DOI: 10.1002/adsc.200900386

First Heterogeneous Ligand- and Salt-Free Larock Indole Synthesis

Nelly Batail,[a] Anissa Bendjeriou,[b] Thierry Lomberget,[c] Roland Barret,[c] Véronique Dufaud,[b,]* and Laurent Djakovitch[a,]*

[a] Université de Lyon, CNRS, UMR 5256, IRCELYON, Institut de recherches sur la catalyse et l'environnement de Lyon, 2 avenue Albert Einstein, F-69626 Villeurbanne, France
Fax: (+33)-4-7244-5399; e-mail: Laurent.Djakovitch@ircelyon.univ-lyon1.fr
[b] Université de Lyon, CNRS, UMR 5182, Laboratoire de Chimie, Ecole Normale Supérieure de Lyon, 46 Allée d'Italie, F-69364 Lyon Cedex 07, France
E-mail: vdufaud@ens-lyon.fr
[c] ISPB-Faculté de Pharmacie, Laboratoire de Chimie Thérapeutique, INSERM U-863, 8 avenue Rockefeller, F-69373 Lyon, France

Received: June 3, 2009; Revised: July 21, 2009; Published online: September 10, 2009

Dedicated to Prof. K. Köhler on the occasion of his 50th birthday.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900386.

Abstract: A new ligand- and salt-free procedure using heterogeneous palladium catalysts for the Larock indole and benzofuran synthesis is reported. After optimisation of the reaction conditions, good to high isolated yields have been achieved for a variety of structures. Recycling studies have shown that the palladium catalysts can be readily recovered and reused. Reactions and recovery of the palladium catalysts can be carried out in the presence of air, without any particular precaution.

Keywords: benzofurans; heterogeneous catalysis; indoles; Larock synthesis; palladium catalysts

The indole nucleus is an important substructure found in numerous natural or synthetic alkaloids.[1,2] The diversity of the structures encountered, as well as their biological and pharmaceutical relevance, have motivated research aimed at the development of new economical, efficient and selective synthetic strategies, particularly for the synthesis of functional indole rings.[3–6] Classical methods include the Fischer indole synthesis from arylhydrazones, the Batcho–Leimgruber synthesis from *o*-nitrotoluenes and dimethylformamide acetals, the Gassman synthesis from *N*-haloanilines, the Madelung cyclisation of *N*-acyl-*o*-toluidines and the reductive cyclisation of *o*-nitrobenzyl ketones. While these procedures have contributed to this important area, some remain limited when the synthesis of functional indoles is required. Recently, transition metal-catalysed transformations, and particularly palladium-catalysed reactions (Figure 1), have been developed providing increased tolerance towards functional groups, and leading generally to higher reaction yields.[7–16] Many of these methods have proven to be most powerful and are currently applied in the target- or the diversity-oriented synthesis of multifunctional indoles but, recently, the palladium-catalysed heteroannulation of 2-iodoanilines with internal alkynes known as the Larock indole synthesis (Figure 1, route 1) has emerged as one of the most powerful synthetic procedures to provide access to 2,3-susbtituted indoles.[17–22]

Benzofurans, isoelectronic to indoles, also show a variety of pharmacological properties and minor changes of their structure offer a high degree of diversity that has proven useful for the search of new therapeutic agents.[23–31] Although the benzofuran motif occurs less often in nature and offers less potential structural multiplicity, the broad spectrum of pharmacological activity of these heterocycles led nevertheless to the elaboration of concise and flexible synthetic methods useful in the production of specific structures.[32] Among all methods reported, again the Larock procedure starting from 2-iodophenols and internal alkynes appeared to be the most versatile procedure to obtain selectively (2),3-subsituted benzofurans.

However, these Larock procedures rely on the use of soluble palladium catalysts, thus involve significant difficulties including the separation of the catalytic

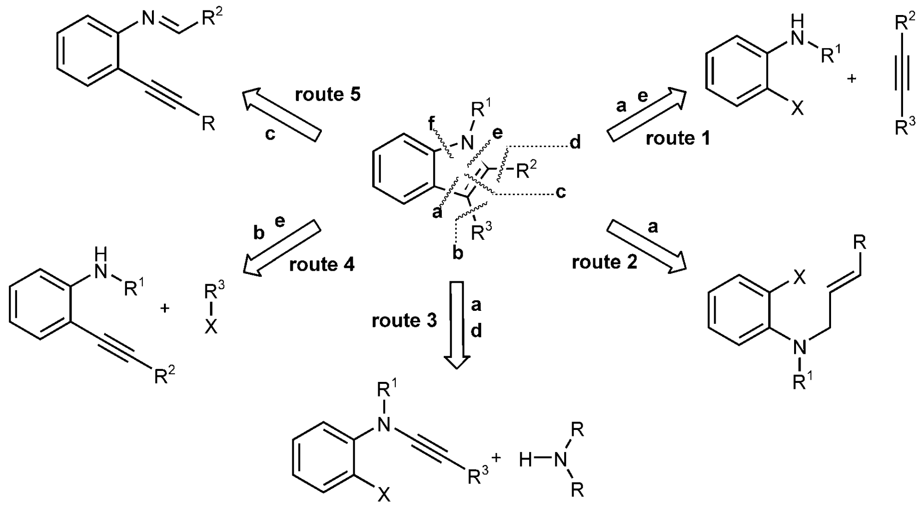


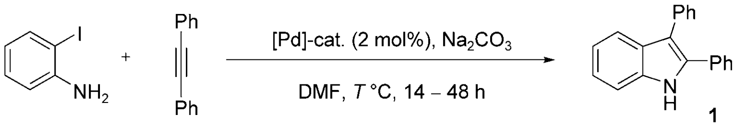
Figure 1. Retro-synthetic approaches toward the synthesis of indole nucleus catalysed by palladium.

material from the reaction mixture, lack of adequate catalyst recycling methods and relatively high palladium and ligand contamination of the products. The latter problems are intolerable in the context of biological applications. Obviously, an analogous catalytic heterogeneous method would eliminate any of these drawbacks but, to the best of our knowledge, there have been no reports on the use of heterogeneous palladium catalysts for the Larock synthesis of indoles and benzofurans while supported palladium was applied to fine chemical syntheses.[33–36]

With the aim of resolving this issue we report, in this paper, the successful use of various heterogeneous palladium catalysts (Pd/C, [Pd]/NaY) for indole and benzofuran syntheses in technical grade solvent under ligand- and salt-free reaction conditions. Moreover, we demonstrate that our procedure tolerates lower catalyst loadings (2 mol%) compared to those reported for homogeneous methods for such syntheses. The resulting protocol features reasonably priced reagents and solvents rendering the method environmentally benign, very practicable, and scalable. Furthermore, we show evidence for the high recyclability of the catalytic materials.

Initially, we adapted the existing homogeneous procedures in order to fit the requirements of heterogeneous catalysis (i.e., ligand- and salt-free) for this kind of reaction. Following the original procedure reported by Larock, a methodology intensively developed since this time, we evaluated various homogeneous catalytic systems under relatively common reaction conditions (1 equiv. 2-iodoaniline, 3 equiv. diphenylacetylene, 2–5 mol% [Pd], 3 equiv. base, 0–1 equiv. LiCl, DMF, 80–120 °C, 24–48 h) (Table 1).

Table 1. Influence of the catalyst nature on the Larock indole synthesis.[a]



1

Entry	Catalyst	LiCl	T [°C]	Time [h]	Conversion [%][b]	Yield [%][c]
1	$Pd(OAc)_2$ (5 mol%)	1 equiv.	80	48	100	67
2	$Pd(OAc)_2$ (5 mol%)	1 equiv.	120	14	100	15
3	$Pd(OAc)_2$ (5 mol%)	–	120	14	100	28
4	$Pd(OAc)_2$ (2 mol%)	–	120	24	100	40
5	$PdCl_2(PPh_3)_2$ (2 mol%)	–	120	24	100	73
6	$PdCl_2(PhCN)_2$ (2 mol%)	–	120	24	100	74
7	$Pd/C_{(EVO)}$ (2 mol%)	–	120	14	100	70

[a] *Reaction conditions:* 2-iodoaniline (1.0 mmol), diphenylacetylene (3.0 mmol), Na_2CO_3 (3 mmol), [Pd] catalyst (2–5 mol%), DMF (4.0 mL), T °C, time.

[b] Conversions based on unreacted 2-iodoaniline were determined by GC with an internal standard (biphenyl) (Δrel = ±5%).

[c] Isolated yields after flash chromatography on silica (purity: ≥97%).

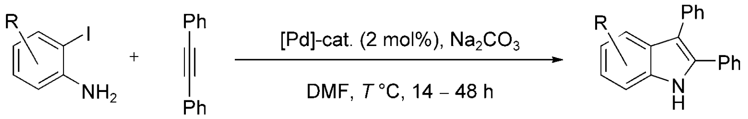
Whatever the catalyst used, all reactions led exclusively to the formation of the expected 2,3-diphenylindole **1**. Under the original Larock conditions (Table 1, entry 1) the expected compound was isolated in 67% yield. Under these conditions, increasing the reaction temperature to 120 °C, working in the presence or not of LiCl, resulted almost always in the formation of degradation products from starting materials leading to poor product yields (Table 1, entries 2 and 3). Improvement was achieved by decreasing the palladium loading to 2 mol% which considerably reduced side product formation and reaction time, leading to a moderate 40% yield (Table 1, entry 4). The other evaluated catalysts (Table 1, entries 5 and 6) gave slightly better results (i.e., *ca* 73% yield) under these conditions (Table 1, entries 5 and 6) that could be attributed to the presence of ligands (i.e., PPh_3 or PhCN).

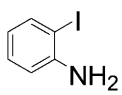
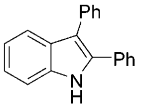
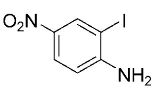
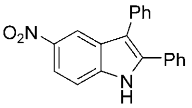
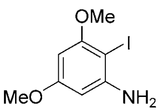
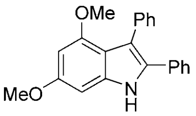
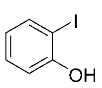
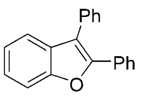
Having thus adapted the reactions conditions, we next evaluated a Pd/C catalyst provided by Evonik (see below) for that reaction (Table 1, entry 7). Unexpectedly, using this heterogeneous catalyst resulted in increased performances: the reaction was complete after only 14 h, giving an isolated yield 70%, which corresponds to 24–48 h of reaction under homogeneous conditions. This result is rather competitive with reported procedures as generally under homogeneous conditions in the absence of bulky ligands the diphenylacetylene tends to give side products due to di- or oligomerisation decreasing thus the yield.[37–39]

Attempting to further improve the reaction conditions towards more economical procedures by decreasing the excess of alkyne used (i.e., 3.0 equiv.) failed as using 1.5–2.0 equiv. led to dramatically decreased yields (i.e., 42% to compare to 73%, Table 1, entry 5).

Further developments concerned the evaluation of various heterogeneous palladium catalysts for the synthesis of different indole nuclei by varying either the nature of 2-the iodoanilines or the alkynes. Additionally, the reaction conditions were applied to the Larock synthesis of benzofurans. As commercial catalysts, the palladium supported on active carbon Degussa type E101 NE/W from Aldrich [Pd/C 10% wt on dry basis, 52% water; labelled herein as $Pd/C_{(ALD)}$] and a palladium supported on active carbon type E105 CA/W available at Evonik [Pd/C 5% wt, 55% water; labelled $Pd/C_{(EVO)}$] were evaluated. The nature of the two catalysts is different: $Pd/C_{(ALD)}$ is characterised by a low degree of reduction and high water content (52%) while $Pd/C_{(EVO)}$, fully described by Köhler and co-workers, is characterised by high Pd dispersion

Table 2. Heteroannulation of various 2-iodoaryls with diphenylacetylene.[a]



Entry	Ar(I)NH$_2$	Catalyst	Base	Time	Conversion [%][b]	Product	Yield [%][c]
1		$Pd/C_{(ALD)}$	Na_2CO_3	9 h	100	**1** 	40
2		[Pd]/NaY	Na_2CO_3	2 h	100		20
3		$Pd/C_{(EVO)}$	Na_2CO_3	14 h	100		70
4	**2** 	$Pd/C_{(ALD)}$	Na_2CO_3	6 d	100	**4** 	70
5		[Pd]/NaY	Na_2CO_3	12 d	0[d]		–
6		[Pd]/NaY	K_2CO_3	12 d	0[d]		–
7		$Pd/C_{(EVO)}$	Na_2CO_3	9 d	0[d]		–
8	**3** 	$Pd/C_{(ALD)}$	Na_2CO_3	6 d	0[d]	**5** 	–
9		[Pd]/NaY	Na_2CO_3	4 h	100		43
10		$Pd/C_{(ALD)}$	Na_2CO_3	5 d	0[d]	**6** 	–
11		[Pd]/NaY	Na_2CO_3	5 d	0[d]		–

[a] *Reaction conditions:* 2-iodoaryl (1.0 mmol), diphenylacetylene (3.0 mmol), base (3 mmol), [Pd] catalyst (2 mol%), DMF (4.0 mL), 120 °C, time.

[b] Conversions based on unreacted 2-iodoaryle were determined by GC with an internal standard (biphenyl) (Δrel = ±5%).

[c] Isolated yields after flash chromatography on silica (purity: ≥97%).

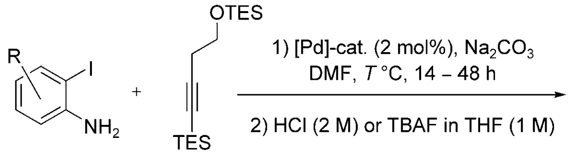
[d] The starting 2-iodoaryl was fully recovered.

(36%), very low reduction degree [no Pd(0) was detected by TPR measurements] and high water content (55%).[40,41] Another catalyst prepared in our laboratory following procedures previously reported was involved in this study: $[Pd(NH_3)_4]$/NaY (1% wt), labelled [Pd]/NaY in following tables, was obtained by ion exchange of a NaY zeolite using a 0.1 M aqueous solution of $[Pd(NH_3)_4]^{2+} 2\,Cl^-$.[42]

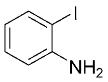
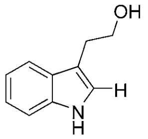
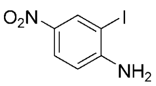
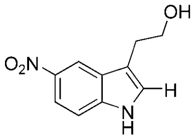
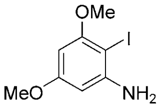
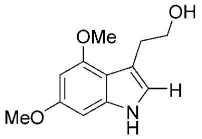
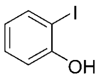
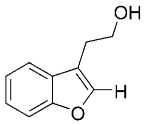
Using diphenylacetylene as coupling partner the results appeared to be strongly dependant on the nature of the iodoaniline (Table 2). While with 2-iodoaniline full conversions were generally achieved whatever the catalyst, other anilines showed strong dependencies on the catalyst's nature. In more detail, it appeared that in the case of 2-iodoaniline the nature of the catalyst influenced strongly the formation of side products from diphenylacetylene (Table 2, entry 1) resulting, in extreme cases, in low product yields (Table 2, entry 2) together with degradation of the starting material. Furthermore, these side reactions decreased dramatically the yield, mainly due to tedious separation of the target molecule. Unexpectedly, with other iodoanilines, only one catalyst was found to be active for the given reaction. Thus using 4-nitro-2-iodoaniline **2**, only the $Pd/C_{(ALD)}$ gave in good yield the expected indole **4**. All other evaluated catalysts generally led only to di- or oligomerisation of diphenylacetylene; generally as observed by GC the iodoaniline was not consumed (Table 2, entries 5–7). With the more electron-rich 3,5-dimethoxy-2-iodoaniline **3**, only the $[Pd(NH_3)_4]$/NaY gave the expected compound **5** in moderate yield due to the formation of diphenylacetylene oligomers while full conversion was observed (Table 2, entries 8 and 9). Unfortunately, all attempts to get benzofurans **6** failed under these conditions.

With triethyl[4-(triethylsilyl)but-3-ynyloxy]silane **7** (Table 3) or triethyl(phenylethynyl)silane **12** (Table 4) as alkyne partner no important catalyst performance differences were shown under the conditions tested. Generally full conversions and selectivities were achieved leading to good to high isolated yields. Noticea-

Table 3. Heteroannulation of various 2-iodoaryls with triethyl[4-(triethylsilyl)but-3-ynyloxy]silane.[a]



7

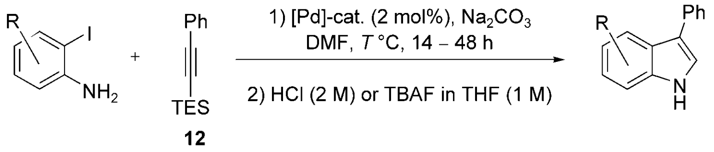
Entry	$Ar(I)NH_2$	Catalyst	Base	Time	Conversion [%][b]	Product	Yield [%][c]
1		$Pd/C_{(ALD)}$	K_2CO_3	14 h	100	**8** 	48
2		$Pd/C_{(ALD)}$	Na_2CO_3	14 h	100		62
3		[Pd]/NaY	Na_2CO_3	14 h	100		98
4	**2** 	$Pd/C_{(ALD)}$	Na_2CO_3	9 d	100	**9** 	60
5		[Pd]/NaY	Na_2CO_3	6 d	100		70
6	**3** 	$Pd/C_{(ALD)}$	K_2CO_3	14 h	100	**10** 	70
7		[Pd]/NaY	K_2CO_3	14 h	100		81
8		$Pd/C_{(ALD)}$	Na_2CO_3	14 h	100	**11** 	60
9		[Pd]/NaY	Na_2CO_3	14 h	100		65

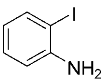
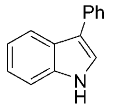
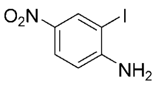
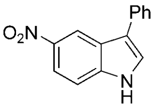
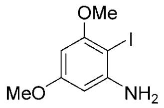
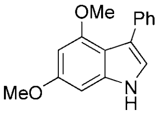
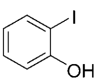
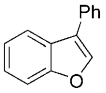
[a] *Reaction conditions:* 2-iodoaryl (1.0 mmol), diphenylacetylene (3.0 mmol), base (3 mmol), [Pd] catalyst (2 mol%), DMF (4.0 mL), 120 °C, time.

[b] Conversions based on unreacted 2-iodoaryl were determined by GC with an internal standard (biphenyl) (Δrel = ±5%).

[c] Isolated yields after flash chromatography on silica (purity: ≥97%).

Table 4. Heteroannulation of various 2- iodoaryls with triethyl(phenylethynyl)silane.[a]



Entry		Ar(I)NH$_2$	Catalyst	Base	Time	Conversion (%)[b]		Product	Yield [%][c]
1			Pd/C$_{(ALD)}$	Na$_2$CO$_3$	24 h	100	**13**		80
2			[Pd]/NaY	Na$_2$CO$_3$	24 h	100			70
3	**2**		Pd/C$_{(ALD)}$	Na$_2$CO$_3$	12 d	100	**14**		42
4			[Pd]/NaY	Na$_2$CO$_3$	7 d	100			80
5	**3**		Pd/C$_{(ALD)}$	K$_2$CO$_3$	14 h	100	**15**		83
6			[Pd]/NaY	K$_2$CO$_3$	14 h	100			88
7			Pd/C$_{(ALD)}$	Na$_2$CO$_3$	14 h	100	**16**		67
8			[Pd]/NaY	Na$_2$CO$_3$	14 h	100			80

[a] *Reaction conditions:* 2-iodoaryl (1.0 mmol), diphenylacetylene (3.0 mmol), base (3 mmol), [Pd] catalyst (2 mol%), DMF (4.0 mL), 120 °C, time.

[b] Conversions based on unreacted 2-iodoaryl were determined by GC with an internal standard (biphenyl) (Δrel = $\pm$5%).

[c] Isolated yields after flash chromatography on silica (purity: $\geq$97%).

bly, 4-nitro-2-iodoaniline **2** and 3,5-dimethoxy-2-iodoaniline **3**, while sometimes unreactive with diphenylacetylene were here fully converted. However, for the electron-rich 3,5-dimethoxy-2-iodoaniline **3**, K$_2$CO$_3$ was required as base, as otherwise only a very poor conversion was achieved (*ca.* <30%). When triethyl[4-(triethylsilyl)but-3-ynyloxy]silane **7** was employed using the heterogeneous [Pd(NH$_3$)$_4$]/NaY catalyst, it leads to generally better isolated yields toward the expected indole, up to 98% in the case of 2-iodoaniline (Table 3, entry 3). With this alkyne the corresponding benzofuran **11** was obtained in good yield (*ca.* 60–65%; Table 3 entries 8 and 9).

Using triethyl(phenylethynyl)silane **12** as alkyne partner gave nearly the same tendencies. However, in that case the heterogeneous catalyst to use depends on the nature of the iodoaniline. The reaction of 2-iodoaniline over the Pd/C$_{(ALD)}$ gave the highest isolated yield (Table 4, entry 1 *vs.* 2). With the other anilines, the Pd(NH$_3$)$_4$]/NaY catalyst gave the best results (i.e., Table 4, 80% yield with 4-nitro-2-iodoaniline **2** – entry 4 *vs.* 3; 88% yield with 3,5-dimethoxy-2-iodoaniline **3** – entry 6 *vs.* 5). Again with 3,5-dimethoxy-2-iodoaniline **3**, K$_2$CO$_3$ had to be used to achieve full conversion under acceptable conditions (short reaction time, higher yields). Applied to the corresponding benzofuran synthesis that alkyne led also to good isolated yields (80%, Table 4 entry 8) when the [Pd(NH$_3$)$_4$]/NaY catalyst was used.

Having demonstrated the applicability of heterogeneous catalysts for the Larock synthesis of indoles and benzofurans, we addressed the recycling of the catalyst. The benchmark reaction chosen for the recycling study was the heteroannulation of 2-iodoaniline with triethyl[4-(triethylsilyl)but-3-ynyloxy]silane **7** under optimised reaction conditions. The procedure, explained elsewhere, was performed as follows: at the completion of the 1st run using fresh catalyst, the suspension was cooled to room temperature and centrifuged. The supernatant was decanted and the solid was washed three times with DMF, then twice with diethylether, then allowed to dry at room temperature overnight. It was then engaged in a new catalytic cycle. The procedure was repeated up to a total of 5 runs (Figure 2). Both catalysts showed high recyclability under our reaction conditions. However differences were observed: while the Pd/C$_{(ALD)}$ gave full conversion until the 3rd run before being deactivated, the

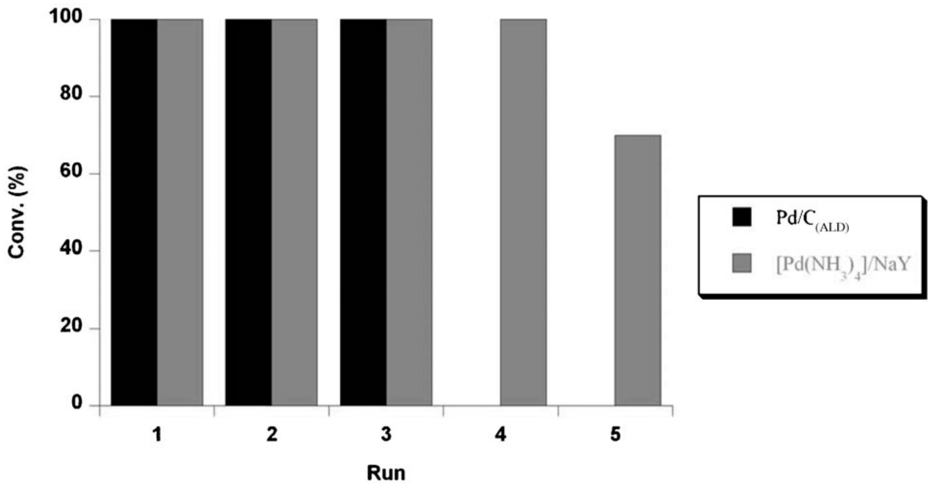


Figure 2. Recyclability of the Pd/C$_{(ALD)}$ and [Pd(NH$_3$)$_4$]/NaY catalysts for the Larock indole synthesis of 2-iodoaniline with triethyl[4-(triethylsilyl)but-3-ynyloxy]silane **7**. *Reaction conditions:* 1.0 mmol iodoaniline, 3.0 mmol alkyne, 3.0 mmol Na$_2$CO$_3$, 2.0 mol% [Pd], 4.0 mL DMF, 120 °C, 14 h.

[Pd(NH$_3$)$_4$]/NaY was fully recyclable until the 4th run before showing a decreased activity in the 5th run. This apparent loss of activity could have several sources, including mechanical mass loss during the recycling protocol (centrifuge, decantation) or real catalytic site deactivation. Nevertheless, the activity of the recycled catalysts remain excellent, the [Pd(NH$_3$)$_4$]/NaY showing definitively a higher behaviour for the potential applications in fine chemical industry.

In conclusion, heterogeneous palladium catalysts offer viable alternatives to the use of soluble palladium complexes for the Larock indole and benzofuran synthesis. Full conversion and relatively high selectivities were achieved for nearly all of the substrates evaluated under common reaction conditions, the exception being the sterically encumbered diphenylacetylene. To the best of our knowledge, this work represents the first application of heterogeneous palladium catalysts in such syntheses. We demonstrated that the use of an active heterogeneous catalyst allowed product yields similar to those observed under homogeneous conditions but without requiring the use of extra salts or ligand.

In summary, the easily home-made [Pd(NH$_3$)$_4$]/NaY catalyst appeared to be the catalyst of choice both for indoles or benzofurans syntheses, even in reactions (i.e., indoles **9** and **14**) where the original Larock procedure failed and for which previous successes required the use of expensive ligand systems. Furthermore, this heterogeneous catalyst was found to be extremely robust despite the use of aerobic conditions and was successfully re-used over several cycles. However, for reactions involving diphenylacetylene, we established that Pd/C catalysts [i.e., Pd/C$_{(ALD)}$ or Pd/C$_{(EVO)}$] have to be used in order to obtain the target compounds (i.e., indoles **1** and **4**).

The experimental simplicity associated with the relatively mild conditions renders the reported method highly competitive with respect to existing procedures.

Experimental Section

All commercial materials were used without further purification. Analytical thin layer chromatography (TLC) was performed on Fluka Silica Gel 60 F$_{254}$. GC analyses were performed on an HP 4890 chromatograph equipped with an FID detector, a HP 6890 autosampler and an HP-5 column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness) with nitrogen as carrier gas. GC-MS analyses were obtained on a Shimadzu GC-MS-QP2010S equipped with a Sulpelco SLB-5MS column (95% methylpolysiloxane + 5% phenylpolysiloxane, 30 m × 0.25 mm × 0.25 μm) with helium as carrier gas. Conversions were determined by GC based on the relative area of GC signals referred to an internal standard (biphenyl) calibrated to the corresponding pure compounds. The experimental error was estimated to be $\Delta_{rel} = \pm 5\%$. Chemical yields refer to pure isolated substances. Purification of products was accomplished by flash chromatography performed at a pressure slightly greater than atmospheric pressure using silica (Macherey–Nagel Silica Gel 60, 230–400 mesh) with the indicated solvent system. Infrared spectra were recorded on a Bruker Vector 22 FT-IR spectrometer. Liquid NMR spectra were recorded on a Bruker AC-250 spectrometer. All chemical shifts were measured relative to residual ^{1}H or ^{13}C NMR resonances in the deuterated solvents: CDCl$_3$, $\delta = 7.26$ ppm for ^{1}H, 77.0 ppm for ^{13}C; DMSO, $\delta = 2.50$ ppm for ^{1}H, 39.5 ppm for ^{13}C. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). High resolution mass spectra (HRMS) were recorded on a Thermo Finnigan MAT 95 XL spectrometer, with isobutane as reactant gas for CI at the "Centre Commun de Spectrométrie de Masse, UMR5246 CNRS-Université Claude Bernard Lyon 1". Melting points were determined in open capillary tubes and are uncorrected.

Typical Procedure for Palladium-Catalysed Heteroannulation

The aryl iodide (1 mmol), the alkyne (3 mmol), the appropriate base (3 mmol), Pd catalyst (2 mol%) and DMF (4 mL) were introduced into a tube and sealed. The reactor was placed under stirring in a preheated oil bath at 120 °C. The reaction completion was monitored by GC. After cooling to room temperature, the reaction mixture was filtered through a celite pad, which was washed with EtOAc (100 mL). The resulting organic layer was washed with Na_2CO_3 (2×40 mL) then brine (40 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. If necessary (for the silylated compounds), the crude product was fully deprotected according to the method **A** or **B** before being purified by flash chromatography over silica.

Method A: To a solution of crude product dissolved into MeOH (20 mL) was added 2N HCl (4 mL, 8 equiv.). After completion (monitored by GC), the resulting mixture was evaporated and the residue was partitioned between AcOEt and saturated Na_2CO_3 solution. The phases were separated and the organic phase was washed with saturated brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to afford the corresponding crude fully deprotected compound.

Method B: To a solution of crude product, a 1M solution of TBAF in THF (2 mL, 2 equiv.) was added. The reaction completion was monitored by GC. After complete desilylation, the solution was taken up in EtOAc and the organic layer washed with saturated Na_2CO_3 solution, brine, dried over Na_2SO_4 and the solvent removed under reduced pressure to afford the corresponding crude desilytated product.

All compounds were fully characterised through ^1H and ^{13}C NMR, IR, melting point, GC-MS. Additionally, HR-MS were measured for products. Aniline **2**,[43] alkynes **7**,[44] **12**,[45] indoles **1**,[38] **4** and **5**,[46,47] **8** and **9**,[48,49] **13–15**,[50–52] and benzofurans **11**,[49] **16**[53] gave analytical data in accordance with the literature. Data are available in the supporting information.

Supporting Information

Complete descriptions of experimental details and product characterisation are available as Supporting Information.

Acknowledgements

NB thanks the Région Rhône-Alpes for grants. The authors gratefully acknowledge the Région Rhône-Alpes, Programme CIBLE-2007 (Contract number 07 016376 01/02/03) for funding and EVONIK for a gift of palladium catalyst.

References

[1] R. J. Sundberg, *Indoles*, Academic Press, London, **1996**.

[2] J. A. Joule, in: *Science of Synthesis*, Vol. 10, (Ed.: E. J. Thomas), Thieme, Stuttgart, **2001**, p 361.

[3] R. J. Sundberg, in: *Comprehensive Heterocyclic Chemistry*, Vol. 4, (Eds.: A. R. Katritzky, C. W. Rees), Pergamon, Oxford, **1984**, p 313.

[4] J. Tois, R. Franzén, A. Koskinen, *Tetrahedron* **2003**, *59*, 5395.

[5] L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673.

[6] B. Robinson, *The Fischer Indole Synthesis*, John Wiley & Sons, Chichester, **1982**.

[7] G. Battistuzzi, S. Cacchi, G. Fabrizi, *Eur. J. Org. Chem.* **2002**, 2671.

[8] S. Chouzier, M. Gruber, L. Djakovitch, *J. Mol. Catal. A: Chem.* **2004**, *212*, 43.

[9] M. Gruber, S. Chouzier, K. Koehler, L. Djakovitch, *Appl. Catal. A: Gen.* **2004**, *265*, 161.

[10] L. Djakovitch, P. Rollet, *Adv. Synth. Catal.* **2004**, *346*, 1782.

[11] S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873.

[12] L. Djakovitch, V. Dufaud, R. Zaidi, *Adv. Synth. Catal.* **2006**, *348*, 715.

[13] L. Djakovitch, P. Rouge, *J. Mol. Catal. A: Chem.* **2007**, *273*, 230.

[14] L. Djakovitch, P. Rouge, R. Zaidi, *Catal. Commun.* **2007**, *8*, 1561.

[15] G. Cusati, L. Djakovitch, *Tetrahedron Lett.* **2008**, *49*, 2499.

[16] L. Djakovitch, P. Rouge, *Catal. Today* **2009**, *140*, 90.

[17] R. C. Larock, S. Babu, *Tetrahedron Lett.* **1987**, *28*, 5291.

[18] R. C. Larock, S. Babu, *Tetrahedron Lett.* **1987**, *28*, 1037.

[19] R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689.

[20] R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652.

[21] G. Huang, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 7342.

[22] G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644.

[23] C. C. Felder, K. E. Joyce, E. M. Briley, M. Glass, K. P. Mackie, K. J. Fahey, G. J. Cullinan, D. C. Hunden, D. W. Johnson, M. O. Chaney, G. A. Koppel, M. Brownstein, *J. Pharmacol. Exp. Ther.* **1998**, *284*, 291.

[24] D. Dauzonne, J. M. Gillardin, F. Lepage, R. Pointet, S. Risse, G. Lamotte, P. Demerseman, *Eur. J. Med. Chem.* **1995**, *30*, 53.

[25] D. J. Sall, D. L. Bailey, J. A. Bastian, J. A. Buben, N. Y. Chirgadze, A. C. Clemens-Smith, M. L. Denney, M. J. Fisher, D. D. Giera, D. S. Gifford-Moore, R. W. Harper, L. M. Johnson, V. J. Klimkowski, T. J. Kohn, H. S. Lin, J. R. McCowan, A. D. Palkowitz, M. E. Richett, G. F. Smith, D. W. Snyder, K. Takeuchi, J. E. Toth, M. Zhang, *J. Med. Chem.* **2000**, *43*, 649.

[26] D. Allsop, G. Gibson, I. K. Martin, S. Moore, S. Turnbull, L. J. Twyman, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 255.

[27] B. Carlsson, B. N. Singh, M. Temciuc, S. Nilsson, Y.-L. Li, C. Mellin, J. Malm, *J. Med. Chem.* **2002**, *45*, 623.

[28] B. L. Flynn, E. Hamel, M. K. Jung, *J. Med. Chem.* **2002**, *45*, 2670.

[29] J.-P. Liou, Y.-L. Chang, F.-M. Kuo, C.-W. Chang, H.-Y. Tseng, C.-C. Wang, Y.-N. Yang, J.-Y. Chang, S.-J. Lee, H.-P. Hsieh, *J. Med. Chem.* **2004**, *47*, 4247.

[30] M. Rida Samia, A. M. El-Hawash Soad, T. Y. Fahmy Hesham, A. Hazzaa Aly, M. M. El-Meligy Mostafa, *Arch. Pharmacal Res.* **2006**, *29*, 826.

[31] L. De Luca, G. Nieddu, A. Porcheddu, G. Giacomelli, *Curr Med Chem.* **2009**, *16*, 1.

[32] K. Hu, J.-H. Jeong, *Arch. Pharmacal Res.* **2006**, *29*, 476.

[33] L. X. Yin, J. Liebscher, *Chem. Rev.* **2006**, *107*, 133.

[34] F.-X. Felpin, E. Fouquet, *ChemSusChem.* **2008**, *1*, 718.

[35] L. Djakovitch, K. Koehler, J. G. De Vries, in: *Nanoparticles and Catalysis*, (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2008**, p 303.

[36] F. o.-X. Felpin, O. Ibarguren, L. Nassar-Hardy, E. Fouquet, *J. Org. Chem.* **2009**, *74*, 1349.

[37] D. A. Alonso, C. Nájera, M. C. Pacheco, *Adv. Synth. Catal.* **2002**, *344*, 172.

[38] X. Cui, J. Li, Y. Fu, L. Liu, Q.-X. Guo, *Tetrahedron Lett.* **2008**, *49*, 3458.

[39] M. Shen, G. Li, B. Z. Lu, A. Hossain, F. Roschangar, V. Farina, C. H. Senanayake, *Org. Lett.* **2004**, *6*, 4129.

[40] K. Köhler, R. G. Heidenreich, J. G. E. Krauter, J. Pietsch, *Chem. Eur. J.* **2002**, *8*, 622.

[41] R. G. Heidenreich, K. Köhler, J. G. E. Krauter, J. Pietsch, *Synlett* **2002**, 1118.

[42] L. Djakovitch, K. Koehler, *J. Am. Chem. Soc.* **2001**, *123*, 5990.

[43] L. Lista, A. Pezzella, A. Napolitano, M. d'Ischia, *Tetrahedron* **2008**, *64*, 234.

[44] C. Y. Chen, R. D. Larsen, T. R. Verhoeven, *Patent* WO-95-US5506 9532197, **1995**.

[45] A. A. Selina, S. S. Karlov, E. V. Gauchenova, A. V. Churakov, L. G. Kuz'mina, J. A. K. Howard, J. Lorberth, G. S. Zaitseva, *Heteroat. Chem.* **2004**, *15*, 43.

[46] G. Baccolini, E. Marotta, *Tetrahedron* **1985**, *41*, 4615.

[47] D. S. C. Black, N. Kumar, L. C. H. Wong, *Aust. J. Chem.* **1986**, *39*, 15.

[48] R. Mehdi-Ben Ameur, L. Mellouli, F. Chabchoub, S. Fotso, S. Bejar, *Chem. Nat. Compd.* **2004**, *40*, 510.

[49] J. Albaneze-Walker, K. Rossen, R. A. Reamer, R. P. Volante, P. J. Reider, *Tetrahedron Lett.* **1999**, *40*, 4917.

[50] Y. Jia, J. Zhu, *J. Org. Chem.* **2006**, *71*, 7826.

[51] R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172.

[52] K. Pchalek, A. W. Jones, M. M. T. Wekking, D. S. C. Black, *Tetrahedron* **2005**, *61*, 77.

[53] I. Kim, S.-H. Lee, S. Lee, *Tetrahedron Lett.* **2008**, *49*, 6579.