Tetrahedron 67 (2011) 976–981

Contents lists available at ScienceDirect

Tetrahedron

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

Heterogeneous metallo-organocatalysis for the selective one-pot synthesis of 2-benzylidene-indoxyl and 2-phenyl-4-quinolone

Marie Genelot [a,b,†,‡], Véronique Dufaud [b,*,‡], 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
[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

ARTICLE INFO

Article history:
Received 12 October 2010
Received in revised form 25 November 2010
Accepted 30 November 2010
Available online 7 December 2010

Keywords:
Metallo-organocatalysis
Heterogeneous catalysis
One-pot synthesis
4-Quinolones
Indoxyls
Mesoporous supports

ABSTRACT

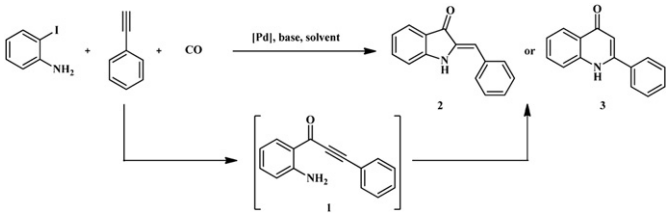
One-pot tandem heterogeneously catalyzed procedures for the selective synthesis of 2-benzylidene-indoxyl and 2-phenyl-4-quinolone have been developed. For this purpose, heterogeneous palladium-, amine-, and phosphine-catalysts were prepared by post-synthetic grafting onto SBA silica. The state of the hybrid materials was characterized using a wide variety of molecular and solid-state techniques. These materials exhibit high activities as 2-benzylidene-indoxyl was obtained in 81% yields through {[**Pd**]**@SBA-15**+**PPh$_3$**} catalysis while 2-phenyl-4-quinolone was prepared by a fully heterogeneous {[**Pd**]**@SBA-15**+[**AMINE**]**@SBA-3**} protocol in 61–75% isolated yield. For the later, we demonstrated that the catalysts mixture could be reused up to three runs without strong deactivation.

1. Introduction

Carbonyl containing *N*-heterocycles like 2-susbtituted-4-quinolones or 2-arylmethylidene indoxyls represent an important class of compounds in medicinal and pharmaceutical fields. 4-Quinolones exhibit various pharmaceutical activities as antibacterials,[1,2] antifungals[3] or anticancer substructures.[4] Both stoichiometric strategies[5–8] and palladium catalyzed procedures have been reported for their synthesis.[9–14] Among these methods, the palladium catalyzed carbonylative coupling of 2-iodoanilines with arylacetylenes initially reported by Torii and co-workers[11,12] appears to be the most versatile as it gives generally good yields toward the expected compounds.

On the other hand, indoxyls represent important synthons for the synthesis of either biologically active indole derivatives or natural pigments (i.e., betanin, indigoid dyes…). Some indoxyls also show by their own biological activities as anti-cancer drugs.[15] These compounds are either isolated from natural sources[16–18] or generally prepared from indoles.[19–21] Interestingly, when considering the 2-arylmethylidene family, the most flexible method reported by Catellani and co-workers[22] involves the reaction of iodoaniline with phenylacetylene under CO atmosphere.

Therefore, under very similar conditions (2-iodoaniline, phenylacetylene, CO, palladium based catalyst) either six-membered-(4-quinolone, i.e., Torii[11,12]) or five-membered ring compounds (indoxyl, i.e., Catellani[22]) can be obtained as they are issued from the same non-cyclic intermediate (Scheme 1). However, these methods tend to give amide containing side-products or mixture of cyclized products along with the non-cyclic intermediate.



Scheme 1.

Interested in developing one-pot selective synthesis of biologically relevant *N*-heterocycles we investigated these methodologies and reported on the way to control carefully the selectivity of the reaction in order to obtain either indoxyls or 4-quinolones from 2-iodoanilines and terminal alkynes.[23] As a result of these studies, we were able to explain clearly the origin of

* Corresponding authors. Tel.: +33 472445381; fax: +33 472445399; e-mail addresses: vdufaud@ens-lyon.fr (V. Dufaud), Laurent.Djakovitch@ircelyon.univ-lyon1.fr (L. Djakovitch).
† Tel.: +33 472445381; fax: +33 472445399.
‡ Tel.: +33 472728857; fax: +33 472728860.

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.11.112

the selectivity toward the five- or six-membered ring compounds as resulting from the respective role of the various catalytic species involved (Fig. 1), whether they are organic or metallic. Thus, the non-cyclic common intermediate **1** results from palladium catalysis {[Pd]} while indoxyls **2** and 4-quinolones **3** are obtained, respectively, through tandem {[Pd]/PR_3} catalysis and two-step multi-catalysis {[Pd]+$HNEt_2$}.[24]

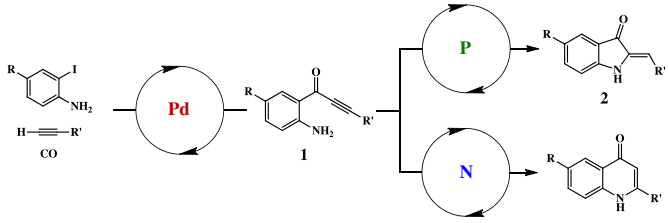


Fig. 1. Involved catalytic species for the selective syntheses of 4-quinolones and indoxyls.

covalent bonding onto SBA type silica supports (Fig. 2). In order to gain insight into the effect of chelation on catalyst performance and stability (notably resistance to leaching) two different palladium complexes bearing either monodentate phosphine or chelating diphosphine linkers were considered (hybrid materials [**PdP_2**]**@SBA-15** and [**PdPNP**]**@SBA-15**).

A silica supported phosphine catalyst, [**P**]**@SBA-15**, was obtained through a multi-step tethering protocol (Supplementary data, Scheme S2). The phosphine was protected as a phosphine–borane complex prior to grafting. After the deactivation of the surface and borane deprotection one obtains the desired diphenylphosphine-based catalyst. In the case of the synthesis of aminosilica derived solids, various mono and polyamines of the type $(EtO)_3SiCH_2CH_2CH_2(NHCH_2CH_2)_nNH_2$ were anchored to a silica material whose surface had been previously organically modified with trimethylsilyl moieties to prevent undesirable interactions between the amine-bound species and the surface silanols. Three catalytic solids, which differ by the number of ethylene amino chain

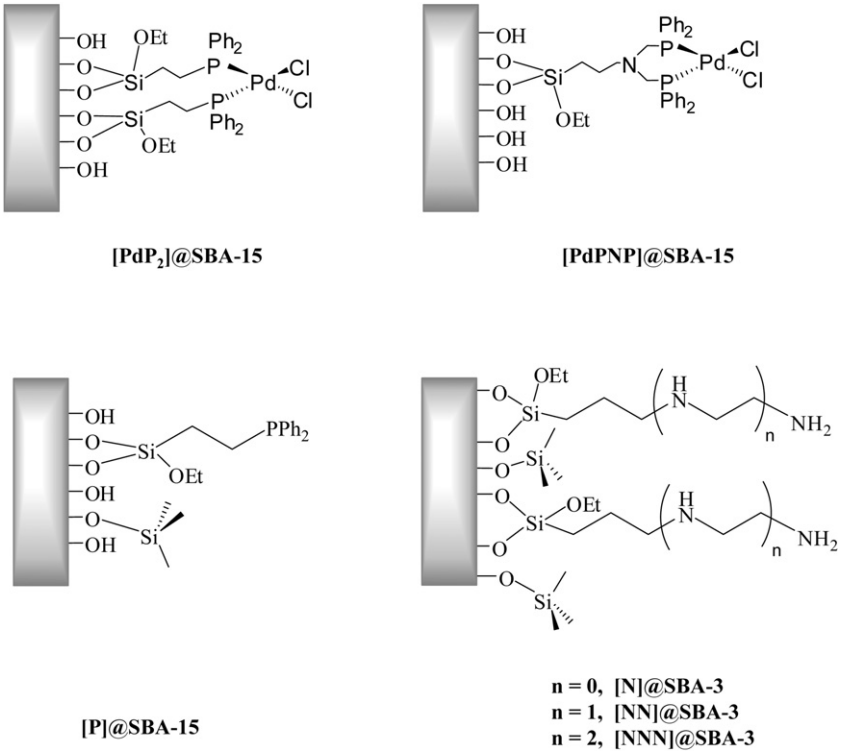


Fig. 2. Targeted palladium, phosphine, and amine functionalized SBA silica materials.

While successful this methodology still suffers from drawbacks, the main being related to the use of homogeneous catalysts that are tedious to remove and could result in high palladium and ligand (i.e., phosphine) contamination of final products, that is, not acceptable when dealing with human and animal health.[25] With this aim in mind, we underwent studies to develop full heterogeneous catalyzed one-pot synthesis of indoxyls and 4-quinolones.

2. Results and discussions

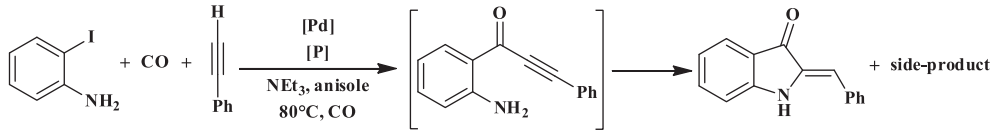
2.1. Catalysts

As shown in Fig. 1, different types of catalytically active species, used alone or in combination, were heterogenized in order to fulfill the requirements for the one-pot synthesis of either indoxyls or 4-quinolones. Thus, palladium complexes, free phosphine, and free amine (preferably primary or secondary) were immobilized by spacers (n=0–2) and referred to as [**N**]**@SBA-3**, [**NN**]**@SBA-3** and [**NNN**]**@SBA-3** were thus prepared. The resulting hybrids were thoroughly characterized using several molecular and surface techniques, which are gathered in Supplementary data: X-ray powder diffraction (XRD) at small angles, elemental analysis, thermogravimetric analysis, infrared spectroscopy, multi-nuclear NMR spectroscopy, and nitrogen sorptions.

2.2. Toward the selective synthesis of indoxyl

Previously, we described a one-pot homogeneous procedure for the selective synthesis of 2-benzylidene-indoxyl **2**. Thus, starting from 2-iodoaniline and phenylacetylene and working under CO atmosphere in presence of [$Pd(PPh_3)_4$] associated to free PPh_3 the 2-benzylidene-indoxyl **2** was obtained in 74% isolated yield as the (*Z*)-isomer.[23] Changing the palladium catalyst for [$Pd(PPh_3)_2Cl_2$] allowed to achieve similar results (Table 1, entry 1).

Table 1
Studies toward the heterogeneously catalyzed synthesis of 2-benzylidene-indoxyl



1 2 4

Entry	Method	Time (h)	GC analysis[a]			Yield[b]	Pd contamination
			1	**2**	**4**		
1	*A*	*24*	*0*	*99*	*0*	—	*94* ppm[c]
2	B	24	2	98	0	81	28 ppm
3[d]	C	24	81	11	2	n.a.	n.a.
4		48	66	19	11		
5		72	56	23	21		
6		96	20	24	53		

Reaction conditions: method A: iodoaniline (3 mmol), phenylacetylene (1.2 equiv), $[PdCl_2(PPh_3)_2]$ (0.2 mol %), PPh_3 (3.6 mol %), triethylamine (4 equiv), anisole (5 mL), CO (20 bar), 80 °C. Method B: iodoaniline (3 mmol), phenylacetylene (1.2 equiv), **[PdP$_2$]@SBA-15** (0.1 mol %), PPh_3 (1 mol %), triethylamine (2.5 equiv), anisole (5 mL), CO (5 bar), 80 °C. Method C: iodoaniline (3 mmol), phenylacetylene (1.2 equiv), **[PdP$_2$]@SBA-15** (0.1 mol %), **[P]@SBA-15** (1 mol %), triethylamine (2.5 equiv), anisole (5 mL), CO (5 bar), 80 °C.

[a] GC-yields were determined with an external standard (biphenyl) ($\Delta_{rel}=\pm5\%$).
[b] When available isolated yields are reported.
[c] Theoretical value, calculated from the amount of Pd introduced in the reaction.
[d] Conversion of 2-iodoaniline (94%) was achieved.

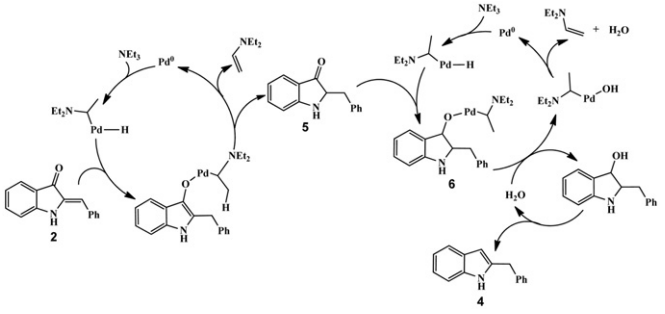
Therefore, in order to address this selective synthesis in a heterogeneous fashion, **[PdP$_2$]@SBA-15** catalyst associated with phosphine catalyst either as homogeneous PPh_3 or heterogeneous **[P]@SBA-15** was used. The results are reported in Table 1, and compared to those achieved using purely homogeneous catalysts.

As expected the use of heterogeneous palladium catalyst as **[PdP$_2$]@SBA-15** did not influence strongly the results of the reaction giving the expected 2-benzylidene-indoxyl **2** in 81% isolated yield. However, as observed from elemental analysis, in spite of the use of a heterogeneous source of palladium, metal contamination in crude product remains high although reduced from 94 ppm to 28 ppm.

Encouraged by this interesting result, we evaluated next the combination of heterogeneous **[PdP$_2$]@SBA-15** and **[P]@SBA-15** catalysts in this reaction. As reported in Table 1, while the palladium catalyzed step (i.e., toward **1**) proceeds as likely giving >90% conversion of 2-iodoaniline in 24 h, selective cyclization toward the indoxyl **2** was not as efficient as expected as only 11% of 2-iodoaniline was effectively transformed in this target compound (Table 1, entry 3). Prolonging the reaction up to 96 h did not allow to increase the production of **2** (Table 1, entries 4–6); rather than that a by-product was almost exclusively formed. Thus, the side-product formation prevented further developments related to heterogeneously {Pd/P} catalyzed indoxyls synthesis.

This side-product **4** obtained from the reaction mixture (Table 1, entry 6) is assumed to be 2-benzyl-1*H*-indole as deducted from ^1H NMR and GC–MS analyses.[26] This product is probably issued from palladium catalyzed hydride transfer on the indoxyl **2** as shown in the proposed mechanism illustrated in Scheme 2. Reduction of C=C bonds activated by carbonyl group through Pd-catalyzed hydride transfer from triethylamine was previously reported. In our case, such a mechanism reduced the indoxyl **2** to give the 3-oxo-indole **5**.[27] While to our knowledge, no such reduction of carbonyl group has been previously described it is highly reasonable to propose that a second hydride transfer to carbonyl group affording the palladacycle **6** occurs. Further steps to **4** would then involved hydrolysis of **6** followed by dehydration. In such consecutive reactions, aromatization delivering indole nucleus is assumed to be the driving force. Further studies to confirm this mechanism toward **4** are currently under progress.

In conclusion, the indoxyl **2** is formed during the reaction, however the rate of formation is probably slower than that of hydride transfers giving the indole **4**.



Scheme 2. Proposed mechanism for the formation of 2-benzyl-1H-indole **4** from 2-benzylidene-indoxyl **2**.

2.3. Toward the selective synthesis of 4-quinolone

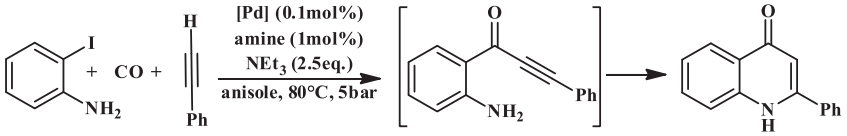
To obtain selectively 4-quinolones, we demonstrated that the best procedure corresponded to multi-catalysis {Pd+Amine}.[23] Thus, side-product formation and eventual negative mutual interaction between metal and organo-catalyst were avoided.

However, when considering fully heterogeneously catalyzed procedure it is not possible to add easily in the reaction media further catalyst. Therefore to solve this difficulty, we first revisited homogeneous protocol to develop tandem {Pd/Amine} catalysis. Thus working with **[PdCl$_2$(dppp)]** in presence of catalytic amount of **HNEt$_2$** under the conditions previously optimized allowed to obtain the target 2-phenyl-4-quinolone **3** in 47% yield, however after 7 days (Table 2, entry 2), that is, close from the result achieved using multi-catalysis procedure (Table 2, entry 1).

Encouraged by this result we then underwent studies in order to develop further this procedure toward the exclusive use of heterogeneous catalysts (Table 2, entries 5–7). For this purpose, a mechanical mixture of the **[PdPNP]@SBA-15** and **[AMINE]@SBA-3** catalysts was used.

Initially, we evaluated the influence of using heterogeneous palladium catalysts as **[PdPNP]@SBA-15**. Unexpectedly, replacing the homogeneous **[PdCl$_2$(dppp)]** by this heterogeneous one resulted in better chemical yields whatever the procedure (i.e., multi-catalysis or tandem catalysis) used. Thus >60% isolated yield toward the expected compound was obtained (Table 2, entries 3–4).

Table 2
Studies toward the heterogeneously catalyzed synthesis of 2-phenyl-4-quinolone



Entry	Method	Catalysts	Time (days)	Yield (%)	Pd contamination
1	Multi-catalysis	[**PdCl$_2$(dppp)**]+**HNEt$_2$**	7	57	n.d.
2	Tandem	[**PdCl$_2$(dppp)**]/**HNEt$_2$**	7	47	40 ppm
3	Multi-catalysis	[**PdPNP**]**@SBA-15**+**HNEt$_2$**	6	63	n.d.
4	Tandem	[**PdPNP**]**@SBA-15**/**HNEt$_2$**	7	65	5 ppm
5	Tandem	[**PdPNP**]**@SBA-15**/[**N**]**@SBA-3**	3	61	5 ppm
6	Tandem	[**PdPNP**]**@SBA-15**/[**NN**]**@SBA-3**	3	68	3 ppm
7	Tandem	[**PdPNP**]**@SBA-15**/[**NNN**]**@SBA-3**	4	75	3 ppm

Reaction conditions: 2-iodoaniline (3 mmol), phenylacetylene (1.2 equiv), [Pd] (0.1 mol %), HNEt$_2$ or [**AMINE**]**@SBA-3** (1 mol %), triethylamine (2.5 equiv), anisole (5 mL), CO (5 bar), 80 °C.

Developing further the procedure toward the exclusive use of heterogeneous catalysts, we engaged the prepared [**PdPNP**]**@SBA-15** and [**AMINE**]**@SBA-3** for the selective transformation of 2-iodoaniline and phenylacetylene toward 2-phenyl-4-quinolone. Surprisingly, using exclusively heterogeneous catalysts allowed to achieve high chemical yields (>60% up to 75%) in shorter reaction time (Table 2, entries 5–7). Therefore apparently, grafted amines exhibited higher behavior in catalyzing the cyclization of **1** toward **3**. This can be related to the higher nucleophilicity of grafted 'primary' amine compared to the homogeneous diethylamine.

These results indicate that the use of mesoporous silica to support the catalytically active species (i.e., palladium and amines) is well adapted to such synthesis as evidently no diffusion limit occurred that is attested by the reduced reaction time observed to full conversion toward the target molecule.

Additionally, the use of heterogeneous palladium catalyst allowed to reduce considerably the palladium contamination of crude product to few parts per million (Table 2, entries 4–7 vs 2).

Being confident with these results, we examined next recycling the [**PdPNP**]**@SBA-15**/[**N**]**@SBA-3** catalysts as follows: after a first run, the catalytic material was separated by filtration, washed successively with methylene chloride, methanol, and diethylether in order to remove all organic materials and to allow drying of the 'catalysts mixture'. The solid thus obtained was engaged in a new run under the same reaction conditions.

The results reported in Table 3 reveal that while the catalytic mixture is still active up to three runs, deactivation occurred as evidenced by the longer reaction times required in the second cycle to achieve full conversions toward **3**.

In more details, our recycling experiments point out a relative stability of the palladium catalyst as up to the third run no strong deactivation was observed. This deactivation can stem from several factors: (1) ineffective redeposition of leached palladium[28,29] due to the nature of the material unable to accommodate it,[30] that is, correlated with determinations of palladium contamination in crude products, which clearly indicate palladium leaching during the reaction; however at low level (3–5 ppm); (2) the presence of salts that can encapsulate leached palladium upon crystallization resulting in the loss of metal during washing; (3) mechanical loss of catalytic material during separation and washing. To date, we cannot with certitude discard one or the other hypothesis.

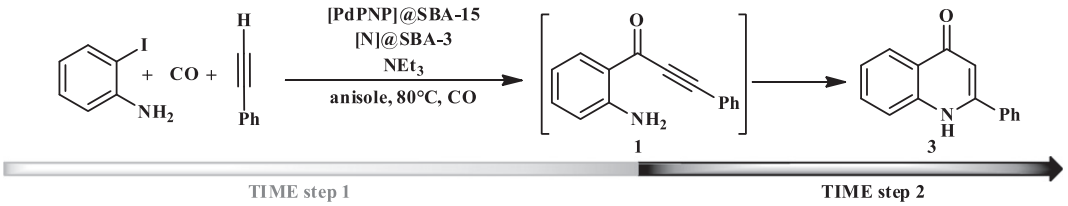
Considering the amine-catalyzed step of the procedure, it seems reasonable to suggest that deactivation is due to protonation of the grafted amines during the reaction, that is, not completely counterbalanced by the presence of triethylamine in the reaction medium.

Whatever the level of {[**PdPNP**]**@SBA-15**/[**N**]**@SBA-3**} catalysts mixture deactivation, high isolated yields toward the target 2-phenyl-4-quinolone are achieved in all runs, given that longer reaction time was used.

3. Conclusion

At this stage of our studies, it is interesting to compare the homogeneous versus the heterogeneous procedures (Fig. 3) for the selective synthesis of 2-benzylidene-indoxyls and 2-phenyl-

Table 3
Recycling the {[**PdPNP**]**@SBA-15**/[**N**]**@SBA-3**} catalysts mixture for the synthesis of 2-phenyl-4-quinolone



Run	Time step 1 (days)	Time step 2 (days)	Yield (%)
1	1	3	60
2	1	5	62
3	2	9	72

Reaction conditions: run 1: 2-iodoaniline (6 mmol), phenylacetylene (1.2 equiv), [**PdPNP**]**@SBA-15** (0.1 mol %), [**N**]**@SBA-3** (1 mol %), triethylamine (2.5 equiv), anisole (10 mL), CO (5 bar), 80 °C, For the next runs: the same stoichiometry was used but the amount of reactants and solvent was adjusted according to the collected amount of recovered catalysts mixture.

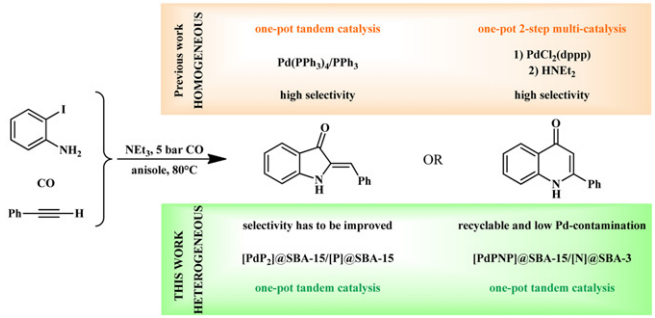


Fig. 3. Homogeneous and heterogeneous procedures for the one-pot syntheses of 2-phenyl-4quinolone and 2-benzylidene-indoxyl.

4-quinolones. While using homogeneous systems, we were able to propose two procedures for either the synthesis of indoxyls or that of 4-quinolones;[23] when using heterogeneous catalysts the formation of the 2-benzyl-1*H*-indole **4** during the synthesis of 2-benzylidene-indoxyl **2** prevented further optimization toward efficient protocols. Nevertheless, the fully heterogeneous approach was successful for 2-phenyl-4-quinolone **3**.

To conclude, a one-pot tandem {Pd/Amine} catalysis procedure for the selective synthesis of 2-phenyl-4-quinolone through a carbonylative Sonogashira cross-coupling has been developed. Compared to previously reported fully homogeneous protocols, the present methodology based on the exclusive use of heterogeneous catalytic materials resulted in noticeable improvement as it allowed to reduce the overall reaction time from 7 to 3 days, to decrease the palladium contamination in crude compound from 40 ppm to >5 ppm and to provide successful recycling of the {[**PdPNP**]**@SBA-15**/[**N**]**@SBA-3**} catalysts mixture. Additionally, the new protocol based on tandem catalysis allowed to introduce both catalytic materials when setting-up the reaction, that is, appreciable since the initial reaction step is performed under CO pressure.

While the study revealed little deactivation of the system upon recycling, prolonging the reaction time allowed to face with this phenomenon giving high isolated yield in 4-quinolone.

4. Experimental

4.1. General

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 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) with nitrogen as carrier gas. GC–MS analyses were obtained on a Shimadzu GC–MS-QP2010S equipped with a Supelco SLB-5MS column (95% methylpolysiloxane+5% phenylpolysiloxane, 30 m×0.25 mm×0.25 μm) with Helium as carrier gas. Ionization was done by electronic impact at 70 eV. 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. 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: DMSO, δ 2.50 ppm for ^1H, 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).

4.2. General procedures

4.2.1. Preparation of 2-benzylidene-indoxyl ***2****.* A mixture of 2-iodoaniline (3 mmol), alkyne (1.2 equiv), [**PdP$_2$**]**@SBA-15** (0.1 mol %), PPh_3 (1 mol %), and triethylamine (2.5 equiv) in anisole (5 mL) was placed in a stainless autoclave, which was purged at 20 bar twice with Ar and once with CO. The autoclave was charged with 5 bar CO. The mixture was stirred at 80 °C. At completion of the reaction, the autoclave was depressurized and purged twice at 20 bar with Ar. The reaction media was taken up with CH_2Cl_2 (30 mL) and filtered on sintered glass. The solid was washed several times with CH_2Cl_2. The filtrate was washed with $NaHCO_3$ (2×20 mL) then with brine (1×20 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was then purified by chromatography on silica gel to give pure indoxyl **2** as an orange solid (81%).

^1H NMR (250 MHz, DMSO) δ 9.83 (s, 1H, NH), 7.78–7.69 (m, 2H, C_6H_5), 7.63–7.56 (m, 1H, C_6H_4), 7.56–7.42 (m, 3H, C_6H_5), 7.40–7.32 (m, 1H, C_6H_4), 7.15 (dt, ^3J=8.1 Hz, ^4J=0.8 Hz, 1H, C_6H_4), 6.97–6.85 (m, 1H, C_6H_4), 6.65 (s, 1H, CH) in agreement with Ref. 23.

4.2.2. Preparation of 2-phenyl-4-quinolone ***3****.* A mixture of 2-iodoaniline (3 mmol), phenylacetylene (1.2 equiv), [**PdPNP**]**@SBA-15** (0.1 mol %), [**N**]**@SBA-3** (1 mol %), and triethylamine (2.5 equiv) in anisole (5 mL) was placed in a stainless autoclave, which was purged at 20 bar twice with Ar and once with CO. The autoclave was charged with 5 bar CO. The mixture was stirred at 80 °C. At completion of the reaction, the autoclave was depressurized and purged twice at 20 bar with Ar. The reaction media was filtered over sintered glass and the solid was washed with CH_2Cl_2. The collected solid was then suspended in methanol in order to solubilize the 4-quinolone and filtered. The methanol filtrate was then evaporated under reduced pressure and dried under vacuum. The 2-phenyl-4-quinolone was obtained pure without further refinement as a beige solid (62%).

^1H NMR (250 MHz, DMSO) δ 11.73 (s, 1H, NH), 8.10 (dd, ^3J=8.0 Hz, ^4J=0.9 Hz, 1H, C_6H_4), 7.90–7.73 (m, 3H, C_6H_4, and C_6H_5), 7.73–7.63 (ddd, ^3J=8.3, 6.9 Hz, ^4J=0.9 Hz, 1H, C_6H_4), 7.63–7.54 (m, 3H, C_6H_5), 7.33 (ddd, ^3J=8.0, 6.9 Hz, ^4J=0.9 Hz, 1H, C_6H_4), 6.35 (s,1H, CH) in agreement with Ref. 23.

Acknowledgements

M.G. is grateful to the National Agency of Research for financial support (No. ANR-07-BLAN-0167-01/02).

Supplementary data

Supplementary data related to this article can be found online version at doi:10.1016/j.tet.2010.11.112. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Grohe, H. *Chem. Brit.* **1992**, 34–36.
2. Wentland, M. P.; Cornett, J. B. *Annu. Rep. Med. Chem.* **1985**, *20*, 145–154.
3. Ward, F. E.; Garling, D. L.; Bickler, R. T.; Lawer, D. M.; Cummings, D. P. *J. Med. Chem.* **1981**, *24*, 1073–1077.
4. Aimi, A.; Nishimura, M.; Miwa, A.; Hoshino, H.; Sakai, S.; Higiniwa, J. *Tetrahedron Lett.* **1989**, *30*, 4991–4994.
5. Leonard, N. J.; Herbrandson, F.-F.; van Heyningen, E. M. *J. Am. Chem. Soc.* **1946**, *68*, 1279–1281.
6. Reitsema, R. H. *Chem. Rev.* **1948**, *43*, 43–68.
7. Chen, B.; Huang, X.; Wang, J. *Synthesis* **1987**, 482–483.
8. Kasahara, A.; Izumi, T.; Watabe, H.; Takahashi, S. *Chem. Ind.* **1981**, 121.
9. Okuro, K.; Alper, H. *J. Org. Chem.* **1997**, *62*, 1566–1567.

10. Grigg, R.; Liu, A.; Shaw, D.; Suganthan, S.; Woodall, D. E.; Yoganathan, G. *Tetrahedron Lett.* **2000**, *41*, 7125–7128.
11. Torii, S.; Okumoto, H.; Xu, L. H. *Tetrahedron Lett.* **1991**, *32*, 237–240.
12. Torii, S.; Okumoto, H.; Xu, L. H.; Sadakane, M.; Shostakovsky, M. V.; Ponomaryov, A. B.; Kalinin, V. N. *Tetrahedron* **1993**, *49*, 6773–6784.
13. Kalinin, V. N.; Shostakovskii, M. V.; Ponomarev, A. B. *Tetrahedron Lett.* **1992**, *33*, 373–376.
14. Haddad, N.; Tan, J.; Farina, V. *J. Org. Chem.* **2006**, *71*, 5031–5034.
15. Gerby, B.; Boumendjel, A.; Blanc, M.; Bringuier, P. P.; Champelovier, P.; Fortuné, A.; Ronot, X.; Boutonnat, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 208–213.
16. Abramovitch, R. A.; Marko, A. M. *Can. J. Chem.* **1960**, *38*, 131–135.
17. Dean, F. M.; Patamapongse, C. *J. Chem. Soc., Perkin Trans. 1* **1974**, 952–955.
18. Wu, E.; Komolpis, K.; Wang, H. Y. *Biotechnol. Tech.* **1999**, *13*, 567–569.
19. Braudeau, E.; David, S.; Fischer, J. C. *Tetrahedron* **1974**, *30*, 1445–1455.
20. Hewitt, M. C.; Shao, L. *ARKIVOC* **2006**, 37–46.
21. Hooper, M.; Pitkethly, W. N. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1607–1613.
22. An, Z. W.; Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1990**, *397*, C31–C32.
23. Genelot, M.; Bendjeriou, A.; Dufaud, V.; Djakovitch, L. *Appl. Catal., A* **2009**, *369*, 125–132.
24. In TANDEM catalysis all catalysts are introduced in the reactor from the start of the reaction; in MULTI-CATALYSIS, the catalysts are introduced in the reactor step by step. See: Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365–2379.
25. Following the European Medicines Agency, in: E.M. Agency (Ed.) 2008 p. 34, acceptable residual palladium content for drugs administered by oral and parental routes should be below 1 ppm and 10 ppm [often <5 ppm in drug testing], respectively.
26. MS m/z (relative intensity): 207(49), 206 (30), 130 (100), 102 (16), 77 (15).1H NMR (250 MHz, DMSO) δ 10.97 (s, 1H), 7.40 (d, J=7.5 Hz, 1H), 7.33–7.11 (m, 6H), 6.95 (m, 2H), 6.13 (s, 1H), 4.05 (s, 2H) in agreement with Ambrogio, I.; Cacchi, S.; Fabrizi, G.; Prastaro, A. *Tetrahedron* **2009**, *65*, 8916–8929.
27. Coquerel, Y.; Bremond, P.; Rodriguez, J. *J. Organomet. Chem.* **2007**, *692*, 4805–4808.
28. Djakovitch, L.; Koehler, K.; De Vries, J. G. In *Nanoparticles and Catalysis*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2008; pp 303–348.
29. Djakovitch, L.; Wagner, M.; Hartung, C. G.; Beller, M.; Koehler, K. *J. Mol. Catal. A: Chem.* **2004**, *219*, 121–130.
30. Batail, N.; Bendjeriou, A.; Djakovitch, L.; Dufaud, V. *Appl. Catal., A* **2010**, *388*, 179–187.