Catalysis Today 140 (2009) 90–99

Contents lists available at ScienceDirect

Catalysis Today

journal homepage: www.elsevier.com/locate/cattod

Environmentally friendly [Pd/Cu]-catalysed C3-alkenylation of free NH-indoles

Laurent Djakovitch [*], Pascal Rouge

IRCELYON-Institut de recherches sur la catalyse et l'environnement de Lyon, UMR 5256 CNRS-Université Claude Bernard Lyon 1, 2 Avenue Albert Einstein, F-69626 Villeurbanne, France

ARTICLE INFO

Article history:
Available online 7 September 2008

Keywords:
3-Vinylindoles
Oxidative coupling
Palladium–copper bimetallic catalysts
Zeolites

ABSTRACT

A new eco-efficient and environmentally friendly palladium/copper catalytic procedure for the C3-alkenylation of free NH-indoles is reported. Using homogeneous or heterogeneous heterobimetallic [Pd/Cu]-catalysts under mild reaction conditions (10 mol% Pd-catalyst and 10 mol% Cu-catalyst, 70 °C, air), substituted indoles are fully (58–82% isolated yields) and selectively (75–100% selectivity) converted to the expected 2-substituted-3-vinylindoles.

1. Introduction

The substituted indole nucleus is a structural fragment found in numerous biologically active natural and synthetic compounds [1,2]. The synthesis and the functionalisation of indoles has been the subject of many researches for over 100 years [3,4], leading to well-established synthesis like the Fisher indole synthesis from aryl hydrazone [5,6], the Batcho–Limgruber synthesis from *o*-nitrotoluenes and dimethylformamide acetals [7], the Gassman synthesis from *N*-haloanilines [8,9] or the Madelung cyclisation of *N*-acyl-*o*-toluidines [10–12].

In the last 40 years, alternative palladium-catalysed syntheses (Fig. 1), generally tolerant to a wide range of substituents, have appeared in the literature [13,14]. These methods include the palladium-induced cycloadditions of 2-haloanilines with terminal (R^3 = H) or internal alkynes (R^3 = alkyl or aryl group) (route 1) [15–19] and the intra- or intermolecular reactions of 2-alkynyl anilides with aryl- or alkylhalides (route 2) [20–23]. Other approaches are based on Heck-type cyclisation reactions (route 3) [24,25], on reactions of alkynes with imines (route 4) [26] or on intramolecular cyclisation of a *N*-alkynyl-2-halogenanilides followed by a C–N coupling reaction with primary or secondary amines (route 5). Heteroannulation sequences achieved through palladium catalysed aryl amination reaction were also reported [27–30]. Most of these methods deal with the synthesis of multi-functional indoles, generally substituted at position 2 and/or 3 of the indole ring [31].

While some of these methods have proven to be most powerful and are currently applied in the target- or the diversity-oriented synthesis of indoles, they remain limited when applied to the synthesis of 2-substituted-3-vinyl-indoles, an important feature of alkaloids and peptide natural products like tryptophan, serotonin or melatonin (Fig. 2), as generally moderate to low yields are obtained. Another difficulty concern the limited choice of substituents at position 3 [32–34].

Recently, a new and elegant palladium catalysed transformation of indoles was reported by Gaunt and co-workers [35]. The methodology, based on the direct palladium(II) catalysed C–H functionalisation of aromatic heterocycles, involves a selective oxidative C3-alkenylation of free NH-indoles (Scheme 1) [36]. Among all procedures reported in this contribution, the one using a large excess of copper salts (mainly $Cu(OAc)_2$) as palladium re-oxidant retained our attention since it allows developing a fully catalytic procedure.

[Pd/Cu]-catalytic systems have been extensively employed for selective catalytic oxidations, mainly of alkenes like in the so-named Wacker process [37–39]. Very few reports concern the use of [Pd/Cu]-catalysts for oxidative C–C coupling reactions [40,41]. In these systems, the redox couple $Pd^{(II)}/Pd^{(0)}$ is believed to act as the active species, while the $Cu^{(I)}/Cu^{(II)}$ redox couple act as a co-catalyst to ensure the palladium re-oxidation under oxygen atmosphere, generally in presence of chloride ions. Based on these mechanistic considerations and following our interest to develop new simple, eco-efficient and environmentally friendly procedures for the synthesis of biologically and pharmaceutically relevant molecules, we explored a fully [Pd/Cu]-catalysed synthesis of 2-substituted-3-vinylindoles by a selective oxidative C3-alkenyla-

---

[*] Corresponding author. Tel.: +33 4 72 44 53 81; fax: +33 4 72 44 53 99.
E-mail address: Laurent.djakovitch@ircelyon.univ-lyon1.fr (L. Djakovitch).

0920-5861/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.cattod.2008.07.013

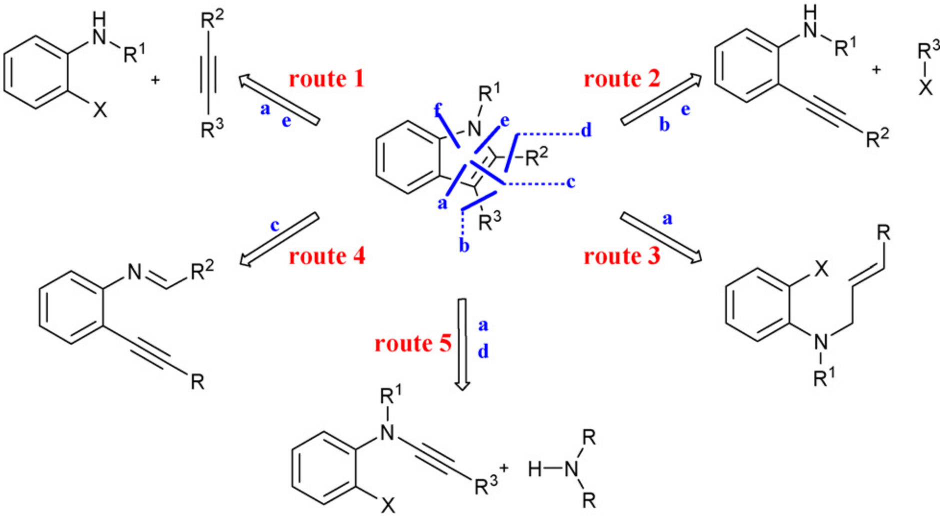


Fig. 1. Retro-synthetic approaches towards the synthesis of indole nucleus catalysed by palladium.

tion of NH-free indoles. In this contribution, we described the results obtained using homogeneous and heterogeneous [Pd/Cu]-catalysts under relatively mild reaction conditions.

2. Experimental

All preparations of catalysts were conducted under a strict inert atmosphere or vacuum conditions using Schlenk techniques. All other reactions were conducted under air atmosphere. The glassware was base- and acid-washed and oven dried.

The solvents used for the synthesis of the molecular palladium precursors and catalysts were dried using standard methods and stored over activated 4 Å molecular sieves. The zeolite NaY was purchased from Sigma–Aldrich Chemical (LZ-Z-52). The support was dried under 5×10^{-2} mmHg at 120 °C for 48 h before synthesis of the catalyst **4**. All other chemicals (organic reagents and solvents) were used as received.

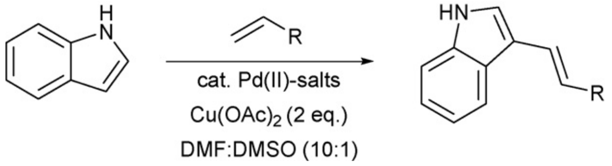
The catalytic reactions were carried out in three necked flask under air flow. The qualitative and quantitative analysis of the reactants and the products was made by gas chromatography. Conversions and yields were determined by GC based on the relative area of GC-signals referred to an internal standard (diethylene glycol di-*n*-butyl ether) calibrated to the corresponding pure compound.

The palladium content determinations of homogeneous catalyst **2** and heterogeneous [Pd/Cu]/NaY catalyst **4** was performed by ICP-AES spectroscopy from a solution obtained by treatment of the catalysts with a mixture of HBF_4, HNO_3 and HCl in a Teflon reactor at 180 °C.

High resolution mass spectra (HRMS) were recorded on a Thermo Finnigan MAT 95 XL spectrometer. Liquid NMR spectra were recorded on a BRUKER AC-250 spectrometer. All chemical shifts were measured relative to residual ^1H or ^{13}C NMR resonances in the deuterated solvents: $CDCl_3$, δ 7.25 ppm for ^1H, 77 ppm for ^{13}C; D_6-DMSO, δ 2.49 ppm for ^1H, 39.5 ppm for ^{13}C. Solid-state ^1H and ^{13}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 ^1H and ^{13}C MAS NMR spectra approximately 300 mg of the sample were packed into 4 mm ZrO_2 Bruker rotors with Kel-F caps. ^1H and ^{13}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 ^{13}C spectrum to 29.472 ppm relative to TMS. ^1H MAS NMR spectra were recorded at a sample spinning speed of 15 kHz. ^{13}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. 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^{2+} (nuclear spin 5/2) embedded in MgO as standard (the forth low field line as $g = 1.981$) and DPPH (2,2-diphenyl-1-picryl-hydrozil; $g = 2.0036$) as additional standard. Experimental errors: $\Delta g = \pm 0.003$, $\Delta A = \pm 5 \times 10^{-4}$ and $\Delta(\Delta B_{pp}) = \pm 10$ G.

Flash chromatography was performed at a pressure slightly greater than atmospheric pressure using silica (Merck Silica Gel 60,

Fig. 2. Some examples of biologically relevant C3-alkylated indoles.



Scheme 1. C3-alkenylation of free NH-indoles.

230–400 mesh). Thin layer chromatography was performed on Fluka Silica Gel 60 F_{254}.

GC analyses 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 is used as carrier gas. The mass spectra were obtained on a HP 6890 gas chromatograph equipped with a HP 5973 mass detector and a HP-5 MS column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness). Helium is used as carrier gas. The experimental error was estimated to be $\Delta_{\text{rel}} = \pm 5\%$.

2.1. Preparation of the [Pd(Hhp)$_2$Cl$_2$] complex **1** [42]

4 mmol of 2-hydroxypyridine (Hhp) (380 mg) was added to 2 mmol (590 mg) of Na_2PdCl_4 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 **1** as a microcrystalline yellow solid.

^{1}H NMR (D_6-DMSO): 8.14 (*pseudo*-d, 1H, C_5H_4NOH); 7.96 (*pseudo*-d, 1H C_5H_4NOH); 7.62 (broad *pseudo*-d, 1H C_5H_4NOH); 7.59 (broad *pseudo*-d, 1H C_5H_4NOH); 6.78 (broad *pseudo*-t, 2H C_5H_4NOH); 6.69 (broad *pseudo*-d, 2H C_5H_4NOH).

^{13}C NMR (D_6-DMSO): 162.33 and 163.06 (C_q–C_5H_5NO); 149.45 and 148.60 (*o*-CH–C_5H_5NO); 141.51 and 140.98 (*p*-CH–C_5H_5NO); 116.70 and 116.56 (*m*-CH–C_5H_5NO); 112.02 (*m*-CH–C_5H_5NO).

2.2. Preparation of the homogeneous [PdCl(hp)$_3$Cu]$_2$ catalyst **2** [43]

4 mmol of 2-hydroxypyridine (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× 5 mL of ethanol. The product was dried under vacuum for 3 days to give 805 mg (82% yield) of compound **2** 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 (calc.)]: 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), and Cl 6.50 (6.57).

2.3. Preparation of the [Pd(Hhp)$_2$Cl$_2$]/NaY **3** [44]

2 mmol (590 mg) of Na_2PdCl_4 was added to a suspension of NaY (3 g) in 200 mL of water. After 1 h, 4 mmol (380 mg) of Hhp was 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 (C–O, C_5H_5NO); 150.18 (*o*-CH, C_5H_5NO); 143.95 (*p*-CH, C_5H_5NO); 118.81 (*m*-CH, C_5H_5NO); 111.99 (*m*-CH, C_5H_5NO). Elemental analysis: 5.57 wt% Pd.

2.4. Preparation of the [Pd–Cu]/NaY catalyst **4** [44]

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 was 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 was 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 **4** 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.

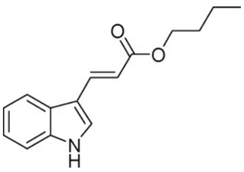
EPR X-band spectra (130 K): $g_\perp = 2.095$ mT. Elemental analysis: 5.37 wt% Pd and 2.17 wt% Cu.

2.5. General procedure for the catalytic tests

3 mmol of indole, 6 mmol of butylacrylate, 0.3 mmol of [Pd]-catalyst, and when applied 0.3 mmol of [Cu]-co-catalyst were introduced in a three necked flask. 8 mL of solvent was added to the mixture. The reactor was set with a cannula to afford a continuous air bubbling through the reaction mixture at a flow of 20 mL/min, and was placed in a pre-heated oil bath at 70 °C under vigorous stirring. The mixture was then cooled to room temperature before the reaction mixture was analyzed by GC. At completion of the reaction, the mixture was diluted with 150 mL of water and the resulting mixture was extracted with 2× 20 mL CH_2Cl_2 or EtOAc. The combined organic layers were washed three times with 15 mL of H_2O, then 15 mL of brine, dried over $MgSO_4$ and evaporated. The residue was then purified by flash chromatography on silica gel. The isolated compounds **5** were characterised through ^{1}H and ^{13}C NMR.

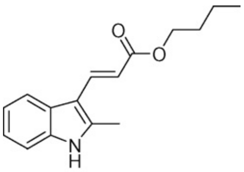
2.6. Charaterisation of indoles

2.6.1. (E)-Butyl 3-(1H-indole-3-yl)acrylate **5a**



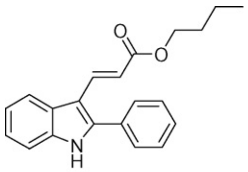
68% as a slightly yellow solid. R_f (petroleum ether (40–60)/ ethyl acetate, 4/1) = 0.22. mp: 81 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 9.62 (s, 1H, *H*–N); 8.06 (d, 1H, ^3J = 15.9 Hz, *H*C=CH–C=O); 7.79 (m, 1H, H_{arom}); 7.42 (m, 2H, H_{arom}); 7.32 (m, 1H, H_{arom}); 6.58 (d, 1H, ^3J = 15.9 Hz, *H*C–C=O); 4.33 (t, 2H, ^3J = 6.6 Hz, H_2C–O); 1.79 (qn, 2H, ^3J = 6.5 Hz, H_2C–CH_2–CH$_2$); 1.54 (sx, 2H, ^3J = 7.8 Hz, H_2C–CH$_3$); 1.05 (t, 3H, ^3J = 7.3 Hz, H_3C–CH$_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): 169.31 (*C*=O); 139.18 (*C*H=CH); 137.56 (C_q–C_6H_4); 130.08 (C=*C*HNH); 125.36 (C_q–C_6H_4); 123.25 (CH=*C*H); 121.49 (C_6H_4); 120.41 (C_6H_4); 112.49 (C_6H_4); 112.39 (C_6H_4); 113.10 (*C*=CNH); 64.42 (CH_2–O); 30.99 (H$_2$*C*–CH$_2$–O); 19.37 (H$_2$*C*–CH$_3$); 13.91 (H$_2$C–*C*H$_3$). HRMS calc. for $C_{15}H_{17}NO_2$ [M$^+$]: 243.1259, found: 243.1259.

2.6.2. (E)-Butyl 3-(2-methyl-1H-indole-3-yl)acrylate **5b**



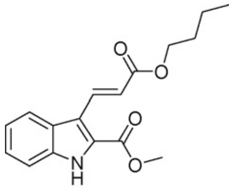
82% as a beige solid. R_f (petroleum ether (40–60)/ethyl acetate, 4/1) = 0.47. mp: 116 °C. ^1H NMR (250 MHz, $CDCl_3$): 8.58 (s, 1H, *H*–N); 7.87 (d, 1H, ^3J = 15.9 Hz, *H*C=CH–C=O); 7.79–7.76 (m, 1H, H_{arom}); 7.25–7.10 (m, 3H, H_{arom}); 6.35 (d, 1H, ^3J = 15.9 Hz, *H*C–C=O); 4.16 (t, 2H, ^3J = 6.6 Hz, H_2C–O); 2.42 (s, 3H, H_3C–CNH); 1.64 (qn, 2H, ^3J = 6.5 Hz, $H_2C–CH_2–CH_2$); 1.38 (sx, 2H, ^3J = 7.8 Hz, $H_2C–CH_3$); 0.90 (t, 3H, ^3J = 7.3 Hz, $H_3C–CH_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): 169.99 (*C*=O); 140.20 ($C_q–C_6H_4$); 137.61 (*C*H=CH); 135.75 (C=*C*NH); 126.33 ($C_q–C_6H_4$); 122.40 (CH=*C*H); 121.33 (C_6H_4); 119.95 (C_6H_4); 111.89 (C_6H_4); 110.92 (C_6H_4); 109.53 (*C*=CNH); 64.05 (CH_2–O); 30.93 ($H_2C–CH_2$–O); 19.26 ($H_2C–CH_3$); 13.80 ($H_2C–CH_3$); 12.25 (CH_3–CNH). HRMS calc. for $C_{16}H_{19}NO_2$ [M^+]: 257.1416; [MNa]: 280.13.13, found: 280.1313.

2.6.3. (E)-Butyl 3-(2-phenyl-1H-indole-3-yl)acrylate **5c**



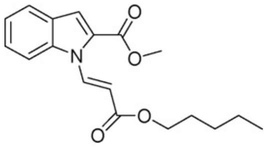
63% as an orange solid. R_f (petroleum ether (40–60)/ethyl acetate, 4/1) = 0.39. mp: 98 °C. ^1H NMR (250 MHz, $CDCl_3$): 9.28 (s, 1H, *H*N); 7.91 (d, 1H, ^3J = 15.9 Hz, *H*C=CH–C=O); 7.83–7.78 (m, 1H,); 7.33–7.08 (m, 8H, H_{arom}); 6.45 (d, 1H, ^3J = 15.9 Hz, *H*C–C=O); 4.02 (t, 2H, 3J = 6.6 Hz, H_2C–O); 1.52 (qn, 2H, ^3J = 6.8 Hz, $H_2C–CH_2–CH_2$); 1.28 (sx, 2H, ^3J = 7.2 Hz, $H_2C–CH_3$); 0.81 (t, 3H, ^3J = 7.3 Hz, $H_3C–CH_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): 169.21 (*C*=O); 142.98 ($C_q–C_6H_4$); 139.30 (*C*H=CH); 136.67 ($C_q–C_6H_4$); 131.25 ($C_q–C_6H_5$); 129.21 (C_6H_5); 128.96 (C_6H_5); 128.86 (C_6H_5); 126.53 (C=*C*NH); 123.36 (C_6H_4); 121.65 (CH=*C*H); 120.80 (C_6H_4); 113.53 (C_6H_4); 111.80 (C_6H_4); 109.61 (*C*=CNH); 64.24 (CH_2–O); 30.89 ($H_2C–CH_2$–O); 19.29 ($H_2C–CH_3$); 13.85 ($H_2C–CH_3$). HRMS calc. for $C_{21}H_{21}NO_2$ [M^+]: 319.1572, found: 319.1573.

2.6.4. (E)-Methyl 3-(3-butoxy-3-oxoprop-1-enyl)-1H-indole-2-carboxylate **5d**



58% as a beige solid. R_f (petroleum ether (40–60)/ethyl acetate, 9/1) = 0.73. mp: 171 °C. ^1H NMR (250 MHz, $CDCl_3$): 9.17 (s, 1H, N*H*); 8.51 (d, 1H, ^3J = 16.3 Hz, *H*C=CH–C=O); 7.95 (d, 1H, ^3J = 8.1 Hz, H_{arom}); 7.40–7.18 (m, 3H, H_{arom}); 6.63 (d, 1H, ^3J = 16.3 Hz, *H*C–C=O); 4.18 (t, 2H, ^3J = 6.6 Hz, H_2C–O); 3.95 (s, 3H, H_3C–O); 1.66 (qn, 2H, ^3J = 6.6 Hz, $H_2C–CH_2$–O); 1.40 (sx, 2H, ^3J = 7.6 Hz, $CH_2–CH_3$); 0.92 (t, 3H, ^3J = 7.3 Hz, $H_3C–CH_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): 167.68 (*C*(=O)–O–CH_2); 162.00 (*C*(=O)–O–CH_3); 137.06 (*C*H=CH); 136.10 ($C_q–C_6H_4$); 126.55 (C=*C*NH); 126.17 (C_6H_4); 125.72 ($C_q–C_6H_4$); 122.30 (br; C_6H_4 and CH=*C*H); 119.35 (C_6H_4); 117.20 (*C*=CNH); 112.32 (C_6H_4); 64.32 (CH_2–O); 52.50 (H_3C–O); 30.82 ($H_2C–CH_2$–O); 19.23 ($H_2C–CH_3$); 13.78 ($H_2C–CH_3$). HRMS calc. for $C_{17}H_{19}NO_4$ [M^+]: 301.1314, found: 301.1315.

2.6.5. (E)-Methyl 1-(3-oxo-3-(pentyloxy)prop-1-enyl)-1H-indole-2-carboxylate

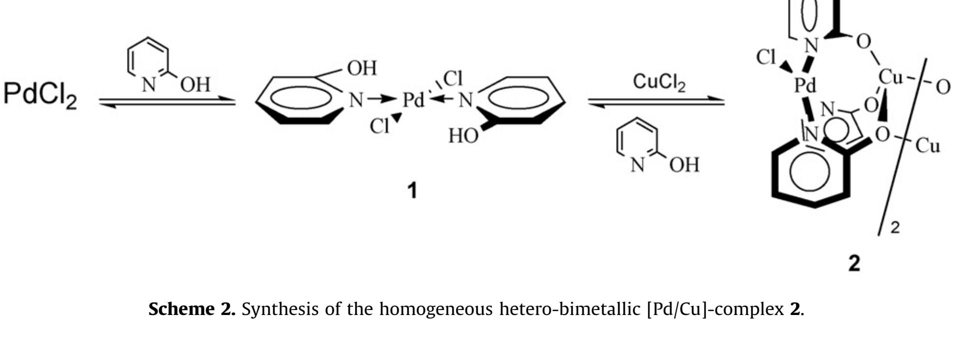


16% as a slightly orange solid. R_f (petroleum ether (40–60)/ethyl acetate, 9/1) = 0.58. mp: 61 °C. ^1H NMR (250 MHz, $CDCl_3$): 8.96 (d, 1H, ^3J = 14.4 Hz; *H*C–N); 7.72 (d, 1H, ^3J = 8.5 Hz, H_{arom}); 7.60 (d, 1H, ^3J = 7.85 Hz, H_{arom}); 7.35 (dt, 1H, ^3J = 6.75 Hz, ^4J = 1.2 Hz, H_{arom}); 7.32 (s, 1H, C*H*=C); 7.18 (dt, 1H, ^3J = 7.8 Hz, ^4J = 0.7 Hz, H_{arom}); 6.22 (d, 1H, ^3J = 14.5 Hz, *H*C–C=O); 4.16 (t, 2H, ^3J = 6.67 Hz, H_2C–O); 3.85 (s, 3H, H_3C–O); 1.64 (qn, 2H, ^3J = 6.50 Hz, $H_2C–CH_2$–O); 1.38 (sx, 2H, ^3J = 7.6 Hz, $CH_2–CH_3$); 0.87 (t, 3H, ^3J = 7.3 Hz, $CH_2–CH_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): 167.15 (*C*(=O)–O–CH_2); 161.53 (*C*(=O)–O–CH_3); 140.02 ($C_q–C_6H_4$); 137.78 (CH=*C*NH); 128.01 ($C_q–C_6H_4$); 127.87 (*C*H=CH); 127.00 (C_6H_4); 123.17 (C_6H_4); 123.03 (C_6H_4); 115.80 (C_6H_4); 113.56 (*C*H=CNH); 107.47 (CH=*C*H); 64.43 (CH_2–O); 52.17 (H_3C–O); 30.80 ($H_2C–CH_2$–O); 19.19 ($H_2C–CH_3$); 13.77 ($H_2C–CH_3$). HRMS calc. for $C_{17}H_{19}NO_4$ [M^+]: 301.1314, found: 301.1316.

3. Results and discussions

3.1. Catalysts

The homogeneous hetero-bimetallic complex $[PdCl(hp)_3Cu]_2$ **2** was synthesised according to the procedure reported by Wada et al. [43] (Scheme 2). Treating sodium tetrachloropalladate in water with 2-hydroxypyridine led to the formation of the intermediate *trans*-$[Pd(Hhp)_2Cl_2]$ **1** as a microcrystalline yellow compound characterised by ^1H and ^{13}C NMR (Fig. 3a) [42]. Further treatment of **1** in ethanol by $CuCl_2$ and Hhp gave the hetero-bimetallic complex $[PdCl(hp)_3Cu]_2$ **2** as a slightly orange microcrystalline compound characterised by X-band EPR spectroscopy in frozen ethanol solution at 130 K showing the paramagnetic nature of the Cu^{2+} complex, giving $g_\perp = 2.078$, $g_{||} = 2.362$ and $A_{||}(^{63,65}Cu) = 12.09$ mT which are



Scheme 2. Synthesis of the homogeneous hetero-bimetallic [Pd/Cu]-complex **2**.

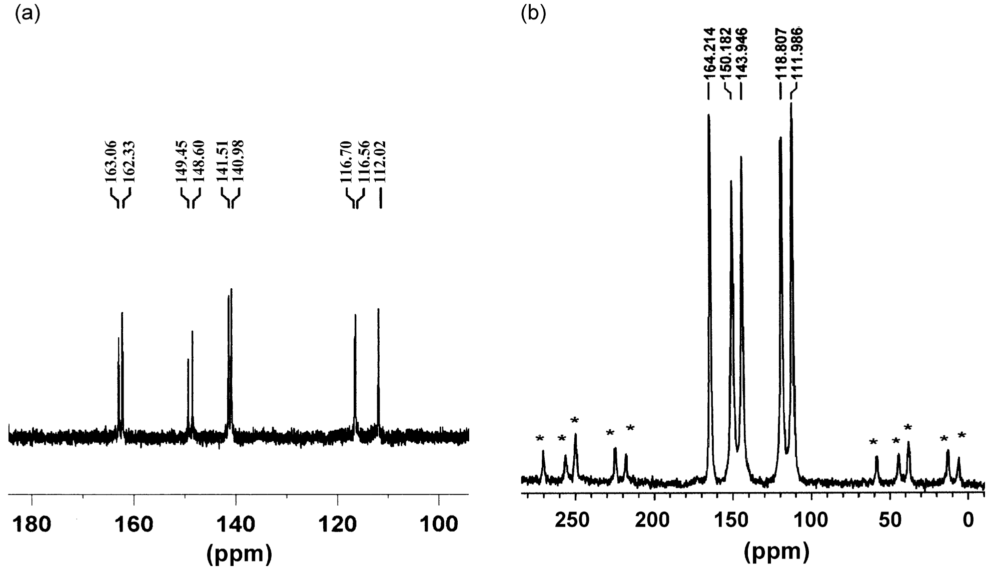


Fig. 3. (a) Solution ^{13}C NMR of the complex [Pd(Hhp)$_2$Cl$_2$] **1** in D_6-DMSO (saturated). (b) ^{13}C MAS-NMR of the complex [Pd(Hhp)$_2$Cl$_2$] in NaY (solid **3**, neat).

consistent with the values reported in the literature for octahedral Cu^{2+} complexes (Fig. 4a). The spectrum exhibits a well resolved ^{63,65}Cu hyperfine structure (quartet) due to the interaction of the unpaired electron (3d^9, S = 1/2, I(^{63,65}Cu) = 3/2) and can be described by an axially symmetric spin Hamiltonian.

Analogous to the synthesis of **2**, we prepared the heterogeneous bimetallic [Pd–Cu]/NaY-catalyst **4** by analogy to the well-described "ship-in-a-bottle" synthesis [45]. Treatment of NaY with sodium tetrachloropalladate in water in presence of Hhp ligand affords the [Pd(Hhp)$_2$Cl$_2$]-complex **1** entrapped into NaY as shown by ^{13}C NMR of the solid **3** (Fig. 3b). The light brown solid exhibits an absolute palladium content of 5.6 wt% Pd which was determined by ICP-AES. Further treatment in water by CuCl$_2$ in presence of Hhp ligand gave after washing and drying an orange material as [Pd–Cu]/NaY **4**. The absolute palladium and copper content were determined by ICP-AES to be 5.4 wt% Pd and 2.2 wt% Cu. While these analyses are close to the expected ones, the calculated atomic ratio Pd/Cu = 1.4 for the catalyst **4** indicates that it contains more Pd-species than expected based on the hetero-bimetallic complex **2** for which the ratio Pd/Cu is equal to 1. These results suggest that not all immobilised palladium species of **4** are present as hetero-bimetallic [Pd–Cu]-species. The EPR spectra of heterogeneous bimetallic [Pd–Cu]-catalyst consists of a superposition of probably two species (Fig. 4b). The ^{63,65}Cu hyperfine structure is not resolved making the quantitative interpretation difficult. The significant broadening of the $g_{||}$ (or g_1, g_3) region may be due to spin–spin interactions of near neighboured paramagnetic copper(II) centres or due to distorted coordination environment (rhombic symmetry of the paramagnetic centre), what can be expected on the surface. The spectral pattern and the g-values $g_\perp$ (or g_2) = 2.095 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 immobilisation procedure.

These homogeneous and heterogeneous bimetallic catalysts were compared to homogeneous catalytic systems made from "mechanical" combination of soluble Pd$^{(II)}$- and Cu$^{(II)}$-salts (i.e. Pd(OAc)$_2$, PdCl$_2$, PdCl$_2$(CH$_3$CN)$_2$, and CuCl$_2$) as equimolar Pd:Cu mixtures.

3.2. Catalytic reactions and optimisation

Initially, the [Pd/Cu]-catalysed C3-alkenylation of free NH-indoles was studied using the indole (R = H) as substrate, evaluating several homogeneous and heterogeneous catalytic systems. Following the procedure reported in the literature [35], all reactions were run in a DMF/DMSO (10/1) solvent mixture.

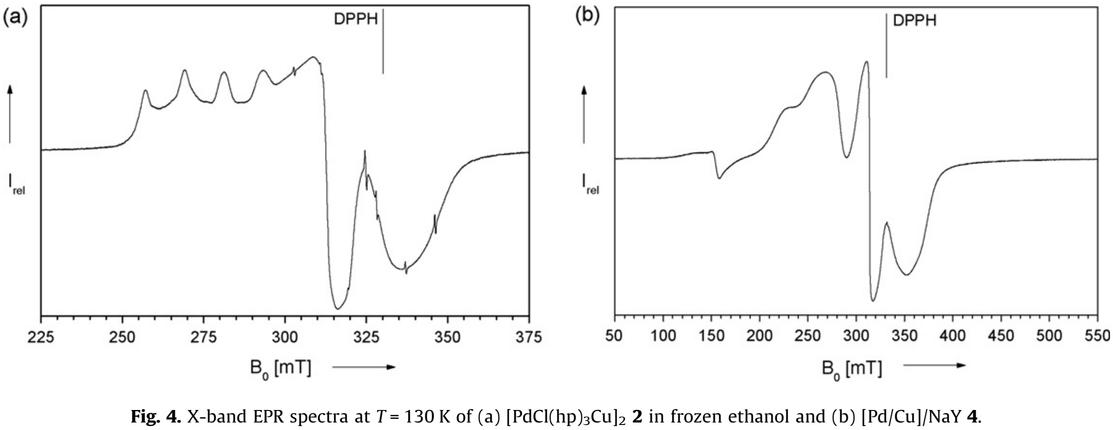


Fig. 4. X-band EPR spectra at T = 130 K of (a) [PdCl(hp)$_3$Cu]$_2$ **2** in frozen ethanol and (b) [Pd/Cu]/NaY **4**.

Table 1
Influence of the catalytic system on the C3-alkenylation of indole (Scheme 3, R = H)

Entry	Catalyst	Conversion[a] (20 h) (%)	Selectivity C2/C3[b]	A_i[c] ($\times 10^{-3}$)
1	$[Pd(OAc)_2/Cu(OAc)_2]$	52	0/100	0.9
2	$[PdCl_2/CuCl_2]$	30	33/67	Negligible
3	$[PdCl_2(CH_3CN)_2/CuCl_2]$	16	20/80	Negligible
4	$[PdCl(hp)_3Cu]_2$ **2**	65	0/100	0.4
5	[Pd/Cu]/NaY **4**	60	0/100	0.4

Reaction conditions: 3 mmol indole, 10 mol% Pd-catalyst + 10 mol% Cu-catalyst or 10 mol% as heterobimetallic catalyst **2** or **4**, 8 mL DMF/DMSO (10/1), 70 °C, air bubbling (20 mL/min).

[a] Conversions based on unreacted indole were determined by GC ($\Delta_{rel} = \pm 5\%$).

[b] Selectivities were determined by GC on the basis of area percentage.

[c] Initial activity (A_i) in mol/(g_{Pd} min).

Table 1 clearly indicates that the catalytic systems made from a mixture of palladium-chloride salts gave low active and selective catalysts (entries 2 and 3). Fig. 5 clearly shows that these catalytic systems are not active at the beginning of the reaction, showing an initiating period of *ca.* 3 h for the $[PdCl_2/CuCl_2]$ and 6 h for the $[PdCl_2(CH_3CN)_2/CuCl_2]$ catalytic system. For the former system, the period was attributed to lower solubility of $PdCl_2$ and $CuCl_2$ in the reaction medium. During this period, we assumed that a more soluble $[PdCl_2(DMF)_2]$ complex is formed [46]; however, the activity (0.03×10^{-3} mol/(g_{Pd} min)) is not as high as expected probably due to the formation of dimeric palladium or heterobimetallic {palladium/copper} poorly active species. For the latter, the longer initiating period and the lower activity (0.015×10^{-3} mol/(g_{Pd} min)) was attributed to the formation of the polymeric brown $[(PdCl_2)_2CuCl_2(DMF)_4]_n$ material which was previously reported in the literature [47,48]. Its low solubility caused probably the low activity observed.

The $[Pd(OAc)_2/Cu(OAc)_2]$ catalytic system, while showing the highest initial activity (0.9×10^{-3} mol/(g_{Pd} min)) led to moderate conversion (55% within 42 h) due to rapid catalyst deactivation by palladium black formation. Unexpectedly, the homogeneous heterobimetallic complex **2**, while showing a lower initial activity (0.4×10^{-3} mol/(g_{Pd} min)) gave finally higher conversion (65% within 20 h) than the "standard" $[Pd(OAc)_2/Cu(OAc)_2]$ catalytic system.

The most interesting result came probably from the heterogeneous catalyst [Pd/Cu]/NaY **4**. This heterogeneous catalyst showed an initial activity of 0.4×10^{-3} mol/(g_{Pd} min) close to that obtained for the homogeneous complex **2** giving a full conversion of the indole within 66 h. If this behaviour could be attributed to site isolation of the Pd- and Cu-species in the zeolite framework that stabilise the catalyst during the reaction, the value obtained for the initial activity suggests that palladium and copper leaching occurred during the reaction as confirmed by ICP-AES analyses performed on a clear filtrate obtained from hot filtration of reaction mixture (*ca.* 12% of the palladium and 23% of the copper leached during the reaction over a period of 60 h). In any cases, this rate of Pd and Cu leaching could account alone for the activity observed using the heterogeneous catalyst **4**. Furthermore, no catalytic activity was observed while using a clear filtrate as "Pd/Cu-catalyst" indicating that the heterogeneous catalyst [Pd/Cu]/NaY **4** could be seen as a continuous source of active species in solution. These results could explain why, to date, our attempts to recycle this catalyst were unsuccessful.

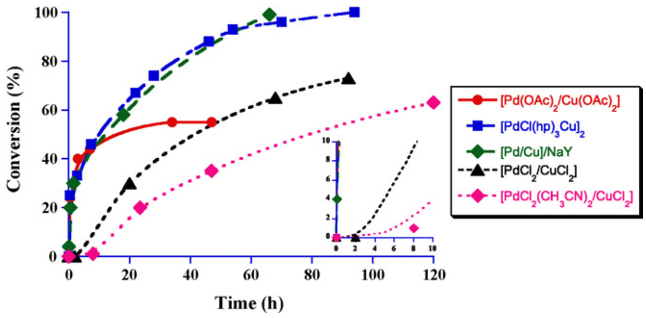
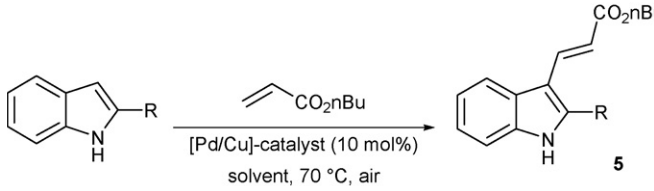


Fig. 5. Influence of the [Pd/Cu]-catalytic system on the C3-alkenylation of Indole. Reaction conditions: 3 mmol indole, 10 mol% Pd-catalyst + 10 mol% Cu-catalyst or 10 mol% [Pd] as heterobimetallic catalyst **2** or **4**, 8 mL DMF/DMSO (10/1), 70 °C, air bubbling (20 mL/min).



Scheme 3. [Pd/Cu]-catalysed C3-alkenylation. Reaction conditions: 3 mmol indole, 10 mol% Pd-catalyst, 10 mol% Cu-catalyst, 8 mL solvent, 70 °C, air (20 mL/min).

To optimise further the C3-alkenylation of indoles, we evaluated various solvent using the mixture of $[Pd(OAc)_2/Cu(OAc)_2]$ (1:1) as catalyst and indole as substrate (Scheme 3).

As reported in Table 2, the solvent was found to play a major role on the reactivity of indole. DMSO was found to be the best solvent to perform the C3-alkenylation under our reaction conditions, giving 85% conversion with a full C3-selectivity within 3 h. Using other solvents like DMF, DMF/H_2O or mixtures DMF/DMSO did not improve the reaction rate, as generally lower conversions are achieved at the same reaction time. Fig. 6 clearly shows that, while presenting interesting initial activities, the reaction carried out in presence of DMF led to catalyst deactivation, probably by palladium agglomeration as observed by the precipitation of black particles.

These behaviours could be better expressed by comparing the initial activity of the catalytic system for each solvent. While the initial activity reached 2.4×10^{-3} mol/(g_{Pd} min) in pure DMSO, adding DMF to the solvent mixture led to decreased activities (Table 2, entries 1 *versus* 2 and 3). Furthermore, in pure DMF, no activity was observed. These results differ from those reported using excess-stoichiometric amount of $Cu(OAc)_2$ as re-oxidant: in the mixture DMF/DMSO (10/1) high conversions and selectivities were achieved [35]. These results could indicate that under our conditions, DMSO act as a "favourable" ligand in the $[Pd(OAc)_2/Cu(OAc)_2]$ catalytic system preventing the palladium precipitation by coordination [49] whereas DMF could led to formation of inactive palladium complexes as reported above. In addition, DMSO was proved to act as an oxygen carrier in many transition

Table 2
Influence of the solvent on the C3-alkenylation of indole (Scheme 3, R = H)

Entry	Solvent	Conversion[a] (3 h) (%)	A_i ($\times 10^{-3}$ mol/(g_{Pd} min))
1	DMSO	85	2.4
2	DMF/DMSO (1/1)	65	1.9
3	DMF/DMSO (10/1)	45	0.9
4	DMF/H_2O (4/1)	25	0.5
5	DMSO/AcOH	85	1.3
6	DMF/H_2O/AcOH (4/1/1)	65	1.1

Reaction conditions: 3 mmol indole, 10 mol% $Pd(OAc)_2$, 10 mol% $Cu(OAc)_2$, 8 mL solvent, and 70 °C, air bubbling (20 mL/min).

[a] Conversions based on unreacted indole were determined by GC ($\Delta_{rel} = \pm 5\%$).

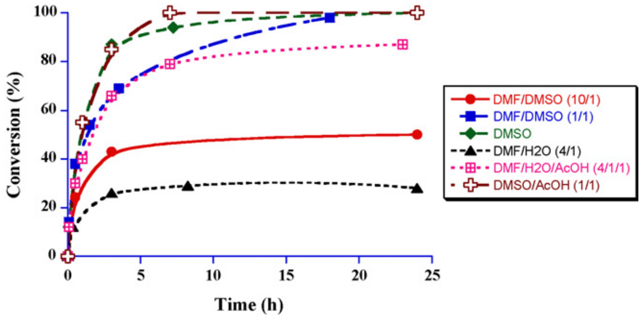


Fig. 6. Influence of the solvent on the reactivity of indole towards C3-alkenylation. Reaction conditions: 3 mmol indole, 10 mol% $Pd(OAc)_2$, 10 mol% $Cu(OAc)_2$, 8 mL solvent, 70 °C, air bubbling (20 mL/min).

metals catalysed oxidations, improving also probably the palladium re-oxidation rate by the couple $Cu^{(I)}/Cu^{(II)}$ under air [50,51].

Interestingly, using acetic acid as co-solvent to DMSO, while leading to slightly decreased initial activity (1.3×10^{-3} mol/(g_{Pd} min) *versus* 2.4×10^{-3} mol/(g_{Pd} min)), improved considerably the rate of the reaction as complete conversion was achieved within 7 h whereas it required 24 h in pure DMSO [52,53]. This could be reasonably attributed to enhanced copper re-oxidation by air in presence of acidic co-solvent improving thus the palladium re-oxidation towards the catalytically active $Pd^{(II)}$-species according to the classical [Pd/Cu] redox equations (Fig. 7), without discarding alternative explanation considering that the acidic co-solvent could favour the formation of highly electrophilic $Pd^{(II)}$-species more reactive towards the attack of the indole ring in the very first steps of the reaction [54]. (Fig. 7: [Pd/Cu] redox equations):

$$Pd^{(0)} + 2Cu^{(II)} \rightarrow Pd^{(II)} + 2Cu^{(I)} \qquad (1)$$

$$2Cu(I) + \tfrac{1}{2}O_2 = 2H^+ \rightarrow 2Cu(II) + H_2O \qquad (2)$$

The influence of the solvent on the activity of the heterogeneous [Pd/Cu]/NaY catalyst was evaluated (Fig. 7). Using pure DMSO did not improve the catalytic activity; however, as expected from the studies described above, using the mixture DMSO/AcOH (1/1) improved noticeably the rate of the reaction (0.9×10^{-3} mol/(g_{Pd} min) *versus* 0.4×10^{-3} mol/(g_{Pd} min)) and the stability of the catalyst since full conversion was achieved within 8 h while it required more than 90 h for other solvents.

The variations observed between homogeneous and heterogeneous catalytic systems in this study can be related to: (1) the different nature of the initial palladium and copper species present in solution, i.e. identified palladium and cooper complexes as $[Pd(OAc)_2/Cu(OAc)_2]$ (1:1) for homogeneous system, or unidentified Pd- and Cu-species generated in solution through the leaching of metal species for the heterogeneous catalyst; (2) the differences in palladium and copper concentrations in the bulk during the reaction: homogeneous catalytic systems use 10 mol% Pd and 10 mol% Cu while the heterogeneous catalyst works with only *ca.* 1.2 mol% Pd and 2.3 mol% Cu due to leaching of active species.

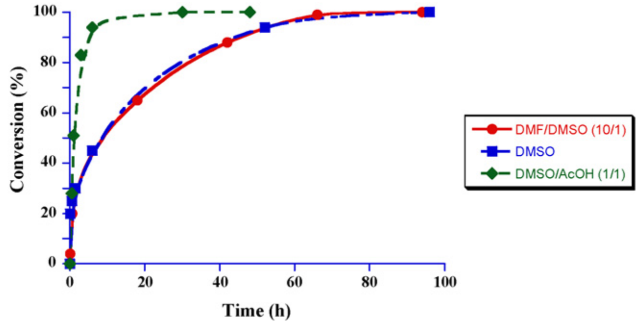


Fig. 7. Influence of the solvent on the activity of the heterogeneous [Pd/Cu]/NaY catalyst **4**. Reaction conditions: 3 mmol indole, 10 mol% [Pd] as heterogeneous [Pd/Cu]/NaY **4**, 8 mL solvent, 70 °C, air bubbling (20 mL/min).

In all cases, a full selectivity towards the C3-alkenylation was observed whatever the solvent or the catalyst used. This fit well with the results obtained by Gaunt and co-workers using excess of $Cu(OAc)_2$ as re-oxidant (i.e. C3-selectivity ≥95%)[35], indicating that the copper co-catalysed procedure presented here did not affect the selectivity of the reaction.

Having demonstrated the applicability of the fully [Pd/Cu]-catalysed C3-alkenylation under air, we extended the procedure to 2-substituted indoles (Scheme 3). All reactions were carried out in the solvent mixture DMSO/AcOH (1/1), comparing the heterogeneous [Pd/Cu]/NaY catalyst **4** to the "standard" $[Pd(OAc)_2/Cu(OAc)_2]$ catalytic system and the corresponding homogeneous complex $[PdCl(hp)_3Cu]_2$ **2**.

Independently on the substrate used, all catalytic system, whatever homogenous or heterogeneous, show approximately to the same activities, leading to close conversions and selectivities. However, strong differences where observed for the reactivity of various indoles under our reaction conditions (Table 3): while the 2-(methyl-carboxylate)indole ($R = CO_2Me$) required up to 120 h to achieve complete conversion, the 2-(methyl)indole (R = Me) was fully converted in 3 h, the indole (R = H) within 24 h and the 2-(phenyl)indole (R = Ph) in 92 h. These differences in reactivity can be reasonably attributed to electronic contributions of the substituents at the position 2 of the indole ring.

Except for the 2-(methyl-carboxylate)indole ($R = CO_2Me$), all substrates gave a full selectivity towards the expected C3-alkenylation (Table 3). To explain the lower C3-selectivity (*ca.* 75%) in the case of the 2-(methyl-carboxylate)indole, we propose that the intermediate $Pd^{(II)}$-complex that follows the indole coordination to the active palladium species is further coordinated by the carboxylate substituent (Fig. 8). In that case two complexes could be obtained: the complex **6** in which the $Pd^{(II)}$-centre is coordinated to the C3-position of the indole ring and to the

Table 3
C3-alkenylation of 2-substituted indoles (Scheme 3)

Entry	R	Catalyst	Conversion[a] (1 h) (%)	C3-selectivity[b] (%)
1	H	$[Pd(OAc)_2/Cu(OAc)_2]$	55	100
2		$[PdCl(hp)_3Cu]_2$ **2**	55	100
3		[Pd/Cu]/NaY **4**	51	100
4	Me	$[Pd(OAc)_2/Cu(OAc)_2]$	89	100
5		$[PdCl(hp)_3Cu]_2$ **2**	85	100
6		[Pd/Cu]/NaY **4**	88	100
7	Ph	$[Pd(OAc)_2/Cu(OAc)_2]$	61	100
8		$[PdCl(hp)_3Cu]_2$ **2**	52	100
9		[Pd/Cu]/NaY **4**	56	100
10	CO_2Me	$[Pd(OAc)_2/Cu(OAc)_2]$	32	73[c]
11		$[PdCl(hp)_3Cu]_2$ **2**	37	78[c]
12		[Pd/Cu]/NaY **4**	28	76[c]

Reaction conditions: 3 mmol indole, 10 mol% $Pd(OAc)_2$, 10 mol% $Cu(OAc)_2$ or 10 mol% as heterobimetallic catalyst **4**, 8 mL DMF/DMSO (10/1), 70 °C, and air bubbling (20 mL/min).

[a] Conversions based on unreacted indole were determined by GC ($\Delta_{rel} = \pm 5\%$).

[b] Selectivities were determined by GC on the basis of area percentage.

[c] In that case the N1-alkenylated compound was formed, in respectively 26% and 24% selectivity.

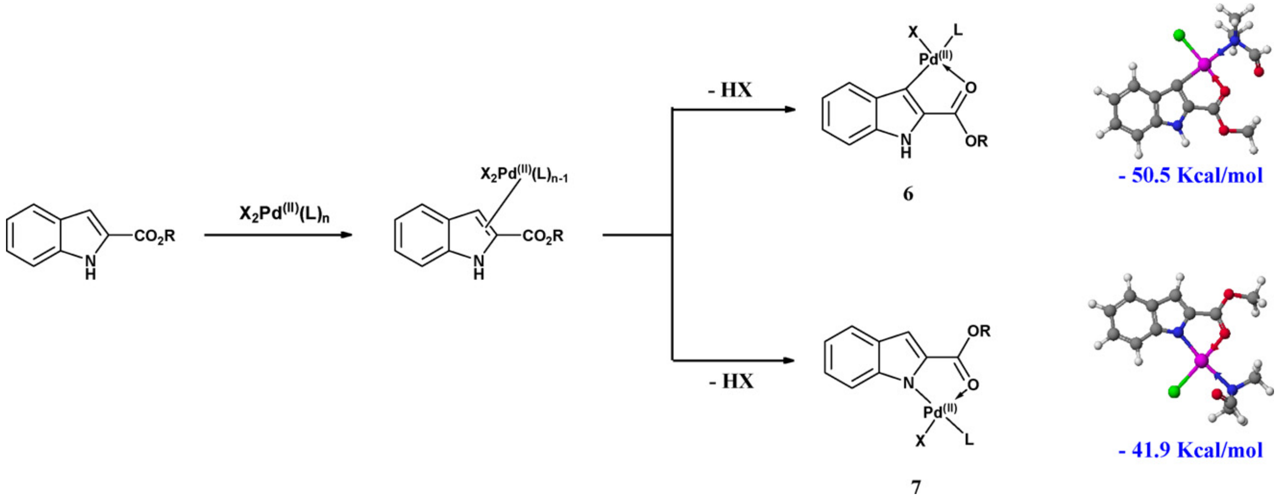


Fig. 8. Proposed reaction pathways to account for the N1/C3-alkenylation selectivity observed for the 2-(methyl-carboxylate)indole.

carboxylate and the complex **7** in which the Pd(II)-centre is link to the N1-position of the indole nucleus and to the carboxylate. As obtained from molecular mechanics MM2-calculations, [55] both complexes have close energy minima; however, the intermediate **6** appears to be slightly more stable than the palladium complex **7**. This difference could account for the N1/C3-selectivity observed.

3.3. About the mechanism?

Several mechanisms based on C–H-activation were proposed in the literature for the functionalisation of indoles, whatever the alkenyl or aryl group introduced on the indole nucleus. Sames and co-workers reported extensive studies on the direct arylation of free NH-indoles. After treating the indole nucleus with Grignard reagents, using iodobenzene as arylating agent and {[Pd(OAc)$_2$], PPh$_3$} as catalyst, selective C3-arylation was observed [56–58]. The mechanism proposed is mainly based on electrophilic substitution mechanism: a Pd$^{(II)}$-complex coordinates the indole ring to afford an intermediate in which the Pd$^{(II)}$-centre is link to the C3-position of the indole ring (electrophilic palladation). In this mechanism, the Pd$^{(0)}$-species produced through the reductive elimination of the expected coupling product are re-oxidised to Pd$^{(II)}$-complexes through the oxidative addition of the aryl iodides. Recently, Sanford and co-workers reported a palladium catalysed C2-arylation of indoles under mild reaction conditions (25 °C, AcOH, 15–24 h) using [Ar$_2$I$^+$, BF$_4$$^-$] as arylating agent. The authors proposed that the palladium catalysed C2-arylation of N-methyl or NH-indoles resulted from a Pd$^{(II)}$/Pd$^{(IV)}$ catalytic cycle [59]. Such Pd$^{(II)}$/Pd$^{(IV)}$ catalytic cycle were recently supported by computational studies for Pd-catalysed domino reactions involving aryl transfer [60]. Belina et al. reported a palladium/copper mediated direct C2-arylation of azoles and indoles [61]. They proposed that an organocopper intermediate is produced under the reaction conditions that led to transmetallation giving the expected product. However, the authors did not exclude the presence of Pd$^{(II)}$/Pd$^{(IV)}$ as intermediate species. Fujiwara and co-workers, in a study related to a palladium catalysed coupling of arene with olefin using benzoquinone as co-catalyst and *tert*-butylperoxide as re-oxidant proposed that after a CH-activation giving a palladium aryl complex, the reaction proceed like to the well documented Heck reaction [52]. Several evidences for such a mechanism are reported by the authors. Grimster et al. proposed that the C3-alkenylation of indoles results from a selective C3-palladation of the indole ring, followed by rearomatisation to furnish the expected compound after a Heck-like reaction pathway [35].

Based on these earlier publications, and our results, we propose the following mechanism (Fig. 9): after the coordination of the indole nucleus to the active [Pd$^{(II)}$X$_2$L$_n$] complex to give the intermediate **8**, an intramolecular CH-activation of the indole nucleus at C3-position occurred, leading to the elimination of HX to afford the complex **9** in which the palladium centre remain linked to the C3-position. This complex is close to those encountered in the Heck reaction (i.e. [ArPd$^{(II)}$XL$_n$] that follows the oxidative addition of ArX), giving then classical steps as involved in the Heck reaction mechanism. The issuing Pd$^{(0)}$-species are then re-oxidised under air by the Cu$^{(II)}$-species according the “Wacker” type chemistry.

4. Conclusions

The synthesis of 2-substituted-3-vinyl indoles remains a very important area of research for the fine chemical industry. Few methods have been developed to meet the growing demand of new active molecules; the most interesting being probably that reported recently by Gaunt and co-workers. However, due to the used of large excess of copper(II) salts to regenerate the active Pd$^{(II)}$-catalysts this method did not know important developments.

For the first time, we reported a fully palladium and copper catalysed economical and ecological benign synthesis of 2-substituted-3-vinyl indoles. Furthermore, we demonstrated that heterogeneous [Pd/Cu]-catalysts could be applied successfully to this project. Generally, full conversion is achieved within 3–48 h using only 10 mol% Pd-catalyst associated to 10 mol% Cu-catalyst. Almost all evaluated substrates, whatever a homogeneous or heterogeneous catalytic system, led to full selectivity towards the expected C3-alkenylation of 2-substituted indoles. Only the 2-(methyl-carboxylate)indole gave a mixture of product: 75% towards the C3-substituted compound together with 25% of the N1-substituted product. This behaviour was attributed to the formation of two stabilised intermediate palladium complexes in which the Pd$^{(II)}$-centre, that is coordinated to the to the C3 or N1-position, is stabilised by additional coordination to the carboxylate function.

Current investigations focus on the preparation of more stable and recyclable heterogeneous [Pd–Cu]-catalysts and

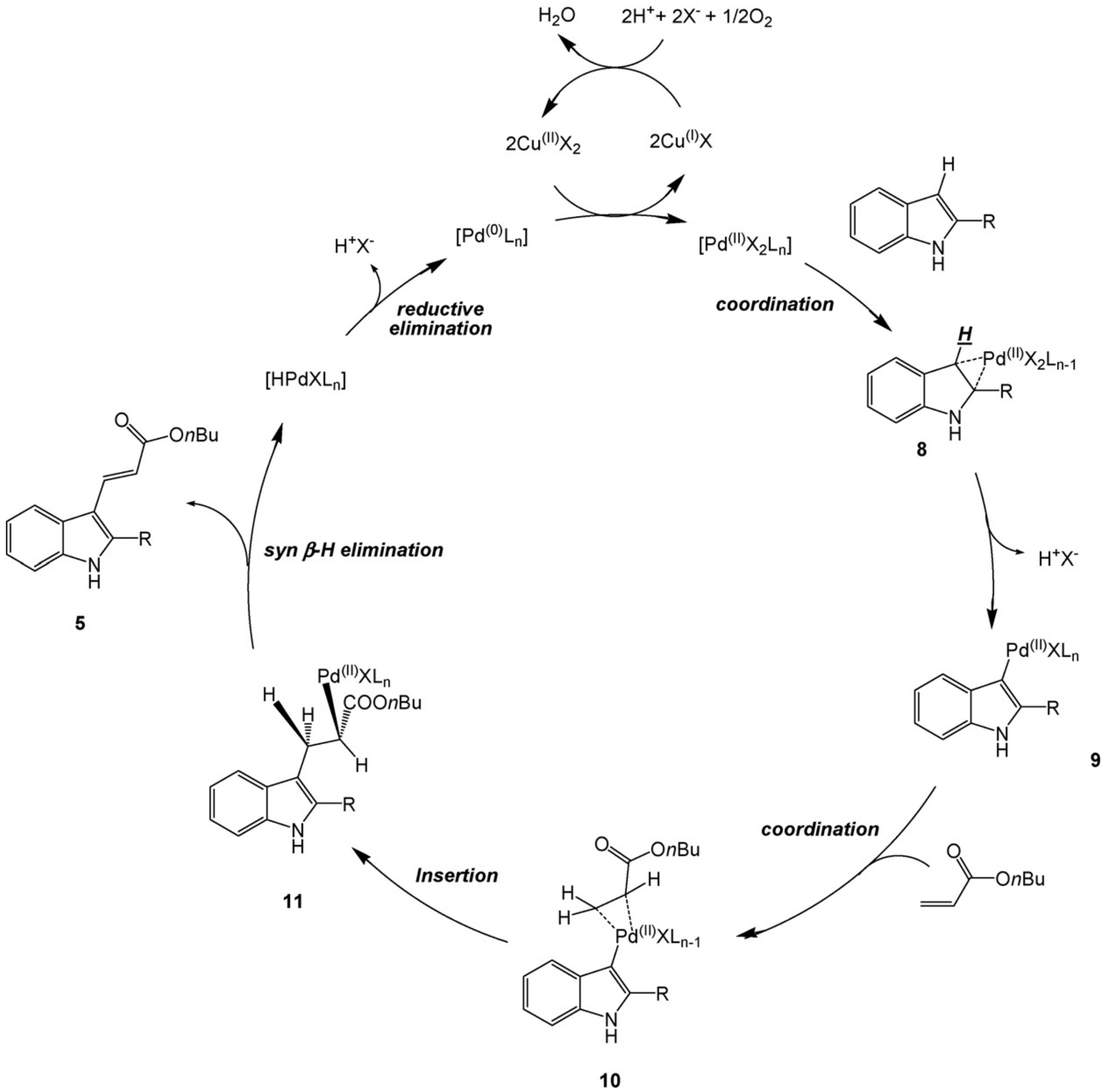


Fig. 9. Proposed mechanism for the [Pd/Cu]-catalysed C3-alkenylation of indoles.

their application towards the selective synthesis of multi-functional indoles.

Acknowledgments

Financial support provided by the Région Rhône-Alpes, France (contract "NAHMOVCA" number 301439201/E038131747/ENS006) is gratefully acknowledged. Authors would like to thank Prof. Klaus Koehler (TU Munich) for his help in measuring and interpreting EPR spectra.

References

[1] R.J. Sundberg, Indoles, Academic Press, London, 1996.
[2] J.A. Joule, in: E.J. Thomas (Ed.), Science of Synthesis, vol. 10, Thieme, Stuttgart, 2001, 361 pp.
[3] R.J. Sundberg, in: A.R. Katritzky, C.W. Rees (Eds.), Comprehensive Heterocyclic Chemistry, vol. 4, Oxford, Pergamon, 1984, p. 314.
[4] J. Tois, R. Franzén, A. Koskinen, Tetrahedron 59 (2003) 5395.
[5] D. Hughes, Org. Prep. Proc. Int. 25 (1993) 607.
[6] B. Robinson, The Fischer Indole Synthesis, John Wiley & Sons, Chichester, 1982 .
[7] R.D. Clark, D.B. Repke, Heterocycles 22 (1984) 195.
[8] P.D. Johnson, P.A. Aristoff, J. Org. Chem. 55 (1990) 1374.
[9] S.W. Wright, L.D. McClure, D.L. Hageman, Tetrahedron Lett. 37 (1996) 4631.
[10] F. Piozzi, M.R. Langella, Gazzetta Chim. Ital. 93 (1963) 1382.
[11] W.J. Houlihan, Y. Uike, V.A. Parrino, J. Org. Chem. 46 (1981) 4515.
[12] D.A. Wacker, P. Kasireddy, Tetrahedron Lett. 43 (2002) 5189.
[13] G. Battistuzzi, S. Cacchi, G. Fabrizi, Eur. J. Org. Chem. (2002) 2671.
[14] S. Cacchi, G. Fabrizi, Chem. Rev. 105 (2005) 2873.
[15] R.C. Larock, S. Babu, Tetrahedron Lett. 28 (1987) 5291.
[16] R.C. Larock, E.K. Yum, J. Am. Chem. Soc. 113 (1991) 6689.
[17] R.C. Larock, E.K. Yum, M.D. Refvik, J. Org. Chem. 63 (1998) 7652.
[18] G. Huang, R.C. Larock, J. Org. Chem. 68 (2003) 7342.
[19] G. Zeni, R.C. Larock, Chem. Rev. 106 (2006) 4644.
[20] K. Iritani, S. Matsubara, K. Uchimoto, Tetrahedron Lett. 29 (1988) 1799.
[21] A. Arcadi, S. Cacchi, F. Marinelli, Tetrahedron Lett. 33 (1992) 3915.
[22] S. Cacchi, G. Fabrizi, D. Lamba, F. Marinelli, L.M. Parisi, Synthesis (2003) 728.
[23] S. Cacchi, G. Fabrizi, M. Parsi, Heterocycles 58 (2002) 667.
[24] S.L. Hegedus, G.F. Allen, J.J. Bozell, E.L. Waterman, J. Am. Chem. Soc. 100 (1978) 5800.
[25] R.C. Larock, S. Babu, Tetrahedron Lett. 28 (1987) 1037.
[26] A. Takeda, S. Kamijo, Y. Yamamoto, J. Am. Chem. Soc. 122 (2000) 5662.
[27] A.J. Peat, S.L. Buchwald, J. Am. Chem. Soc. 118 (1996) 1028.
[28] S. Wagaw, B.H. Yang, S.L. Buchwald, J. Am. Chem. Soc. 121 (1999) 10251.

[29] M. Watanabe, T. Yamamoto, M. Nishiyama, Angew. Chem. Int. Ed. Engl. 39 (2000) 2501.
[30] L. Ackermann, Org. Lett. 7 (2005) 439.
[31] B. Witulski, C. Alayrac, L. Tevzadze-Saeftel, Angew. Chem. Int. Ed. Engl. 42 (2003) 4257.
[32] S. Nunomoto, Y. Kawakami, Y. Yamashita, H. Takeuchi, S. Eguchi, J. Chem. Soc., Perkin Trans. 1 (1990) 111.
[33] J. Chengguo, W. Lu, T. Kitamura, Y. Fujiwara, Org. Lett. 1 (1999) 2097.
[34] E. Capito, J.M. Brown, A. Ricci, Chem. Commun. (2005) 1854.
[35] N.P. Grimster, C. Gauntlett, C.R.A. Godfrey, M.J. Gaunt, Angew. Chem. Int. Ed. Engl. 44 (2005) 3125–3129.
[36] In some cases, C2-alkenylation is observed. The C2/C3 selectivity could be oriented through the catalytic system and the reaction conditions.
[37] P.M. Henry, Palladium Catalyzed Oxidation of Hydrocarbons, Riedel, Dordrecht, 1980.
[38] J. Tsuji, Synthesis (1984) 369.
[39] J. Tsuji, Palladium Reagents and Catalysts: Innovations in Organic Synthesis, John Wiley & Sons, Chichester, 1996.
[40] M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art, M. Nomura, J. Org. Chem. 63 (1998) 5211.
[41] H. Miura, T. Tsuda, T. Satoh, M. Nomura, Chem. Lett. (1997) 1103.
[42] P.-C. Kong, F.D. Rochon, Can. J. Chem. 59 (1981) 3293.
[43] M. Higashijima, T. Masunaga, Y. Kojima, E. Watanabe, K. Wada, Stud. Surf. Sci. Catal. 92 (1995) 319.
[44] S. Chouzier, M. Gruber, L. Djakovitch, J. Mol. Catal. A: Chem. 212 (2004) 43.
[45] B.C. Gates, Catalytic Chemistry, John Wiley & Sons, Inc., NewYork, 1992.
[46] B. Crociani, J. Organomet. Chem. 190 (1980) C97.
[47] T. Hosokawa, M. Takano, S.-I. Murahashi, H. Ozaki, Y. Kitagawa, K.-i. Sakaguchi, Y. Katsube, J. Chem. Soc., Chem. Commun. (1994) 1433.
[48] T. Hosokawa, M. Nomura, S.-I. Murahashi, J. Organomet. Chem. 551 (1998) 387.
[49] H. Grennberg, A. Gogoll, J.-E. Bäckwald, J. Org. Chem. 56 (1991) 5808.
[50] B.A. Steinhoff, S.R. Fix, S.S. Stahl, J. Am. Chem. Soc. 124 (2002) 766.
[51] M.S. Chen, M.C. White, J. Am. Chem. Soc. 126 (2004) 1346.
[52] Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, J. Am. Chem. Soc. 91 (1969) 7166.
[53] C. Jia, W. Lu, T. Kitamura, Y. Fujiwara, Org. Lett. 1 (1999) 2097.
[54] C. Jia, T. Kitamura, Y. Fujiwara, Acc. Chem. Res. 34 (2001) 633.
[55] MM2 parameters, extended to transition metals by the user, implemented in CAChe (Futjitsu) version 6.1 was used for calculation.
[56] B.S. Lane, D. Sames, Org. Lett. 6 (2004) 2897.
[57] B.S. Lane, M.A. Brown, D. Sames, J. Am. Chem. Soc. 127 (2005) 8050.
[58] X. Wang, B.S. Lane, D. Sames, J. Am. Chem. Soc. 127 (2005) 4996.
[59] N.R. Deprez, D. Kalyani, A. Krause, M.S. Sanford, J. Am. Chem. Soc. 128 (2006) 4972.
[60] D.J. Cardenas, B. Martin-Matute, A.M. Echavarren, J. Am. Chem. Soc. 128 (2006) 5033.
[61] F. Bellina, S. Cauteruccio, R. Rossi, Eur. J. Org. Chem. 2006 (2006) 1379.