

# New hetero-bimetallic Pd-Cu catalysts for the one-pot indole synthesis via the Sonogashira reaction

Sandra Chouzier<sup>a</sup>, Markus Gruber<sup>a,b</sup>, Laurent Djakovitch<sup>a,\*</sup>

<sup>a</sup> Institut de Recherches Sur la Catalyse—UPR CNRS 5401, 2 Avenue Albert Einstein, 69626 Villeurbanne, France

<sup>b</sup> Technische Universität München, Anorganisch-Chemisches Institut, Lichtenberg Strasse 4, 85747 Garching, Germany

Received 22 August 2003; accepted 30 November 2003

## Abstract

For the first time the one-pot indole synthesis catalyzed by new heterogeneous bimetallic [Pd-Cu] catalysts is described. Based on a domino reaction, 2-phenylindole was synthesized via the Sonogashira C–C coupling reaction with up to 100% yield in short reaction times. In all cases, a complete selectivity towards the indole compound is observed. The heterogeneous catalysts, while being deactivated during the extraction procedure in air, remain highly active and selective when used in a continuous manner.

© 2003 Elsevier B.V. All rights reserved.

**Keywords:** One-pot synthesis; Sonogashira reaction; Zeolite; Hetero-bimetallic catalyst; Domino reaction; Indole

## 1. Introduction

The indole nucleus is an important substructure of numerous natural and pharmacologically active compounds such as bufotenine or lysergide [1]. The chemistry of indoles is a well-studied field and many methods have been developed for their synthesis [2–4]. Generally, the availability of the starting materials and their compatibility with the reaction conditions dictate the synthetic method towards the target molecule. The oldest and most widely used method is the “Fischer indole synthesis”, in which an *N*-aryl hydrazone undergoes acid-catalysed or thermal sigmatropic rearrangement to generate the indole skeleton [3]. However, this method is not regioselective if used for the synthesis of substituted indoles with electron-withdrawing groups and results in the formation of a mixture of isomers [4]. Such problems have been partially resolved by the use of the so-called “solid-phase indole synthesis” which is really applicable to the generation of an indole-based combinatorial library [5]. However, the use of these solid-phase synthetic methods remains limited to synthesis at the laboratory scale and is not reasonably applicable for industrial preparations of indole compounds.

The last decade has seen the development of the “palladium-copper” catalyzed indole synthesis via the Sonogashira cross-coupling reaction leading to a useful heteroannulation of 2-iodoanilines with alkynes [6]. Compared to classical methods this approach presents many advantages. (1) The Sonogashira reaction has proven to be a reliable reaction, leading to a powerful method for the synthesis of arylethylenes in high yields. (2) It is widely employed as a key step for the synthesis of natural and pharmaceutical products. (3) It tolerates a broad variety of functional groups [7]. (4) Applied to the synthesis of substituted indoles, it is completely regioselective as the 2,3-regioselectivity in the indole-ring is directed by the choice of the alkyne used in the Sonogashira cross-coupling [8].

Generally, the indole synthesis via the Sonogashira reaction is carried out in two steps. (1) The palladium-copper catalyzed Sonogashira cross-coupling between a 2-aminoaryl halide and an alkyne. (2) A copper(I) or palladium(II) catalyzed ring-closure by hydroamination/cyclization giving the indole product. The two step procedure is generally required since usually the Sonogashira cross-coupling proceeds efficiently under mild reaction conditions, while the intramolecular heteroannulation, which depends on the amino substituent, generally requires stronger reaction conditions, such as the use of strong bases and high temperature, in order to obtain high conversion. However, when the aniline is activated, e.g. substituted by electron withdrawing

\* Corresponding author. Tel.: +33-4-72-44-53-81; fax: +33-4-72-44-53-99.

E-mail address: [laurent.djakovitch@catalyse.cnrs.fr](mailto:laurent.djakovitch@catalyse.cnrs.fr) (L. Djakovitch).

groups such as sulfonyl, the heteroannulation can occur under relatively mild reaction conditions [9].

However, for industrial applications these methodologies remain too expensive, due mainly to the costs linked to handling, separation and refining procedures. An emerging strategy to minimize these difficulties is the so-called one-pot synthesis based on domino (or cascade) and tandem (or consecutive) reactions. While several methods—mainly based on the Fischer indole synthesis—have been reported for one-pot indole syntheses [2–4,10], to our knowledge no general simple and economical procedure has been described via the Sonogashira cross-coupling reaction with heterogeneous catalysts.

We report herein an efficient one-pot indole synthesis via the Sonogashira cross-coupling reaction catalyzed by homogeneous and heterogeneous catalysts based on hetero-bimetallic complexes.

## 2. Experimental

All preparations, manipulations and reactions were carried out under argon, including the transfer of the catalyst to the reaction vessel. All glassware was base- and acid-washed and oven dried.

The zeolite NaY was purchased from Sigma–Aldrich Chemical (LZ-Z-52). Alumina (Aluminiumoxid C) and silica (Aerosil 200) were obtained from Degussa AG. Silica Aerosil 200 was agglomerated prior to use by treatment with water. After evaporation and drying at 120 °C for 3 days, the resulting material was crushed and sieved to give a selected fraction with a particle size of 40–60 mesh. BET of a silica sample dehydroxylated at 500 °C under 10<sup>-5</sup> mmHg for 6 h gave the following characteristics: specific surface = 240 ± 4 m<sup>2</sup>/g, pore diameter = 32–36 nm. All supports were dried under 5 × 10<sup>-2</sup> mmHg at 120 °C for 48 h before synthesis of the catalyst 6–16. All other chemicals (organic reagents and solvent) were deaerated by argon flow before they were used. The catalysts were stored, after drying, under Ar atmosphere.

Solution NMR spectra of the organic products were recorded with a Bruker AM 250 spectrometer (<sup>1</sup>H NMR were referenced to the residual protio-solvent: CDCl<sub>3</sub>, δ = 7.25 ppm and D<sub>6</sub>-DMSO, δ = 2.49 ppm; <sup>13</sup>C NMR were referenced to the C-signal of the deuterio solvent: CDCl<sub>3</sub>, δ = 77 ppm and D<sub>6</sub>-DMSO, δ = 39.5 ppm).

Solid-state <sup>1</sup>H and <sup>13</sup>C MAS NMR spectra of the Pd loaded zeolites were recorded on a Bruker MSL 300 spectrometer operating at a field strength of 7.05 T. For the <sup>1</sup>H and <sup>13</sup>C MAS NMR spectra approximately 300 mg of the sample were packed into 4 mm ZrO<sub>2</sub> Bruker rotors with Kel-F caps. <sup>1</sup>H and <sup>13</sup>C NMR shifts were referenced to an external sample of adamantane; the proton signal was set to 2 ppm and the low-frequency signal of the <sup>13</sup>C spectrum to 29.472 ppm relative to TMS. <sup>1</sup>H MAS NMR spectra were recorded at a sample spinning speed of 15 kHz. <sup>13</sup>C CP-MAS NMR spectrum was recorded at a spinning speed of 8 kHz,

using high-power proton decoupling, with a recycle time of 8 s and a contact time of 5 ms. GC were performed on a HP 4890 chromatograph equipped with a FID detector, a HP 6890 autosampler and a HP-5 column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness). Nitrogen was used as the carrier gas. GC–MS were performed on a HP 6890 chromatograph equipped with a Mass detector HP 5973 and a HP-5 MS column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness). Helium was used as the carrier gas. The experimental error was Δ<sub>rel</sub> = ±10%.

Continuous wave EPR spectra were recorded at 130 K on a JEOL JES-RE2X system at X-band frequency. The spectra were measured at a microwave frequency of 9.05 GHz with a microwave power of 5 mW, with a modulation amplitude of 0.4 mT, a sweep time of 4 min, a sweep width of 100 mT, a time constant of 0.1 s and a modulation frequency of 100 kHz. The microwave frequency was measured with a microwave frequency Adventest R5372. The temperature was monitored with a JEOL ES DVT2 temperature controller equipped with a calibrated thermocouple. The *g* and *A* values were determined using Mn<sup>2+</sup> (nuclear spin: 5/2) embedded in MgO as standard (the fourth low field line as *g* = 1.981) and DPPH (2,2-diphenyl-1-picryl-hydrozyl; *g* = 2.0036) as additional standard. Experimental errors: Δ*g* = ±0.003, Δ*A* = ±5 × 10<sup>-4</sup> and Δ(Δ*B*<sub>pp</sub>) = ±10 G.

Flash chromatography was performed at a pressure slightly greater than atmospheric pressure using silica (Merck Silica Gel 60, 230–400 mesh). Thin layer chromatography was performed on Fluka Silica Gel 60 F<sub>254</sub>.

After drying, calcination and reduction of the catalysts (in order to remove all organic material) the absolute palladium and copper content was determined by ICP–AES from a solution obtained by treatment with a mixture of HBF<sub>4</sub>, HNO<sub>3</sub> and HCl in a Teflon reactor at 180 °C.

### 2.1. Catalysts preparation

#### 2.1.1. Preparation of the [Pd(Hhp)<sub>2</sub>Cl<sub>2</sub>] complex 4 [11]

4 mmol of 2-hydroxypyridine (Hhp) (380 mg) was added to 2 mmol (590 mg) of Na<sub>2</sub>PdCl<sub>4</sub> in water (10 ml). After 12 h the yellow precipitate was filtered off and washed carefully with 4 × 4 ml water and then with 3 × 10 ml ether. The product was dried under vacuum for 3 days to give 640 mg (87% yield) of compound 4 as a microcrystalline yellow solid.

<sup>1</sup>H NMR (D<sub>6</sub>-DMSO): 8.14 (pseudo-d, 1H, C<sub>5</sub>H<sub>4</sub>NOH); 7.96 (pseudo-d, 1H C<sub>5</sub>H<sub>4</sub>NOH); 7.62 (broad pseudo-d, 1H C<sub>5</sub>H<sub>4</sub>NOH); 7.59 (broad pseudo-d, 1H C<sub>5</sub>H<sub>4</sub>NOH); 6.78 (broad pseudo-t, 2H C<sub>5</sub>H<sub>4</sub>NOH); 6.69 (broad pseudo-d, 2H C<sub>5</sub>H<sub>4</sub>NOH).

<sup>13</sup>C NMR (D<sub>6</sub>-DMSO): 162.33 and 163.06 (C<sub>q</sub>-C<sub>5</sub>H<sub>5</sub>NO); 149.45 and 148.60 (*o*-CH-C<sub>5</sub>H<sub>5</sub>NO); 141.51 and 140.98 (*p*-CH-C<sub>5</sub>H<sub>5</sub>NO); 116.70 and 116.56 (*m*-CH-C<sub>5</sub>H<sub>5</sub>NO); 112.02 (*m*-CH-C<sub>5</sub>H<sub>5</sub>NO).

### 2.1.2. Preparation of the homogeneous $[PdCl(hp)_3Cu]_2$ catalyst **5** [12]

4 mmol of 2-hydroxypyridine (Hhp) (380 mg) was added to 2 mmol (590 mg) of  $Na_2PdCl_4$  in ethanol (30 ml). After 12 h the yellow suspension was treated with 2 mmol (340 mg) of  $CuCl_2 \cdot 2H_2O$  and 2 mmol (190 mg) of Hhp to give an orange compound. After 24 h the orange precipitate was filtered off and washed carefully with  $4 \times 5$  ml of ethanol. The product was dried under vacuum for 3 days to give 805 mg (82% yield) of compound **5** as a microcrystalline orange solid.

EPR X-band spectra (130 K):  $g_{\perp} = 2.078$ ;  $g_{\parallel} = 2.362$ ;  $A_{\parallel} = 12.09$  mT. Elemental analysis:  $C_{34}H_{36}N_6O_8Pd_2Cu_2Cl_2$  [found (calculated)]: C 38.55 (38.35), H 3.42 (3.43), N 7.87 (7.90), Pd 19.87 (19.91), Cu 11.80 (11.83), Cl 6.50 (6.57).

### 2.1.3. General procedure for heterogenization of $[PdCl(hp)_3Cu]_2$ complex **5**

An amount of 0.2 mmol of **5** in ethanol (3 ml) was added to a suspension of the metal oxide ( $SiO_2$  or  $Al_2O_3$ ) in ethanol (10 ml). Stirring for 12 h at room temperature, the solvent is evaporated. Finally, the solid was dried under vacuum at room temperature for 24 h.

On silica (Catalyst **6**), a slightly orange solid was obtained. Elemental analysis: 0.77 wt.% Pd and 0.54 wt.% Cu.

On alumina (Catalyst **7**), a slightly green solid was obtained. Elemental analysis: 0.82 wt.% Pd and 0.53 wt.% Cu.

### 2.1.4. Preparation of the $[Pd(Hhp)_2Cl_2]$ -NaY **8**

2 mmol (590 mg) of  $Na_2PdCl_4$  were added to a suspension of NaY (3 g) in 200 ml of water. After 1 h, 4 mmol (380 mg) of Hhp were added. The resulting mixture was allowed to stir at room temperature for 4 days. The suspension was filtered off and washed with water until no trace of chloride was detected in the clear filtrate by  $AgNO_3$  test. The Pd loaded zeolite was then allowed to dry at room temperature for 3 days and then under high vacuum for additional 48 h to give a slightly brown material.

$^{13}C$  MAS-NMR: 164.21 ( $\bar{C}$ -O,  $C_5H_5NO$ ); 150.18 ( $o$ - $\bar{C}H$ ,  $C_5H_5NO$ ); 143.95 ( $p$ - $\bar{C}H$ ,  $C_5H_5NO$ ); 118.81 ( $m$ - $\bar{C}H$ ,  $C_5H_5NO$ ); 111.99 ( $m$ - $\bar{C}H$ ,  $C_5H_5NO$ ). Elemental analysis: 5.57 wt.% Pd.

### 2.1.5. Preparation of the $[Pd-Cu]$ -NaY catalyst **9**

2 mmol (590 mg) of  $Na_2PdCl_4$  were added to a suspension of NaY (3 g) in 200 ml of water. After 1 h, 4 mmol (380 mg) of Hhp were added. After 4 days at room temperature under stirring, 2 mmol (340 mg)  $CuCl_2 \cdot 2H_2O$  and 2 mmol (190 mg) of Hhp were added. The suspension was stirred for 4 days, then filtered off and washed with water until no trace of chloride was detected in the clear filtrate by  $AgNO_3$  test. The  $[Pd-Cu]$ -loaded zeolite **9** was then allowed to dry at room temperature for 3 days and

then under high vacuum for additional 48 h to give a brown material.

Elemental analysis: 5.37 wt.% Pd and 2.17 wt.% Cu.

### 2.1.6. General procedure for the preparation of metallic catalysts on silica **10–12**

38 ml (corresponding to 3.8 mmol of Pd and/or Cu) of a 0.1 M ammonia solution of  $[M(NH_3)_4]Cl_2$  (prepared from  $MCl_2$  and a commercial ammonia solution; M: Pd, Cu) was added dropwise to a suspension of  $SiO_2$  in water (50 ml/g). The mixture was stirred for 12 h and the solvent evaporated. The solid was then treated under air flow (120 ml/min) in a U-reactor using a heating rate of 5 K/min from 30 to 300 °C. The temperature was maintained at 300 °C for 2 h and the reactor was allowed to cool to room temperature under nitrogen to give the M(II)/ $SiO_2$  catalysts.

Color and elemental analysis: Pd(II)/ $SiO_2$  **10**: brown, 7.77 wt.% Pd; Cu(II)/ $SiO_2$  **11**: light green, 4.70 wt.% Cu;  $[Pd(II)-Cu(II)]/SiO_2$  **12**: copper-like, 7.56 wt.% Pd and 4.64 wt.% Cu.

### 2.1.7. General procedure for the preparation of metallic catalysts on NaY **13–16**

38 ml (corresponding to 3.8 mmol of Pd and/or Cu) of a 0.1 M ammonia solution of  $[M(NH_3)_4]Cl_2$  (prepared from  $MCl_2$  and a commercial ammonia solution; M: Pd, Cu) was added dropwise to a suspension of NaY in water (100 ml/g). The mixture was stirred for 12 h at room temperature and the exchanged zeolite was filtered off and washed with water until no trace of chloride is detected in the filtrate ( $AgNO_3$  test). The zeolite was then treated under air flow (120 ml/min) in a U-reactor using a heating rate of 2 K/min from 30 to 300 °C. The temperature was maintained at 300 °C for 2 h and the reactor was allowed to cool to room temperature under nitrogen to give the M(II)/NaY catalysts.

Color and elemental analysis: Pd(II)-NaY **13**: light brown, 4.85 wt.% Pd; Cu(II)-NaY **14**: blue, 2.31 wt.% Cu;  $[Pd(II)-Cu(II)]$ -NaY **16**: beige, 4.40 wt.% Pd and 2.09 wt.% Cu.

Summary of the elemental analysis for the catalysts **5–18** is presented in Table 1.

## 2.2. Test of the catalytic activity

The catalytic reactions were carried out in a three-necked flask under argon. The qualitative and quantitative analysis of the reactants and products were done by GC. GC-yields were determined by the relative area of GC signal referred to an internal standard calibrated to the corresponding pure compound,  $\Delta_{rel} = \pm 10\%$ . If available, yield of isolated compound is given in parentheses.

### 2.2.1. General procedure for the first run and the recycling of the catalysts **5–18**

A total of 5 mmol of 2-iodoaniline (1.095 g), 5 mmol of ethynylbenzene (510 mg), 15 mmol of triethylamine (2.1 ml)

Table 1  
Elemental analysis for the heterogeneous catalysts 5–18

Catalyst	Pd wt. %	Cu wt. %
[PdCl(hp) <sub>3</sub> Cu] <sub>2</sub> <b>5</b>	19.87	11.80
[PdCl(hp) <sub>3</sub> Cu] <sub>2</sub> /SiO <sub>2</sub> <b>6</b>	0.77	0.54
[PdCl(hp) <sub>3</sub> Cu] <sub>2</sub> /Al <sub>2</sub> O <sub>3</sub> <b>7</b>	0.82	0.53
[Pd-Cu]/NaY <b>9</b>	5.37	2.17
Pd(II)/SiO <sub>2</sub> <b>10</b>	7.77	–
Cu(II)/SiO <sub>2</sub> <b>11</b>	–	4.70
[Pd(II)-Cu(II)]/SiO <sub>2</sub> <b>12</b>	7.56	4.64
Pd(II)-NaY <b>13</b>	4.85	–
Cu(II)-NaY <b>14</b>	–	2.31
[Pd(NH <sub>3</sub> ) <sub>4</sub> ]-[Cu(NH <sub>3</sub> ) <sub>4</sub> ]-NaY <b>15</b>	3.98	1.89
[Pd(II)-Cu(II)]-NaY <b>16</b>	4.40	2.09
[Pd(NH <sub>3</sub> ) <sub>4</sub> ]-NaY <b>17</b>	4.02	–
[Cu(NH <sub>3</sub> ) <sub>4</sub> ]-NaY <b>18</b>	–	1.95

and 2 mol% Pd catalysts (or 2 mol% Cu for catalyst **11**, **14** and **18**) were introduced into a three-necked flask under argon. Then, 15 ml of DMF/H<sub>2</sub>O 1:1 (previously deaerated) was added, and the mixture was further deaerated by argon flow for 5 min. The reactor was placed in a preheated oil bath at 100 °C. The reaction was conducted under vigorous stirring for 3 h, and then the reaction mixture was cooled to room temperature before GC analysis.

Recycling studies were performed with a washed catalyst (DMF, 2 × 10 ml) under reaction conditions as described before.

### 2.2.2. General procedure for leaching studies by hot-filtration

A total of 5 mmol of 2-iodoaniline (1.095 g), 5 mmol of ethynylbenzene (510 mg), 15 mmol of triethylamine (2.1 ml) and 2 mol% Pd catalyst were introduced into a three-necked flask under argon. Then, 15 ml of DMF/H<sub>2</sub>O = 1:1 (previously deaerated) was added, and the mixture was further deaerated by argon flow for 5 min. The reactor was placed in a preheated oil bath at 100 °C with and vigorously stirred. After 1 h the supernatant solution was filtered through a cannula with a microglass Whatman filter (in order to remove all fine particles) and then treated for further 3 h under the standard reaction conditions.

The reaction was monitored over the total period by GC and the results compared to a standard catalytic reaction.

### 2.2.3. General procedure for the examination of the presence of catalytically active species in homogeneous/bulk solution as a residual activity

A clear filtrate of the first run of the catalyst (obtained by filtration over a Celite pad) was used as the solvent basis for these experiments. The filtrate (free of catalyst) was placed in a three-necked flask and deaerated by argon flow for 5 min. Then new organic reactants (5 mmol of 2-iodoaniline, 5 mmol of ethynylbenzene, 15 mmol of triethylamine) were added and the mixture was well homogenized. An analysis of the composition was made by GC before the reactor was placed in a preheated oil bath at 100 °C for 3 h and vigor-

ously stirred. After the reaction was cooled to room temperature a second GC sample was withdrawn. The comparison between the two GC analyses gave a qualitative measure for the presence of active species in homogeneous/bulk solution.

### 2.2.4. GC-sample

A homogeneous 3 ml sample of the reaction mixture was sampled and quenched with 3 ml of water in a test tube. The mixture was extracted with 2 ml of CH<sub>2</sub>Cl<sub>2</sub>, washed three times with 1 ml of a aqueous 10% HCl solution in order to remove all metallic salts and then filtered off through a MgSO<sub>4</sub> pad. The resulting dry organic layer was then analyzed by GC at constant pressure (130 kPa): 2 min at 100 °C, heating 15 K/min up to 170 °C, 2 min at 170 °C, heating 35 K/min up to 240 °C, 10 min at 240 °C, heating 50 K/min up to 280 °C and 5 min at 280 °C.

### 2.2.5. Purification of the 2-phenylindole 3

The reaction mixture was diluted with 250 ml of water, and the resulting mixture was extracted with 4 × 20 ml CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed three times with 15 ml 10% HCl<sub>(aq)</sub>, once with 15 ml brine, dried over MgSO<sub>4</sub> and evaporated. The residue was then purified by flash chromatography on silica gel eluting with “petroleum ether (35–60 °C)"/CH<sub>2</sub>Cl<sub>2</sub> 2:1 to give a light brown compound. *R*<sub>f</sub> = 0.72.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz): 6.84 (s,  $\text{--CH=C--}$ , 1H); 7.10–7.27 (m, C<sub>6</sub>H<sub>4</sub>, 2H); 7.30–7.50 (m, C<sub>6</sub>H<sub>4</sub> and C<sub>6</sub>H<sub>5</sub>, 4H); 7.61–7.72 (m, C<sub>6</sub>H<sub>4</sub> and C<sub>6</sub>H<sub>5</sub>, 3H); 8.34 (broad s, N–H, 1H)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 62.9 MHz): 99.56 ( $\text{CH=C--NH}$ ); 110.51 (*o*-C–N C<sub>6</sub>H<sub>4</sub>); 119.86 (*o*-C–C C<sub>6</sub>H<sub>4</sub>); 129.86 and 120.26 (*m*-C–N C<sub>6</sub>H<sub>4</sub>); 121.94 (*p*-C–N C<sub>6</sub>H<sub>4</sub>); 124.74 (*o*-C<sub>6</sub>H<sub>5</sub>); 127.30 (*p*-C<sub>6</sub>H<sub>5</sub>); 128.61 (*m*-C<sub>6</sub>H<sub>5</sub>); 129.73 (C<sub>q</sub>–C–C C<sub>6</sub>H<sub>4</sub>); 132.54 (C<sub>q</sub>–C–N C<sub>6</sub>H<sub>4</sub>); 136.82 (C=C–H); 137.73 (C<sub>q</sub> C<sub>6</sub>H<sub>5</sub>).

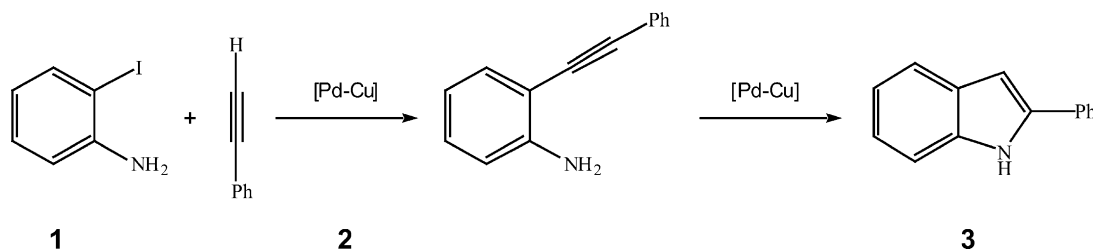
C<sub>14</sub>H<sub>11</sub>N, molecular weight: 193.25, MS: *m/z* (%): [M<sup>+</sup>] 193 (100) [M<sup>+</sup>–CHNH] 165 (43) [M<sup>+</sup>–NH–C–C<sub>6</sub>H<sub>5</sub>] 89 (22).

## 3. Results and discussion

To test our strategy in developing new hetero-bimetallic Pd-Cu catalysts for the one-pot domino indole synthesis with wide applicability, we chose the condensation between 2-iodoaniline with ethynylbenzene as model reaction (Scheme 1).

### 3.1. Catalyst preparation

The development of new catalysts for the one-pot indole synthesis was mainly motivated by observing the reaction mechanisms involved during the overall procedure: (1) the Sonogashira cross-coupling between the 2-iodoaniline **1** is generally catalyzed by a mixture of a palladium



Scheme 1. One-pot synthesis of 2-phenylindole. Reaction conditions: 5 mmol of 2-iodoaniline, 5 mmol of ethynylbenzene, 15 mmol Et<sub>3</sub>N, 2 mol% palladium catalyst, 15 ml DMF/H<sub>2</sub>O 1:1, 100 °C, 3 h.

complex with CuI as co-catalyst [7]; (2) the resulting amino-aryl-ethylene **2** led to intramolecular cyclization catalyzed by copper(I) species (Scheme 1) [6,9].

As a consequence, Pd-Cu bimetallic catalysts are interesting as potential catalysts for the one-pot domino synthesis of indoles.

### 3.1.1. Synthesis of the homogeneous catalyst [PdCl(hp)<sub>3</sub>Cu]<sub>2</sub> **5**

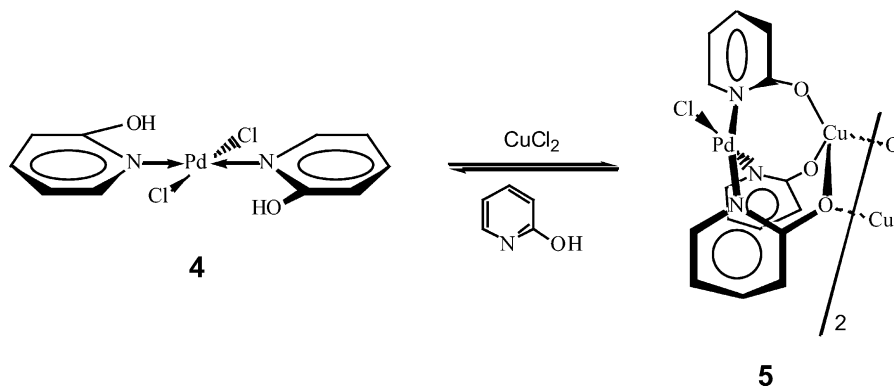
The homogeneous catalyst was synthesized according to the procedure reported by Wada and co-workers [12]. Treating sodium tetrachloropalladate in water with 2-hydroxypyridine (Hhp) led to the formation of the intermediate *trans*-[Pd(Hhp)<sub>2</sub>Cl<sub>2</sub>] **4** (Scheme 2) [11]. This complex was isolated as a microcrystalline yellow compound that was characterized by <sup>1</sup>H and <sup>13</sup>C NMR (Scheme 2, Fig. 1a). Treatment of **4** in ethanol by CuCl<sub>2</sub> and Hhp give the hetero-bimetallic complex [PdCl(hp)<sub>3</sub>Cu]<sub>2</sub> **5** as a slightly orange microcrystalline compound [12]. The complex **5** was characterized by X-band EPR spectroscopy (Fig. 2a) in frozen ethanol solution at 130 K showing the paramagnetic nature of the Cu<sup>2+</sup> complex, giving  $g_{\perp} = 2.078$ ,  $g_{\parallel} = 2.362$  and  $A_{\parallel}({}^{63,65}\text{Cu}) = 12.09$  mT which are consistent with the values reported in the literature for octahedral Cu<sup>2+</sup> complexes [13]. The spectrum exhibits a well resolved <sup>63,65</sup>Cu hyperfine structure (quartet) due to the interaction of the unpaired electron (3d<sup>9</sup>,  $S = 1/2$ ,  $I({}^{63,65}\text{Cu}) = 3/2$ ) and can be described by an axially symmetric spin Hamiltonian.

### 3.1.2. Heterogeneous [PdCl(hp)<sub>3</sub>Cu]<sub>2</sub> catalysts on silica, alumina and NaY zeolite

Heterogeneous [PdCl(hp)<sub>3</sub>Cu]<sub>2</sub>/SiO<sub>2</sub> **6** (as [Pd-Cu]/SiO<sub>2</sub>) or [PdCl(hp)<sub>3</sub>Cu]<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub> **7** (as [Pd-Cu]/Al<sub>2</sub>O<sub>3</sub>) catalysts charged with approximately 1 wt.% Pd and 0.5 wt.% Cu were prepared by impregnation of silica or alumina by [PdCl(hp)<sub>3</sub>Cu]<sub>2</sub> in ethanol [14]. The [Pd-Cu]/SiO<sub>2</sub> catalyst **6** was obtained as a slightly orange solid and the [Pd-Cu]/Al<sub>2</sub>O<sub>3</sub> catalyst **7** as a light green solid. These catalysts were submitted to washing tests: treatment with ethanol at room temperature for 4 h did not show any leaching of the immobilized [PdCl(hp)<sub>3</sub>Cu]<sub>2</sub> complex in solution (ICP-AES). Therefore, we can assume that this simple impregnation method gives stable heterogeneous [Pd-Cu] bimetallic catalysts. The absolute palladium and copper content was determined by ICP-AES as 0.77 wt.% Pd and 0.54 wt.% Cu for **6** and 0.82 wt.% Pd-0.53 wt.% Cu for **7**, in good agreement with expectations.

Analogous to the synthesis of **5**, we prepared the hetero-bimetallic [Pd-Cu]-catalyst entrapped into NaY **9** by analogy to the well-described “ship-in-a-bottle” synthesis [15].

Treatment of NaY with sodium tetrachloropalladate in water in the presence of Hhp ligand affords the [Pd(Hhp)<sub>2</sub>Cl<sub>2</sub>] complex **4** entrapped into NaY as shown by <sup>13</sup>C NMR of the solid **8** (Fig. 1b). The light brown solid exhibits an absolute palladium content of 5.57 wt.% Pd which was determined by ICP-AES. Further treatment in water by CuCl<sub>2</sub> in presence of Hhp ligand gave, after washing and drying, an orange material ([Pd-Cu]/NaY, **9**). The absolute palladium and copper



Scheme 2. Synthesis of the [Pd-Cu] hetero-bimetallic complex **5**. Reaction conditions: 2 mmol of Na<sub>2</sub>PdCl<sub>4</sub>, 4 mmol of 2-hydroxypyridine (Hhp), 30 ml EtOH, room temperature, 12 h, then 2 mmol CuCl<sub>2</sub> and 2 mmol Hhp, room temperature, 24 h.

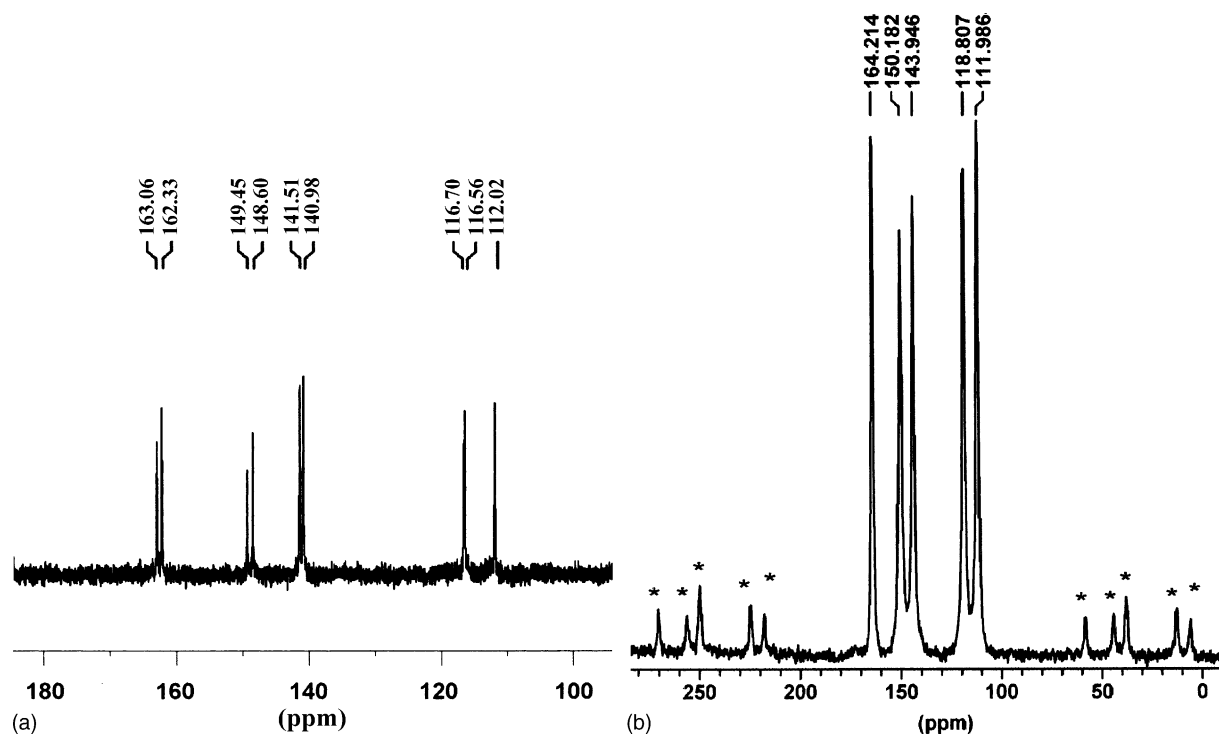


Fig. 1. (a) Solution  $^{13}\text{C}$  NMR of the complex  $[\text{Pd}(\text{Hhp})_2\text{Cl}_2]$  in  $\text{D}_6\text{-DMSO}$  (saturated). (b)  $^{13}\text{C}$  MAS-NMR of the complex  $[\text{Pd}(\text{Hhp})_2\text{Cl}_2]$  in  $\text{NaY}$  (neat).

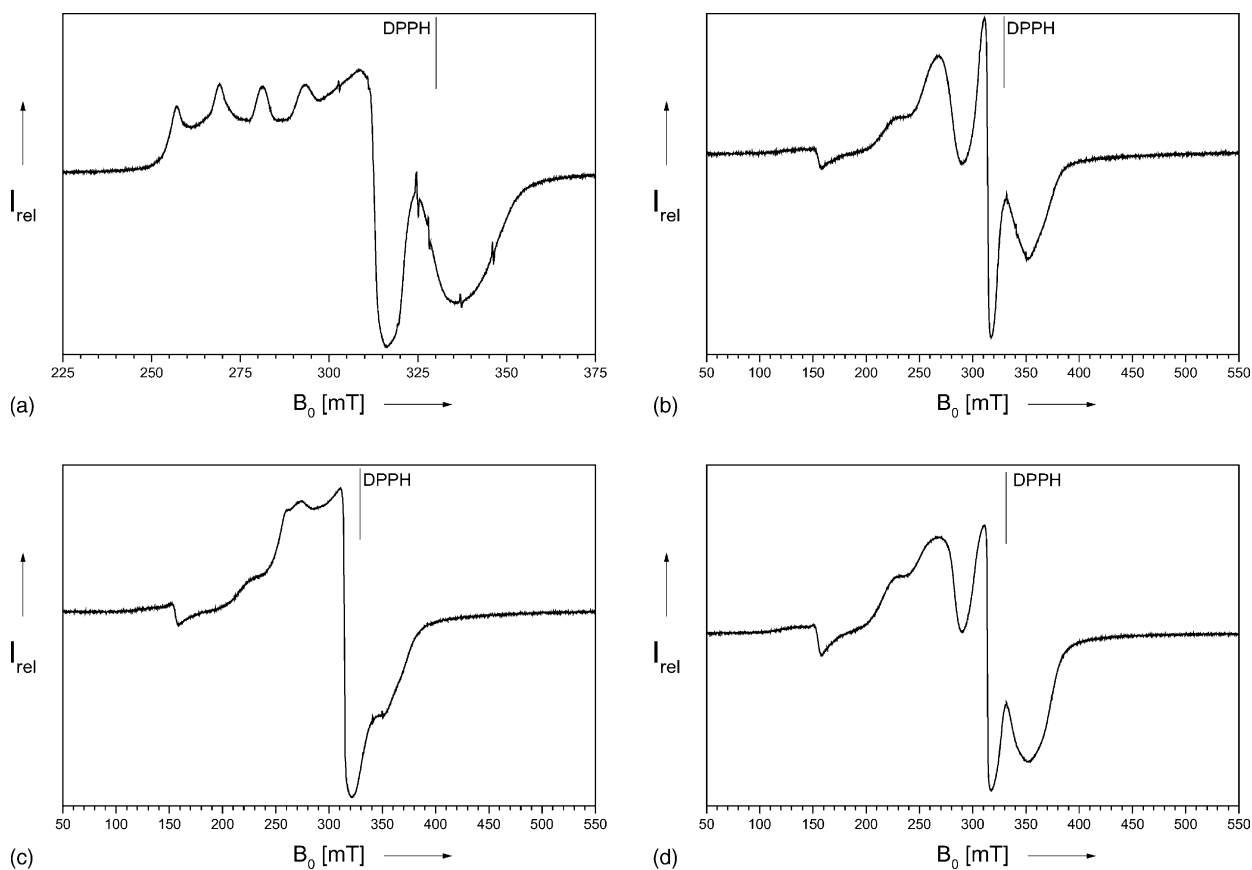


Fig. 2. X-band EPR spectra at  $T = 130\text{ K}$  of: (a)  $[\text{PdCl}(\text{hp})_3\text{Cu}]_2$  **5** in frozen ethanol; (b)  $[\text{PdCl}(\text{hp})_3\text{Cu}]_2/\text{SiO}_2$  **6**; (c)  $[\text{PdCl}(\text{hp})_3\text{Cu}]_2/\text{Al}_2\text{O}_3$  **7**; and (d)  $[\text{Pd-Cu}]/\text{NaY}$  **9**.

content was determined by ICP–AES to be 5.37 wt.% Pd and 2.17 wt.% Cu. While these analyses are close to the expected ones, the Pd/Cu = 2.5 calculated for the catalyst **9** indicates that it contains more Pd-species than expected based on the hetero-bimetallic complex **5** for which the ratio Pd/Cu is equal to 1.7. These results suggest that not all immobilized palladium species of **9** are present as hetero-bimetallic [Pd-Cu]-species.

The EPR spectra of the supported bimetallic [Pd-Cu]-complex consist of a superposition of probably two species (Fig. 2b–d). The  $^{63,65}\text{Cu}$  hyperfine structure is not resolved making the quantitative interpretation difficult. The significant broadening of the  $g_{\parallel}$  (or  $g_1$  or  $g_3$ ) region may be due to spin–spin interactions of near neighbored paramagnetic copper(II) centers or due to distorted coordination environment (rhombic symmetry of the paramagnetic center), which can be expected on the surface. The spectral pattern and the  $g$ -values  $g_{\perp}$  (or  $g_2$ ) = 2.095 (for  $\text{SiO}_2$  and zeolite NaY) and  $g_{\perp}$  = 2.091 (for  $\text{Al}_2\text{O}_3$ ) are different from the precursor complex in frozen solution ( $g_{\perp}$  = 2.078). This indicates clearly that the coordination environment of copper(II) and the structure of the bimetallic system changed significantly during the immobilization procedure.

### 3.1.3. Supported metallic catalysts

The other catalysts, i.e. Pd(II)/ $\text{SiO}_2$  **10**, Cu(II)/ $\text{SiO}_2$  **11** and [Pd(II)-Cu(II)]/ $\text{SiO}_2$  **12** or Pd(II)-NaY **13**, Cu(II)-NaY **14** and [Pd(II)-Cu(II)]-NaY **16**, were prepared by impregnation [14] or ion-exchange [16], respectively. After treatment at 300 °C under air (80 ml/min), according to literature procedure, they were ready for use. The absolute palladium and/or copper content was determined by ICP–AES to be 7.56–7.77 wt.% Pd and 4.64–4.70 wt.% Cu for the catalysts based on  $\text{SiO}_2$  and 4.40–4.85 wt.% Pd and 2.09–2.31 wt.% Cu for the catalysts prepared from the zeolite NaY, as expected from the different procedures.

### 3.2. Catalytic activity

The conversion and selectivity obtained for the [Pd-Cu] hetero-bimetallic catalysts are reported in Table 2.

All catalysts gave exclusively the 2-phenylindole as product, showing one of the highest selectivities for a one-pot indole synthesis. The intermediate 2-(phenylethynyl)-aniline was not detected by GC–MS in any sample. This is attributed to a rapid intramolecular cyclization, probably by a Pd-catalyzed hydroamination, directly giving the expected 2-phenylindole [17].

The homogeneous  $[\text{PdCl}(\text{hp})_3\text{Cu}]_2$  complex **5** is the most active catalyst, leading to a complete conversion of 2-iodoaniline to 2-phenylindole (100% yield after 3 h) under mild reaction conditions (100 °C, DMF/ $\text{H}_2\text{O}$  1:1).

Generally, the heterogeneous  $[\text{PdCl}(\text{hp})_3\text{Cu}]_2$  on silica or alumina gave similar results, i.e.  $\approx 80\%$  yield after 3 h. Interesting to note is the comparatively high activity observed for the hetero-bimetallic [Pd-Cu] catalyst **9** entrapped into NaY

Table 2

Comparison between different bimetallic [Pd-Cu]-catalysts for the synthesis of 2-phenylindole (Scheme 1)

Catalyst	Conversion <sup>a</sup>	Yield of 2-phenylindole [%] <sup>b</sup>
$[\text{PdCl}(\text{hp})_3\text{Cu}]_2$ <b>5</b>	100	100 (78)
$[\text{PdCl}(\text{hp})_3\text{Cu}]_2/\text{SiO}_2$ <b>6</b>	79	76
$[\text{PdCl}(\text{hp})_3\text{Cu}]_2/\text{Al}_2\text{O}_3$ <b>7</b>	83	81
[Pd-Cu]/NaY <b>9</b>	100	100 (65)
[Pd(II)-Cu(II)]/ $\text{SiO}_2$ <b>12</b>	85	82
[Pd(II)-Cu(II)]-NaY <b>16</b>	21	18
$[\text{Pd}(\text{NH}_3)_4]\text{-}[\text{Cu}(\text{NH}_3)_4]\text{-NaY}$ <b>15</b>	89	87

Reaction conditions: 5 mmol of 2-iodoaniline, 5 mmol of ethynylbenzene, 15 mmol  $\text{Et}_3\text{N}$ , 2 mol% Pd-catalyst, 15 ml DMF/ $\text{H}_2\text{O}$  1:1, 100 °C, 3 h.

<sup>a</sup> Based on unreacted 2-iodoaniline determined by GC.

<sup>b</sup> GC yields and when available (isolated yield) are given ( $\Delta_{\text{rel}}$  =  $\pm 10\%$ ).

zeolite. After 3 h complete conversion of 2-iodoaniline to 2-phenylindole is achieved. This result is comparable to the homogeneous  $[\text{PdCl}(\text{hp})_3\text{Cu}]_2$  complex. However, we cannot conclude that both catalysts have the same activity as all catalytic tests were performed using the same reaction time. Limitation due to diffusion of educts and products to/from the zeolite microstructure is probably not well represented by our experiments.

While the activity of these hetero-bimetallic catalysts based on the homogeneous  $[\text{PdCl}(\text{hp})_3\text{Cu}]_2$  complex **5**—is high, their preparation remains too complicated for industrial application of the one-pot indole synthesis. Therefore, we decided to prepare a hetero-bimetallic [Pd-Cu]-catalyst by co-impregnation on silica which represents a very simple and well-established procedure used at an industrial scale. After calcination in air for 3 h, the catalyst **12** gave 82% yield of the expected 2-phenylindole, showing an activity comparable to that of other heterogeneous catalysts prepared from **5**.

Similarly, we prepared hetero-bimetallic [Pd-Cu]-catalysts supported on NaY zeolite by ion co-exchange. Surprisingly, after calcination, the [Pd-Cu]-catalyst **16** led to very low conversion of 2-iodoaniline compared to the mono-metallic [Pd]-catalyst **13**, probably due to migration of copper(II) ions in the sodalite cavities during the thermal treatment, thus preventing copper to play the role of co-catalyst during the reaction [18]. To confirm this hypothesis, we used the catalyst precursor  $\{[\text{Pd}(\text{NH}_3)_4]\text{-}[\text{Cu}(\text{NH}_3)_4]\}$ -NaY **15** after drying without any thermal treatments. This catalyst led to high conversion of 2-iodoaniline, giving 87% yield in 2-phenylindole, that is comparable to the yields obtained with the other heterogeneous hetero-bimetallic catalysts; however, we cannot exclude that the remaining water in the zeolite cavities plays an important role during the reaction.

With such activities and selectivities, these hetero-bimetallic heterogeneous catalysts are really applicable for the fine chemical industry.

In order to elucidate the individually played role of palladium and copper in the hetero-bimetallic catalysts, we tested

Table 3  
Activity of mono-metallic vs. bi-metallic catalysts for the synthesis of 2-phenylindole (Scheme 1)

Catalyst	Conversion <sup>a</sup>	Yield of 2-phenylindole [%] <sup>b</sup>
Pd(II)/SiO <sub>2</sub> <b>10</b>	46	42
Cu(II)/SiO <sub>2</sub> <b>11</b>	0	0
[Pd(II)-Cu(II)]/SiO <sub>2</sub> <b>12</b>	85	82
Pd(II)-NaY <b>13</b>	16	13
Cu(II)-NaY <b>14</b>	0	0
[Pd(II)-Cu(II)]-NaY <b>16</b>	21	18
[Pd(NH <sub>3</sub> ) <sub>4</sub> ]-NaY <b>17</b>	55	52
[Cu(NH <sub>3</sub> ) <sub>4</sub> ]-NaY <b>18</b>	0	0
[Pd(NH <sub>3</sub> ) <sub>4</sub> ]-[Cu(NH <sub>3</sub> ) <sub>4</sub> ]-NaY <b>15</b>	89	87

Reaction conditions: 5 mmol of 2-iodoaniline, 5 mmol of ethynylbenzene, 15 mmol Et<sub>3</sub>N, 2 mol% Pd or Cu catalyst, 15 ml DMF/H<sub>2</sub>O 1:1, 100 °C, 3 h.

<sup>a</sup> Based on the unreacted 2-iodoaniline determined by GC.

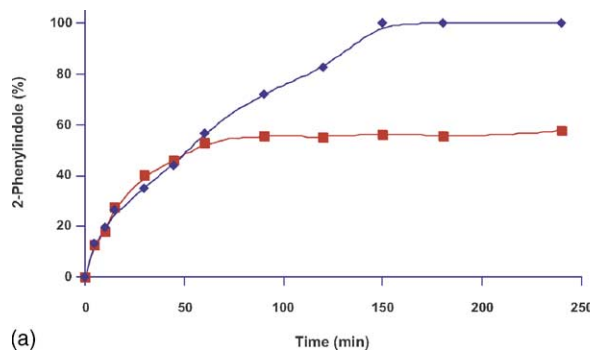
<sup>b</sup> GC yields are given ( $\Delta_{rel} = \pm 10\%$ ).

the activity of heterogeneous [Pd(II)]- and [Cu(II)]-catalysts (Table 3).

As expected, copper catalysts were not active towards the transformation, according to the generally accepted mechanism for the Sonogashira cross-coupling reaction of aryl halides with alkynes. On the contrary, the [Pd(II)]-catalysts showed a good activity (42% yield for **10**), nevertheless, not reaching the best results obtained with the hetero-bimetallic [Pd-Cu] heterogeneous catalysts (up to 87% yield). Based on the relative activities, these results point out that copper(II)/copper(I) species act as co-catalysts for the Sonogashira reaction, and to some extent for the hetero-annulation, leading to the formation of the indole ring that is probably catalyzed by both Pd and Cu species.

### 3.3. Leaching studies for the heterogeneous bimetallic [Pd-Cu]-catalysts

Leaching of active species when heterogeneous metallic catalysts are used in liquid phase must be evaluated to identify whether those active species are dissolved metal complexes or remnants of active centers on surfaces.



For our investigations, we used two complementary methods: (1) hot filtration (over a Celite pad and under argon) of the heterogeneous catalysts from the reaction media after  $\approx 1$  h of reaction, treating the clear filtrate, like for the catalytic runs, up to 6 h; (2) filtration of the heterogeneous catalysts after a catalytic run (3 h), investigating the residual activity of the clear solution after introduction of new reagents. The new homogeneous reaction mixture was then treated as a standard catalytic run and monitored by GC-analysis (see Section 2 for a description of the overall method).

While these methods did not allow an absolute quantification of the dissolved metal species, it gave information on the presence or absence of active species in the reaction media, and their relative activity.

Fig. 3 shows the results obtained from the hot filtration of the two selected heterogeneous catalysts: [Pd(II)-Cu(II)]/SiO<sub>2</sub> **12** and [Pd-Cu]/NaY **9**. All other heterogeneous catalysts gave the same results. The curves clearly show that, after filtration, no activity remained for the clear filtrate. This result is particularly interesting for the heterogenized bimetallic [Pd-Cu]-complex on silica (and alumina), and in some extent for zeolites, indicating that the complex is not leached from the surface during the reaction, considering the high activity of the homogeneous [PdCl(hp)<sub>3</sub>Cu]<sub>2</sub> catalyst **5**.

The second method used for investigation of the residual catalytic activity of the clear filtrate confirms these results. Generally, a difference between the two GC-determinations (at  $t = 0$  and 3 h) of 2–4% is observed in keeping with the error limit of the analytical method. This indicates that no leaching of active species occurs during the catalytic runs.

However, ICP–AES determination of the clear filtrates gave evidence that some metal is dissolved during the reaction, however, at a very low level (i.e. Pd < 5 ppm and Cu < 10 ppm).

### 3.4. Recovery of the heterogeneous bimetallic [Pd-Cu]-catalysts

For industrial application, the recyclability of heterogeneous catalysts still remains a determining factor. We

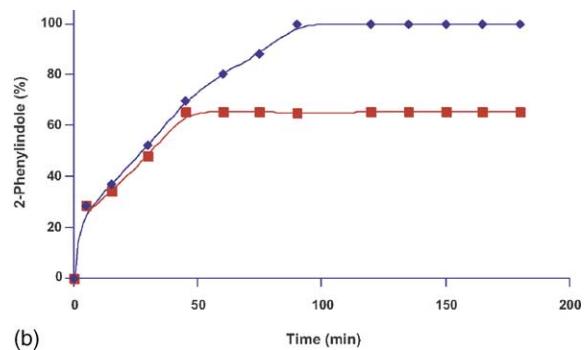


Fig. 3. Residual activity after hot-filtration (■) vs. standard catalyst run (◆) for: (a) catalyst [Pd(II)-Cu(II)]/SiO<sub>2</sub> **12** with filtration after 1 h; (b) catalyst [Pd-Cu]/NaY **9** with filtration after 45 min. Reaction conditions: 20 mmol of 2-iodoaniline, 20 mmol of ethynylbenzene, 60 mmol Et<sub>3</sub>N, 2 mol% Pd catalyst, 60 ml DMF/H<sub>2</sub>O 1:1, 100 °C.



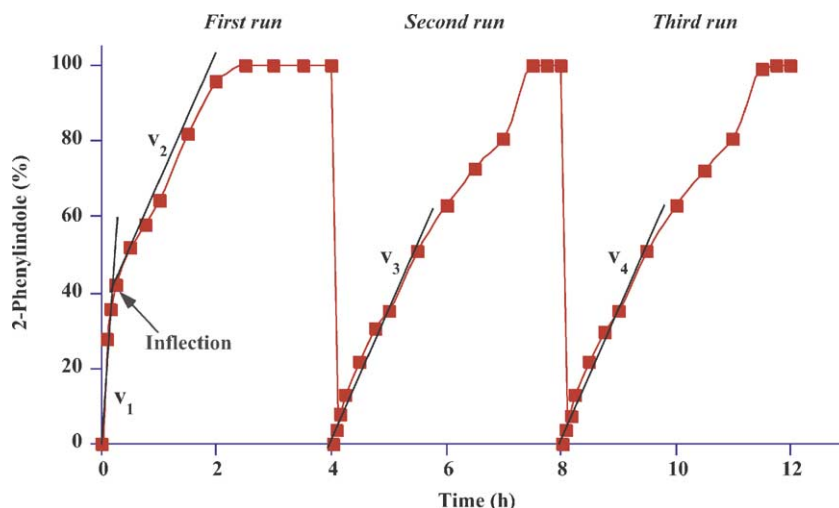


Fig. 4. Study of catalyst deactivation for the [Pd-Cu]/NaY **9**. Reaction conditions: 20 mmol of 2-iodoaniline, 20 mmol of ethynylbenzene, 60 mmol Et<sub>3</sub>N, 2 mol% palladium catalyst, 60 ml DMF/H<sub>2</sub>O 1:1, 100 °C.

investigated this for the heterogeneous catalysts based on silica (**6** and **12**) and NaY (**9**, **15** and **16**).

After separation, washing and drying, the heterogeneous catalysts were used under the same conditions as for the initial run without any regeneration or reactivation. The results obtained showed that none of these heterogeneous catalysts were active after separation, while they exhibit a high activity when used as fresh catalysts. This may suggest that the heterogenized species undergo strong modifications during the reaction resulting in a deactivation of the catalyst, probably during their separation from the reaction media.

In order to determine whether the deactivation occurs during the catalytic run or during the extraction procedure, we performed additional experiments using [Pd-Cu]/NaY, **9**, as it was one of the most active heterogeneous catalysts for the studied reaction. The deactivation of **9** was studied as follows: after the completion of a reaction catalyzed by a fresh catalyst (i.e., after 4 h), new educts were added under argon to the reaction mixture and the yield of 2-phenylindole was set to 0 at the corresponding “initial time” for the next run of the catalyst. To confirm the result thus obtained, the procedure was repeated once. Fig. 4 shows clearly that a deactivation occurs during the first run of the catalyst after a relatively short reaction time (20–25 min), as indicated by the determination of the initial rate ( $v_1 = 0.75 \text{ mmol}/(\text{min g}_{\text{cat}})$ ) and of the rate at 30 min corresponding to the inflection of the curve ( $v_2 = 0.11 \text{ mmol}/(\text{min g}_{\text{cat}})$ ). However, the catalyst **9** is still very active and led to a quantitative yield of 2-phenylindole in 3 h. After introduction of new educts, **9** still showed the same activity, as indicated by the determination of the initial rates ( $v_3 = v_4 = 0.12 \text{ mmol}/(\text{min g}_{\text{cat}})$ ) for both additional runs).

These results confirmed our hypothesis for catalyst deactivation during the extraction procedure and demonstrated clearly that such hetero-bimetallic catalysts can be successfully applied to continuous reactions.

#### 4. Conclusion

The synthesis of substituted indole derivatives still remains a very important area of research for the fine chemical industry. Several methods have been developed to meet the growing demand of new active molecules; however, no efficient heterogeneously catalyzed one-pot synthesis has been reported.

For the first time, we have demonstrated that simple heterogeneous bimetallic [Pd-Cu] catalysts are highly active and selective for the one-pot synthesis of 2-phenylindole—as a model reaction—leading to high yields. Depending on the catalyst, up to 100% yield in 2-phenylindole could be obtained with only 2 mol% Pd at a relatively mild temperature (100 °C) and after a short reaction time (<3 h).

Some of these catalysts are readily available or could be prepared at an industrial scale by a simple impregnation procedure, a method often used in the chemical industry. Though they are less active (compared to the general 81–87% yield), these catalysts are ready for industrial applications, especially due to their high selectivity.

Our results showed that these heterogeneous catalysts are active over several reaction cycles, leading to their use for continuous reactions; however, their strong deactivation after separation remains a major challenge for application.

Current investigations focus on the preparation of stable hetero-bimetallic [Pd-Cu]-catalysts and their application towards the selective synthesis of highly substituted indoles starting from functionalized precursors, as these syntheses were often described in the literature leading to a mixture of isomers.

#### Acknowledgements

We gratefully acknowledge the European Community (Marie-Curie Program) for a research grant (4 months) to Markus Gruber.

## References

- [1] (a) J.E. Saxton, *The Chemistry of Heterocyclic Compounds*, vol. 25, Part IV, Wiley, New York;  
(b) R.J. Sundberg, *Indoles*, Academic Press, London (1996), and references cited therein;  
(c) E. Mutschler, *Arzneimittelwirkungen*, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 7th ed., 1996.
- [2] (a) S. Raucher, G.A. Koolpe, *J. Org. Chem.* 48 (1983) 2066;  
(b) R.J. Sundberg, in: W.B. Clive, G.W.H. Cheeseman (Eds.), *Comprehensive Heterocyclic Chemistry*, vol. 4, Pergamon, Oxford, 1984, 313;  
(c) A. Kasahara, T. Izumi, L. Xiao-ping, *Chem. Indust.* (1988) 50.;  
(d) U. Pindur, R. Adam, *J. Heterocycl. Chem.* 25 (1988) 1;  
(e) M. Beller, C. Breindl, T.H. Riermeier, M. Eichberger, H. Trauthwein, *Angew. Chem. Int. Ed. Engl.* 37 (1998) 3389;  
(f) G. Battistuzzi, S. Cacchi, G. Fabrizi, *Eur. J. Org. Chem.* (2002) 2671.
- [3] (a) R.H. Brown, *Synthesis of the indole nucleus*, in: W.J. Houlihan (Ed.), *Indoles*, Part 1, John Wiley & Sons, New York, 1972;  
(b) D.L. Hughes, *Org. Prep. Proced. Int.* 25 (1993) 607;  
(c) S. Wagaw, B.H. Yang, S.L. Buchwald, *J. Am. Chem. Soc.* 120 (1998) 6621.
- [4] (a) R.J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, 1970, Chapter 3;  
(b) I.I. Grandberg, L.D. Belyaeva, L.B. Dimitriev, *Khim. Geterotsikl. Soedin.* (1971) 1204;  
(c) J.E. Nordlander, D.B. Catalane, K.D. Kotian, R.M. Stevens, J.E. Haky, *J. Org. Chem.* 46 (1981) 778.
- [5] (a) D.A. Goff, R.N. Zuckermann, *J. Org. Chem.* 60 (1995) 5748;  
(b) H.-C. Zhang, B.E. Maryanoff, *J. Org. Chem.* 62 (1997) 1804;  
(c) H.-C. Zhang, K.K. Brumfield, L. Jaroskova, B.E. Maryanoff, *Tetrahedron Lett.* 39 (1998) 4449;  
(d) K. Yamazaki, Y. Nakamura, Y. Kondo, *J. Chem. Soc. Perkin Trans. 1* (2002) 2137.
- [6] (a) J. Ezquerra, C. Pedregal, C. Lamas, J. Barluenga, M. Pérez, M.A. García-Martín, J.M. González, *J. Org. Chem.* 61 (1996) 5804;  
(b) M.C. Fagnola, I. Candiani, G. Visentin, W. Cabri, F. Zarini, N. Mongelli, A. Bedeschi, *Tetrahedron Lett.* 38 (1997) 2307;  
(c) H.-C. Zhang, K.K. Brumfield, B.E. Maryanoff, *Tetrahedron Lett.* 38 (1997) 2439;  
(d) H.-C. Zhang, H. Ye, A.F. Moretto, K.K. Brumfield, B.E. Maryanoff, *Org. Lett.* 2 (2000) 89;  
(e) H. Siebeneicher, I. Bystschkov, S. Doye, *Angew. Chem. Int. Ed.* 42 (2003) 3042.
- [7] (a) K. Sonogashira, in: B.M. Trost, I. Fleming (Eds.), *Comprehensive Organic Synthesis*, vol. 3, Pergamon Press, New York, 1991, p. 521;  
(b) J.S. Moore, *Acc. Chem. Res.* 30 (1997) 402;  
(c) K. Sonogashira, in: F. Diederich, P.J. Stang (Eds.), *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, New York, 1998, p. 203.
- [8] (a) L.S. Hegedus, *Angew. Chem. Int. Ed. Engl.* 27 (1988) 1113;  
(b) R.C. Larock, S. Babu, *Tetrahedron Lett.* 28 (1987) 5291;  
(c) R.C. Larock, E.K. Yum, *J. Am. Chem. Soc.* 113 (1991) 6689;  
(d) R.C. Larock, T.R. Hightower, L.A. Hasvold, K.P. Peterson, *J. Org. Chem.* 61 (1996) 3584;  
(e) R.C. Larock, E.K. Yum, M.D. Refvik, *J. Org. Chem.* 63 (1998) 7652;  
(f) Q. Huang, R.C. Larock, *J. Org. Chem.* 68 (2003) 7342;  
(g) S.K. Osagawa, *Heterocycles* 41 (1995) 1627.
- [9] (a) T. Sakamoto, Y. Kondo, S. Iwashita, T. Nagano, H. Yamanaka, *Chem. Pharm. Bull.* 36 (1988) 1305;  
(b) D. Villemain, D. Goussu, *Heterocycles* 29 (1989) 1255.
- [10] (a) R. Beugelmans, G. Roussi, *J. Chem. Soc., Chem. Commun.* (1979) 950;  
(b) M.P. Prochazka, R. Carlson, *Acta Chem. Scand.* 44 (1990) 614;  
(c) J.G. Rodriguez, P. Gil-Lopetegui, *J. Heterocycl. Chem.* 30 (1993) 373;  
(d) O. Miyata, Y. Kimura, T. Naito, *Synthesis* (2001) 1635;  
(e) M. Tokunaga, M. Ota, M.-A. Haga, Y. Wakatsuki, *Tetrahedron Lett.* 42 (2001) 3865.
- [11] P.-C. Kong, F.D. Rochon, *Can. J. Chem.* 59 (1981) 3293.
- [12] M. Higashijima, T. Masunaga, Y. Kojima, E. Watanabe, K. Wada, in: Y. Izumi, H. Arai, M. Iwamoto (Eds.), *Elsevier, Stud. Surf. Sci. Catal.* 92 (1994) 319.
- [13] (a) J. Peisach, W.E. Blumberg, *Electron Spin Resonance of Metal Complexes*, Plenum, New York, 1969;  
(b) A. Abragam, B. Bleaney, *Electron Paramagnetic Resonance of Transition Ions*, Clarendon, Oxford, 1970.
- [14] (a) M.A. Ugina, G. Ovejero, R. van Grieken, D.P. Serrano, M. Camacho, *J. Chem. Soc., Chem. Commun.* (1994) 27;  
(b) M. Wagner, K. Koehler, L. Djakovitch, S. Weinkauff, V. Hagen, M. Muhler, *Top. Catal.* 13 (2000) 319.
- [15] (a) G. Schulz-Elkoff, S. Ernst, in: G. Ertl, H. Knözinger, J. Weitkamp (Eds.), *Handbook of Heterogeneous Catalysis*, vol. 1, VCH, Weinheim, 1997, p. 374;  
(b) L. Djakovitch, H. Heise, K. Koehler, *J. Organomet. Chem.* 584 (1999) 16.
- [16] (a) J. Michalik, M. Narayana, L. Kevan, *J. Phys. Chem.* 89 (1985) 4553;  
(b) W.M.H. Sachtler, F.A.P. Cavalcanti, *Catal. Lett.* 9 (1991) 261;  
(c) L. Djakovitch, K. Koehler, *J. Mol. Catal. A: Chem.* 142 (1999) 275;  
(d) L. Djakovitch, K. Koehler, *J. Am. Chem. Soc.* 123 (2001) 5990.
- [17] For a review on catalytic hetero functionalisation by hydroamination see: J.-J. Brunet, D. Neibecker, in: A. Togni, H. Grützmacher (Eds.), *Catalytic Heterofunctionalization*, Wiley-VCH, Weinheim, 2001, pp. 91–141.
- [18] (a) Z. Zhang, W.M.H. Sachtler, *J. Catal.* 118 (1989) 266;  
(b) H. Yamashita, M. Matsuoka, K. Tsuji, Y. Shioya, M. Anpo, M. Che, *J. Phys. Chem.* (1996) 397;  
(c) P.H. Espeel, G. de Peuter, M.C. Tielen, P.A. Jacobs, *J. Phys. Chem.* 98 (1994) 11588.