sup>** (40 mg, 10%) as an inseparable *trans* : *cis* 4.5 : 1 mixture, then *syn*-**12a** (13.4 mg, 5%), and a 1 : 1 mixture of *syn*-**12a** and *syn*-**12b** (86.5 mg, 33%). Eluted last was **10<sup>24</sup>** (70 mg, 20%) as an inseparable *trans* : *cis* 4.5 : 1 mixture.

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