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Palladium-based innovative catalytic procedures: Designing new homogeneous and heterogeneous catalysts for the synthesis and functionalisation of N-containing heteroaromatic compounds

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ABSTRACT

N-containing heteroaromatics, particularly those owning an indole or quinolone substructure, are found in numerous natural or synthetic alkaloids of biological and pharmaceutical relevance. Therefore, various synthetic methodologies have been reported to access these backbones. The most advanced procedures use transition metal catalysts, usually as soluble (homogeneous) materials. In this short review article, we report our recent developments devoted to improving current catalytic pathways toward greener processes and to designing new heterogeneous Pd-based catalysts. The latter approach brings as main advantages low metal contamination and recyclability. The potential of these developments is demonstrated through the selective synthesis, as well as the functionalisation, of (NH)-indoles, quinolones, indoxyls or stilbenes.

1. Introduction

Condensed heteroaromatics are important (sub)structures present in numerous natural or synthetic alkaloids finding applications in pharmaceuticals, agrochemicals and cosmetics [1–5]. Among heterocycles belonging to this class of compounds, those containing at least one nitrogen atom, like indoles and quinolones, are undoubtedly the most important as they usually concern the human health. The diversity of the structures encountered, as well as their biological and pharmaceutical relevance, have motivated researches aimed at the development of economical, efficient and selective synthetic strategies [6–13]. These methodologies, while successful and commonly applied in the chemical industry, suffer from a low structural diversity and are thus not suitable for the selective synthesis of highly functionalised compounds. Therefore, transition metal-catalyzed procedures dedicated either to the construction or the transformation of such heterocycles have been developed. These methods provide generally an increased tolerance toward functional groups and higher chemical yields [14–31] and are currently applied in target- or diversity-oriented syntheses at the laboratory scale [26,27,32–37]. Comparatively, concerning indoxyls, only few transition metal catalyzed procedures have been reported [38–41].

Whatever the nucleus considered, these procedures suffer from several drawbacks, the main being unacceptable metal contamination of the product, generally over the accepted limits as expressed

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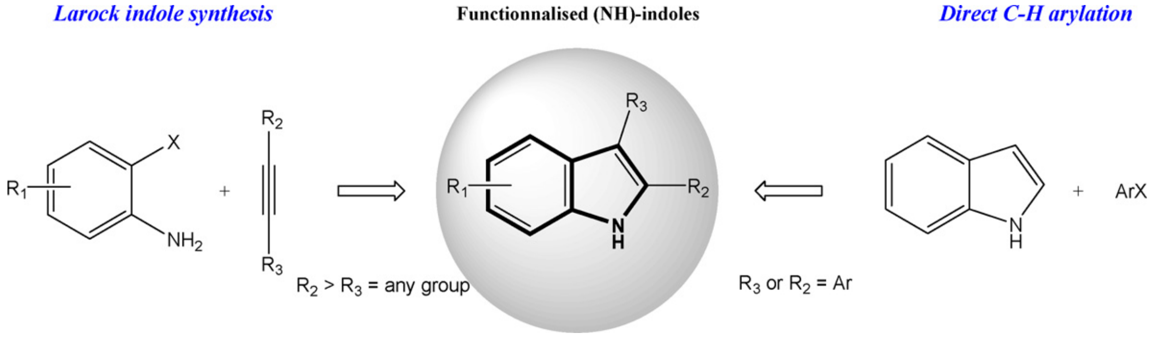


Fig. 1. Larock indole synthesis *versus* direct C-H arylation toward the synthesis of functionalised (NH)-indoles.

in the medicinal regulations that often prevented further industrial developments [42]. This situation encouraged us to develop alternative methodologies with respect to environment and economy in order to offer viable procedures for the preparation of such compounds at the industrial scale.

The aim of this review article is not to be exhaustive but rather to report our recent research progresses aiming at developing greener processes for the synthesis of N-containing heteroaromatics by using, for example water as solvent and one-pot multi-component reactions, or by replacing homogeneous Pd-catalysts commonly used by either commercially available or specifically designed heterogeneous Pd-catalysts. The powerful applications of these alternative approaches are demonstrated by the selective syntheses and functionalisations of (NH)-indoles, quinolones, indoxyls and stilbenes.

2. When indole met palladium: direct C-H arylation *versus* Larock heteroannulation

Among the amazing diversity of heteroaromatic compounds, indole can be considered as “the special one” with respect to its outstanding reactivity and the numerous biological activities [1,6] of natural alkaloids or synthetic derivatives. Since several decades, chemists have thus developed and improved new catalytic methodologies to access and/or functionalise this unique backbone [43]. In our opinion, two of the most advanced procedures, which avoid traditional cross-coupling reactions [44], have been brought through the well-known Larock heteroannulation and the direct C–H arylation of such heterocycles (Fig. 1) [8]. Therefore, we present in this chapter our recent progresses toward the development of innovative reaction conditions dedicated to these two special topics.

2.1. “On water” direct and site-selective C-H arylation of (NH)-indoles

Since the pioneering work of Ohta in the middle 1980s, considerable improvements have been achieved in the field of the indole direct C-H arylation [8,45]. Nevertheless, these methodologies suffer from several drawbacks which relay on the use of sophisticated catalytic systems (design of carbenes or phosphines, co-catalyst...), prior syntheses of arylating agents from commercially available aryl halides ($ArB(OH)_2$, $ArBF_3K$ or [Ar-I-Ar]OTf), the often required nitrogen protecting groups or the need of high-boiling, toxic and non environmentally friendly solvents. Furthermore, only few reports deal with site-selective arylation and the control of regioselectivity is closely linked to a specific nitrogen activation (respectively N-magnesium and N-acetyl indoles with respect to Sames [46] and Gaunt [47] work). Recently, our group was the first to report the use of a versatile catalytic system (i.e. metal/ligand) that allows either the C2- or the C3-arylation of (NH)-indoles and works “on water” [48], an alternative eco-friendly solvent which found some recent exciting applications in the field of direct C-H arylation [49–53].

Initially, we turned out our attention to the development of a selective C2-arylation protocol. Inspired by Sames work [54], we examined the performance of $Pd(OAc)_2$ (5 mol%) for the coupling of indole with iodobenzene. A base screening revealed that AcOK gave the highest selectivity toward the expected 2-phenylindole. Nevertheless, the poor yield obtained (20% after 24 h) prompted us to evaluate the role of phosphine ligands. While bulky, electron rich or hydrosoluble phosphines were found to be unsuitable for this transformation, mono- or bidentate arylphosphines resulted in improved yields (50–75%), the highest activity (i.e. 75% yield within 24 h; 20/1 C2/C3 selectivity) being achieved with the system $\{Pd(OAc)_2/dppm\}$ in a Pd/P ratio of 1/2. During these studies, a base-controlled regioselectivity was uncovered as mainly C3-arylation occurred while replacing AcOK by MOH (M = Li, Na or K) whether bromobenzene or iodobenzene is used; nevertheless, higher conversions and C3-selectivities were generally obtained with the cheaper aryl bromides and $LiOH{\cdot}H_2O$ as a base. Fig. 2 illustrates the broad scope of this versatile catalytic system applied either to the C2- or the C3-arylation of diversely substituted (NH)-indoles, with AcOK/Ar-I and $LiOH{\cdot}H_2O$/Ar-Br partners respectively.

From a mechanistic point of view, these results support an electrophilic palladation pathway at the C3-position of the indole nucleus and suggest that two kind of active palladium species are involved (Scheme 1). Indeed, the highly electrophilic cationic Pd-complex **A**, which formation would result from the higher dissociation behavior of iodides, is expected to easily undergo a C3-palladation. On the other hand, the activation of the neutral complex **B** requires the synergistic action of a stronger base than AcOK, probably through *in situ* deprotonation of the indole nitrogen. Therefore, the key intermediate **C** is expected to follow two pathways: (a) a C3 → C2 migration of the palladium center favored in the presence of the weak base AcOK, affording the complex **D** which leads to the C2-regioisomer; (b) a rearomatization privileged with stronger bases such as OH^- affording the σ–Pd complex **E**, precursor of the C3-regioisomer after reductive elimination of Pd(0). Notably, such a rearomatization could be elsewhere promoted by the presence of the more nucleophilic bromide anions compared to the iodide ones. However, we cannot rule out the co-existence of the so-called “concerted metallation-deprotonation” pathway when AcOK/ArI partners are used.

In summary, we have developed a unique catalytic system allowing an innovative “on water” direct and site-selective arylation of (NH)-indoles. This palladium-catalyzed C-H functionnalization reaction highlighted a [base/halide]-controlled regioselectivity, so that the arylation can be directed to either the 2- or the 3-position of (NH)-indoles. These procedures exhibit good to high regio- and chemoselectivities, displaying high structural versatility with regard to both indole and aryl moieties.

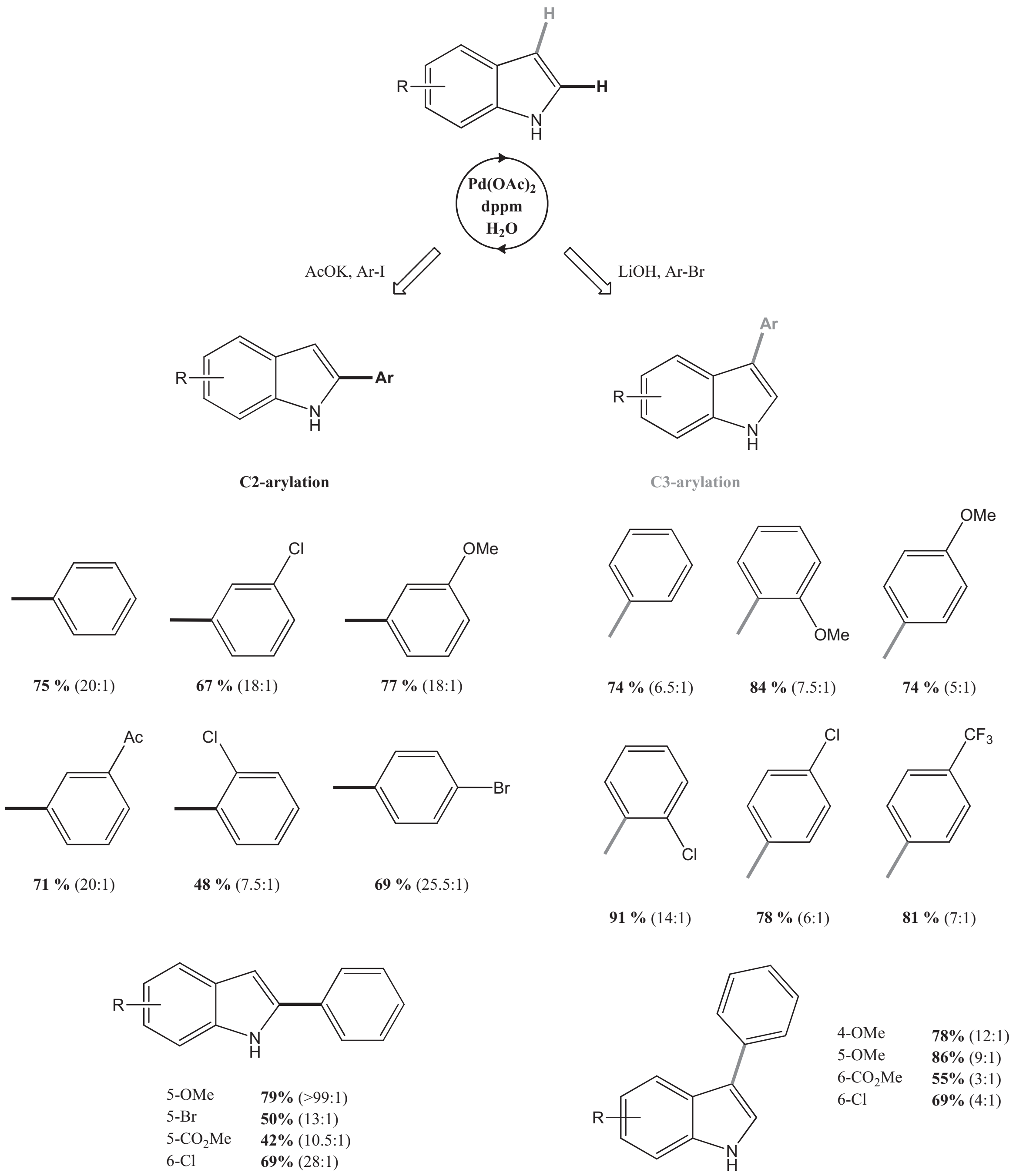
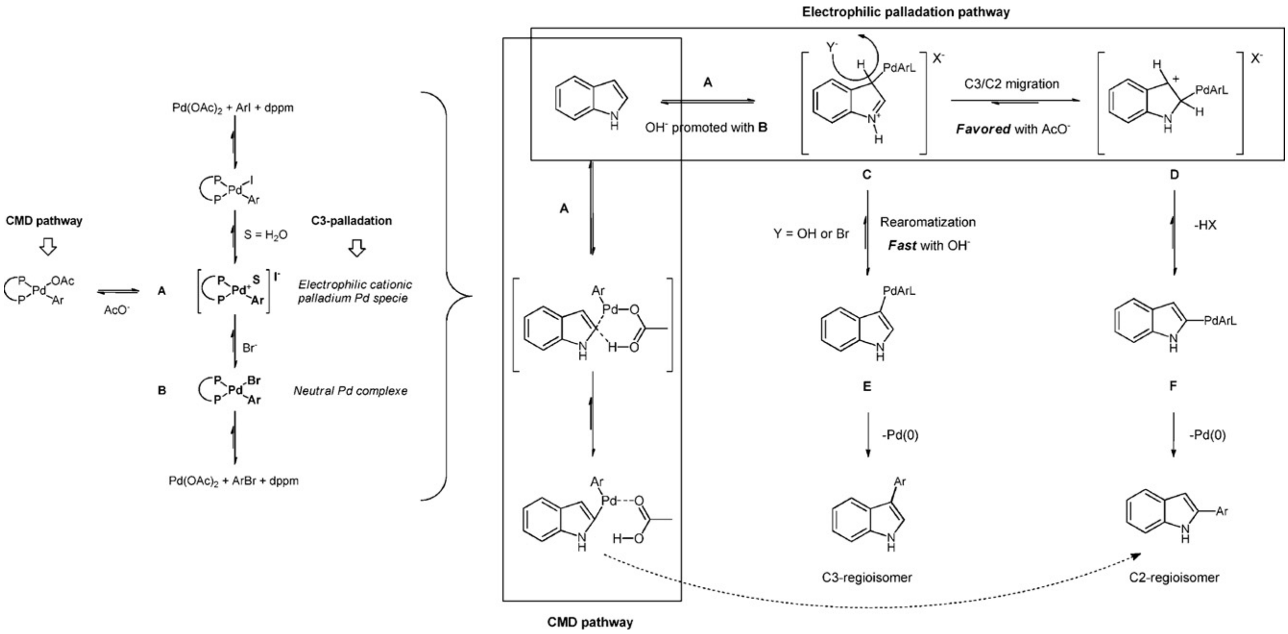


Fig. 2. Tunable functionalisation of (NH)-indoles through [base/halide]-controlled regioselective Pd-catalyzed C-H arylation. Reaction conditions: indole (1.0 mmol), aryl halide (1.2 mmol), base (3.0 mmol), $Pd(OAc)_2$ (5 mol%), dppm (5 mol%), H_2O (2 mL), 110 °C, 18–24 h. Selectivity of crude material determined by GC in brackets. Isolated yield of pure C2 and C3-isomer after flash column chromatography over silica.

2.2. Toward an additive-free Larock heteroannulation featuring heterogeneous Pd-catalysts

The well-known Larock heteroannulation [37], an original Pd-catalyzed coupling between 2-iodoanilines and disubstituted alkynes, became very popular during the last two decades as it features a one-step preparation of 2,3-functionnalized indoles (Scheme 2) [34,35]. However, despite its usefulness, this methodology still suffers from several drawbacks linked to the use of non-recyclable homogeneous Pd-catalysts ($Pd(OAc)_2$ ...), phosphine ligands, salts (mainly LiCl) and large excess of base or alkyne (3–5 equiv.). To overcome such limitations, we underwent researches aiming at performing an additive-free (i.e. ligand and salt) Larock indole synthesis using easily separable and potentially recyclable heterogeneous palladium catalysts [55].

Initial studies concerning the coupling between 2-iodoaniline and diphenylacetylene using $Pd(OAc)_2$ as catalyst pointed out the uselessness of any additives (i.e. LiCl and PPh_3) under optimized conditions [56]. Such a remarkable improvement encouraged us to support these results while using heterogeneous catalysts. Therefore, we engaged the classical and commercially available Pd/C (Degussa type E101 NE/W from ALDRICH, 10 wt% on dry basis, 52% water) or the easily home-made $[(Pd(NH_3)_4]/NaY$ (3.8 wt%, prepared by ion exchange of a NaY zeolite using a 0.1 M aqueous solution of $[Pd(NH_3)_4]Cl_2$ according to [57,58]) catalyst. To our delight, the coupling between 2-iodoaniline and diphenylacetylene



Scheme 1. Possible reaction mechanisms explaining the regioselectivity observed in the C-H arylation of (NH)-indoles.

(3 equiv.) in presence of Pd/C (2 mol%) using Na_2CO_3 as the base (3 equiv.) in DMF at 120 °C afforded the desired 2,3-diphenylindole in 70% isolated yield after 14 h. We have thus studied the scope of this new and improved procedure using various alkynes and 2-iodoanilines (Table 1).

As one could expect from the use of diphenylacetylene, known to easily provide dimerization adducts under Pd-catalysis, the yields were highly dependent on the nature of the catalyst used or that of the aniline substituents [59]. Otherwise, full conversions and good to excellent isolated yields (70–98%) were obtained whatever the catalyst used. Generally, $[Pd(NH_3)_4]$/NaY afforded better yields explained by its superior catalytic activity compared to Pd/C, as supported by kinetic studies (0.8 mmol $mmol_{Pd}^{-1}$ min^{-1} *vs* 0.3 mmol $mmol_{Pd}^{-1}$ min^{-1} respectively). It is noteworthy that this methodology is as well applied to the synthesis of benzo[*b*]furan derivatives in good yields (65–80%). Furthermore, these catalysts were easily recovered and showed only slight deactivation upon recycling, as close yields were obtained up to three times for Pd/C (100%, 100%, 100% yield) and up to five cycles for $[Pd(NH_3)_4]$/NaY (100%, 100%, 100%, 100%, 73% yield).

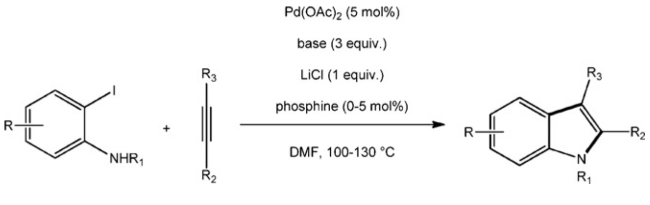
At this stage, our methodology was supposed to be limited to the use of the expensive and relatively unstable aryl iodides while other groups already explored the potential of the cheaper and more robust 2-bromo- or 2-chloroanilines. However, the successful transformation of such lower reactive substrates was subjected to the use of expensive ferrocenyl phosphines ligands (D*t*BPF) at a 10 mol% loading in combination with $Pd(OAc)_2$ (5 mol%) like reported by Lu and co-workers [60] or to the use of an economical phenylurea ligand as optimized by Cui et al. in order to replaced the costly phosphine ligand [61].

Therefore it was very challenging for us to face our heterogeneous and additive-free procedure with the use of 2-bromoanilines [112]. Remarkably, under the previously optimized reaction conditions (2 mol% Pd/C, 3 equiv. Na_2CO_3, DMF, 120 °C), 2-bromoaniline was fully converted within 18 h and afforded the expected indole in an excellent 85% isolated yield (Scheme 3).

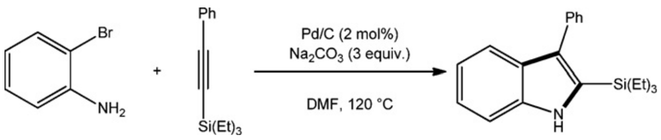
We have then extended this methodology to a variety of substituted 2-bromoanilines and alkynes. Whatever the nature of the substrates, indoles were obtained in good to high yields (55–95%) supporting the efficiency and the versatility of this heterogeneous procedure toward the weakly activated 2-bromoanilines (Table 2). Notably, in spite of a higher temperature (i.e. 140 °C) and longer reaction times inherent to the use of diphenylacetylene, good yields of the targeted indoles were obtained as side reactions (multiple insertions or amination/dimerization of the substrates) were almost suppressed. To date, the challenging sterically congested 2,6-dibromoaniline afforded only a moderate conversion (50% after 10 days) toward the desired indole.

In summary, this new and attractive protocol highlighted an unprecedented additive-free Larock indole synthesis through the use of recyclable Pd-based heterogeneous catalysts. While more competitive than the homogeneous version, this procedure affording new prospects toward the challenging 2-bromoanilines, we remained frustrated by the relative low catalyst activity with deactivated or bulky substrates.

Suspecting that the lack of activity was due to the use of Pd-particle based catalysts unable to activate efficiently refractive substrates, as supported by available literature related to the use of Pd-salts associated to phosphine ligands [62], we decided to turn our attention toward the use of immobilized palladium complexes inside the pores of mesoporous SBA-15 silica whose large

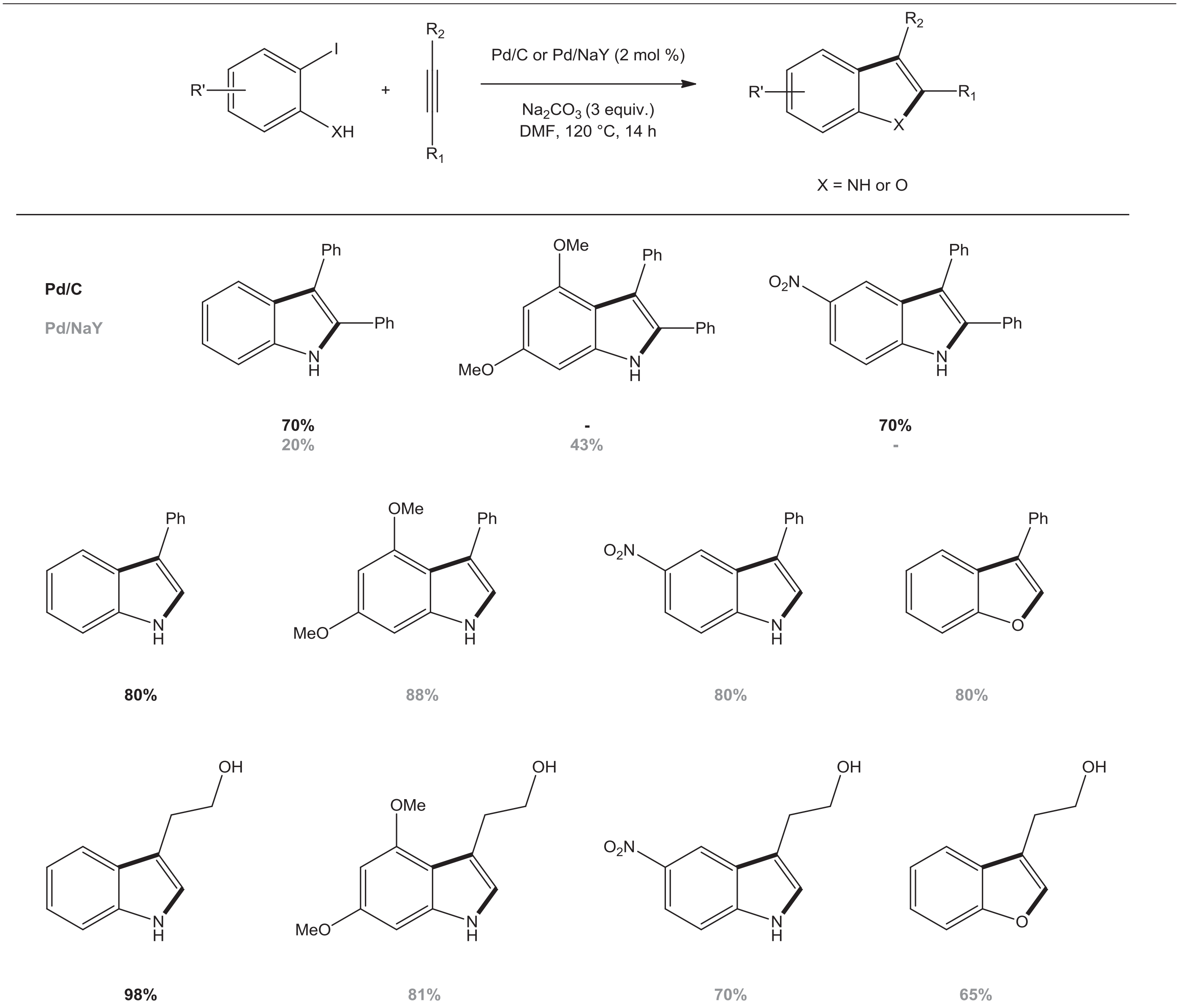


Scheme 2. Usual conditions for the Larock indole synthesis [34].



Scheme 3. Expanding the scope of the heterogeneous additive-free Larock heteroannulation through the use of 2-bromoaniline.

Table 1
Larock heteroannulation through heterogeneous additive-free catalysis.[a]



[a] Reaction conditions: 2-iodoaniline (1.0 mmol), alkyne (3 mmol), Na_2CO_3 (3.0 mmol), [Pd] (2 mol%), DMF (4 mL), 120 °C, 14 h. Isolated yield of pure indole after flash column chromatography over silica. When R_1 or R_2 = Si(Et)$_3$, hydrolysis of the silyl group using HCl 2 M or TBAF 1 M is performed, leading to the reduced compound.

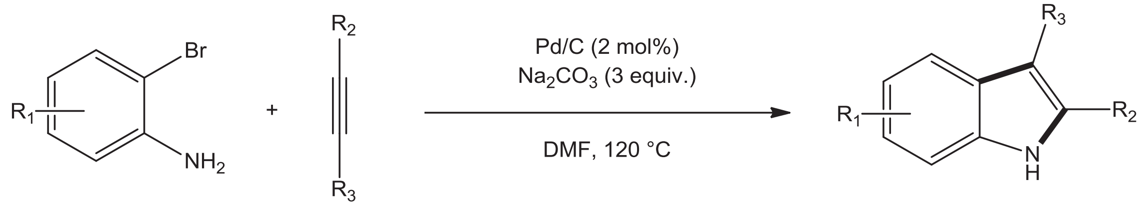
pore aperture (up to 80 Å) allows efficient substrate and product diffusion reducing thus mass transfer limitations even for large molecules. Therefore, we designed new Pd-based hybrid materials by grafting onto SBA-15 mesoporous silica Pd-complexes which were expected to exhibit enhanced intrinsic activities.

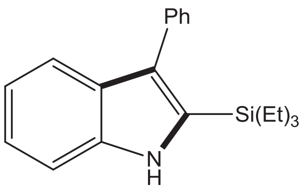
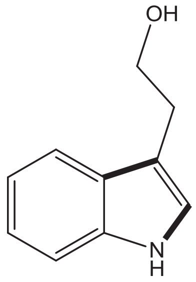
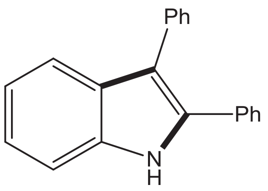
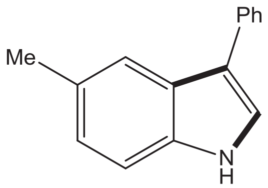
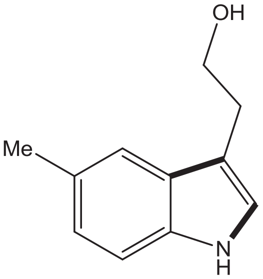
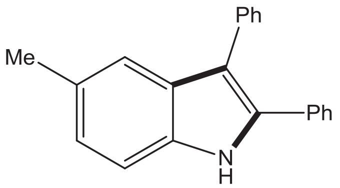
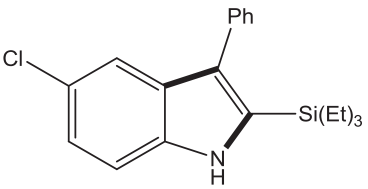
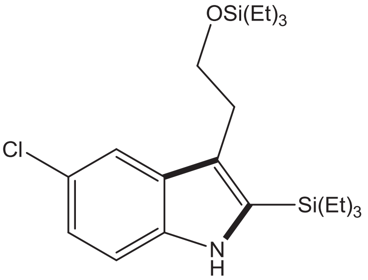
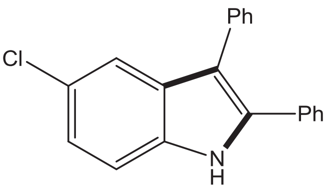
Thus, a variety of palladium-containing mesostructured hybrid materials bearing either cyano ligands, monodentate or chelating phosphine linkers with various steric and electronic properties have been prepared following procedures previously reported [63]. The structures of those hybrid materials are depicted in Fig. 3.

These Pd hybrid materials were applied to the Larock indole synthesis using the optimized reaction conditions previously described for [Pd(NH$_3$)$_4$]/NaY and Pd/C but using only 1 mol% Pd-catalyst (i.e. 2-iodoaniline (1.0 mmol), alkyne (3.0 mmol), Na_2CO_3 (3 mmol), [Pd]@SBA-15 catalyst (1 mol%), DMF (4 mL), 120 °C). Initially, we evaluated their catalytic performance over a period of 24 h for the synthesis of 3-phenyl-2-(triethylsilyl)-1*H*-indole; in all cases isolated yields of 80–85% were achieved (Scheme 4).

More insights were obtained from kinetic studies (Fig. 4). Interestingly, except for the Pd(PCy$_2$)$_2$@SBA-15 catalyst, all these materials showed higher activities than the previously evaluated catalysts; Pd/C (0.5 mmol $\text{mmol}_{\text{Pd}}^{-1}$ min^{-1}) and [Pd(NH$_3$)$_4$]/NaY (1.3 mmol $\text{mmol}_{\text{Pd}}^{-1}$ min^{-1}). The best catalysts are Pd(CN)$_2$@SBA-15 and Pd(PPh$_2$)$_2$@SBA-15 with initial rates of 3.8 and 2 mmol $\text{mmol}_{\text{Pd}}^{-1}$ min^{-1} respectively; the latter giving besides a full conversion within 3 h. In spite of moderate leaching of active palladium species in solution during the reaction – typically 20–25% of initially introduced palladium; however, associated to palladium redeposition at reaction completion (see [64] for details on these specific phenomena also called “boomerang effect”) – the [Pd]@SBA-15 catalysts were found to be recyclable up to five runs giving generally quantitative conversions [63]. Indeed, efficient reuse of [Pd]@SBA-15 catalysts is related to increased reaction times from 2 h to 14 h in order to circumvent an apparent deactivation as indicated by a lower initial rate after the first run [63]. Detailed and comprehensive studies of the catalytic phenomena

Table 2
Larock heteroannulation of 2-bromoanilines through heterogeneous additive-free catalysis.[a].



 **85%**, 18 h	 **87%**, 18 h	 **70%**, 3 d [b]
 **95%**, 4 h	 **81%**, 2 h	 **71%**, 3 d [b]
 **90%**, 3 h	 **60%**, 24 h	 **55%**, 6 d [b,c]

[a] Reaction conditions: 2-bromoaniline (1.0 mmol), alkyne (3 mmol), Na_2CO_3 (3.0 mmol), Pd/C (2 mol%), DMF (2 mL), 120 °C. Isolated yield of pure indole after flash column chromatography over silica.

[b] Reaction performed at 140 °C.

[c] 70% conversion.

showed it to be homogeneous in nature, the solid apparently serving as a "continuous source" of palladium between cycles (see [64] for details on these aspects, also called "reservoir catalysts").

Given the efficiency of these materials compared to that of Pd/C or $[Pd(NH_3)_4]$/NaY, we engaged them in the Larock indole synthesis from 2-bromoaniline. The initial experiment between 2-bromoaniline with triethyl(phenylethynyl)silane gave, for all materials described, the expected indole in high isolated yields (up to 85%). We believe that these materials offer real alternatives to the use of homogeneous catalytic systems for the Larock indole synthesis as they proved to be robust, able to quantitatively convert 2-iodo- and especially 2-bromoaniline toward the target compounds and they exhibit a good recyclability.

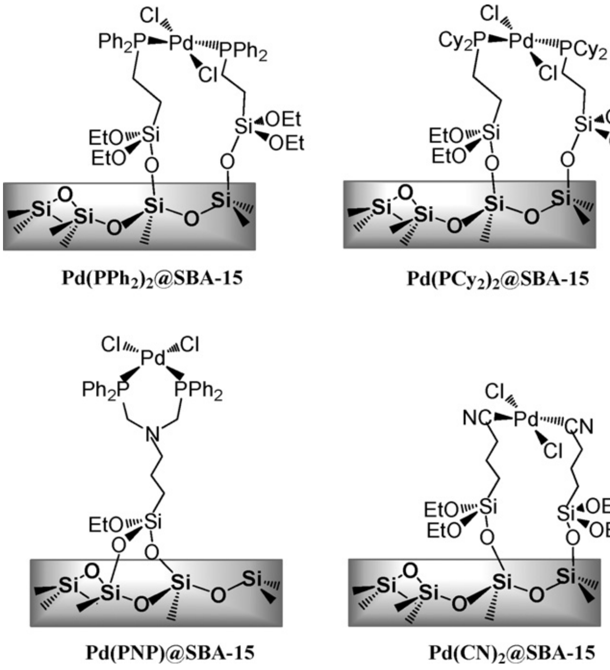
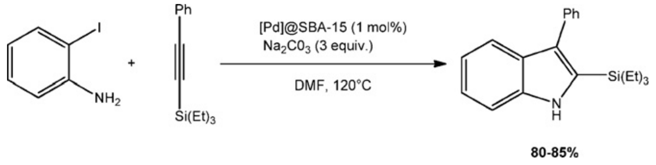


Fig. 3. Targeted palladium catalysts based on SBA-15 silica materials generally denoted as [Pd]@SBA-15. Individual short-names used throughout the text are reported under the schematic structures.



Scheme 4. Larock heteroannulation performed with hybrid materials.

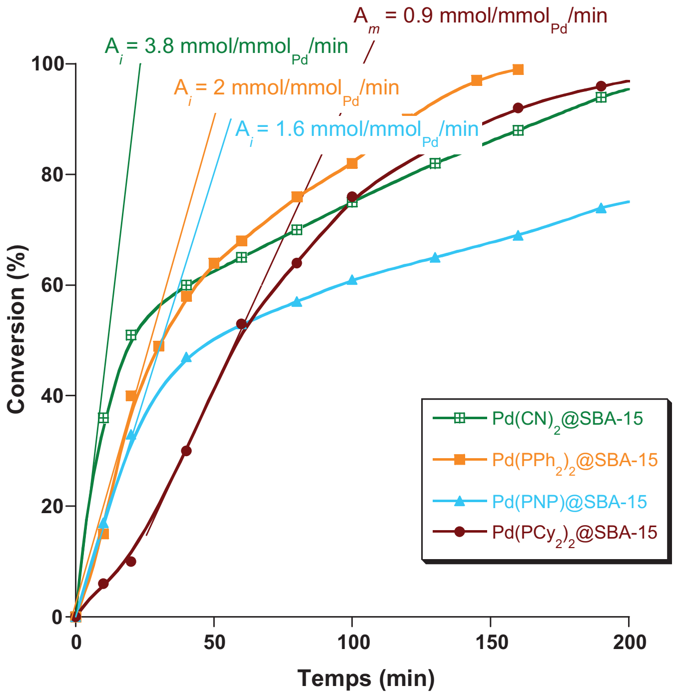
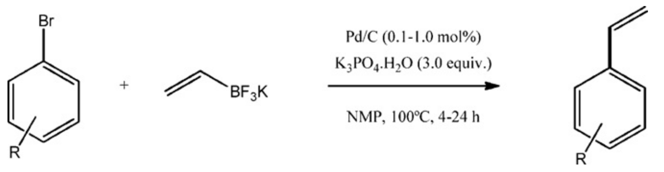


Fig. 4. Catalytic activity of well-defined heterogeneous hybrid materials for the synthesis of 3-phenyl-2-(triethylsilyl)-1H-indole.



Scheme 5. Heterogeneous vinylation of aryl bromides using potassium vinyltrifluoroborate.

In conclusion, we demonstrated that the Larock indole synthesis could be performed using heterogeneous palladium catalysts without any additives as ligands or salts. The corresponding 2,3-disubstituted indoles, as well as benzo[*b*]furan derivatives, are obtained in good to excellent yields. Furthermore, the heterogeneous catalysts can be recovered and reused over several cycles with only a slight deactivation. The high reactivity of 2-bromoanilines while using commercially available Pd/C features this new methodology as a real alternative to the use of homogeneous salty systems. We have confidence that the transformation of less reactive substrates will found answers thanks to the specifically designed new hybrid [Pd]@SBA-15 materials presented herein. Indeed, initial studies highlighted their higher catalytic activity and further studies will be oriented toward their application on refractive substrates.

3. Challenging multi-component reactions using heterogeneous Pd-catalysts: from carbonylative Sonogashira coupling to sequential Suzuki/Heck couplings

During the last 10 years, the inherent property of heterogeneous catalysts to achieve successive chemical transformations in a single pot has emerged as a powerful tool for organic chemists [65]. Particularly, multifunctional heterogeneous Pd-catalysts [66,67] have attracted much attention due to their ability to achieve the most relevant chemical transformations like C–C couplings, heteroannulation or hydrogenation. Following this approach, one-pot multi-step sequences have been the subject of recent contributions dealing with the synthesis of biological relevant compounds [16,68–75]. In this context, we have recently addressed new insights toward the application of heterogeneous Pd catalysts in multi-component reactions with emphasis on two main topics: sequential Suzuki/Heck couplings for the synthesis of quinoline-based stilbenes[76] and a selective carbonylative Sonogashira/cyclization strategy for the preparation of indoxyls or 4-quinolones (Fig. 5) [77,78].

3.1. *One-pot Suzuki/Heck sequence for the synthesis of (E)-stilbenes*

Stilbenes, an important class of biologically active molecules including the well-known Resveratrol and Combretastatin A-4, are commonly prepared by a Heck coupling between aryl halides and styrenes. Nevertheless, only few and poorly substituted of these latter are commercially available. Therefore, we have recently disclosed the vinylation of aryl halides thanks to the use of simple Pd/C catalysts [79,80]. Further studies have thus been devoted to the extension of such a methodology toward one-pot synthesis of (*E*)-stilbenes.

Initially, we have developed a new heterogeneous {Pd/C, $K_3PO_4 \cdot H_2O$, NMP} catalytic system, using catalyst loading as low as 0.1 mol% of [Pd], allowing an efficient synthesis of styrenes from aryl halides and potassium vinyltrifluoroborate *via* a Suzuki–Miyaura coupling (Scheme 5). We especially addressed the reactivity of aryl bromides bearing electron donating groups and found that even phenol and aniline were unusual and suit-

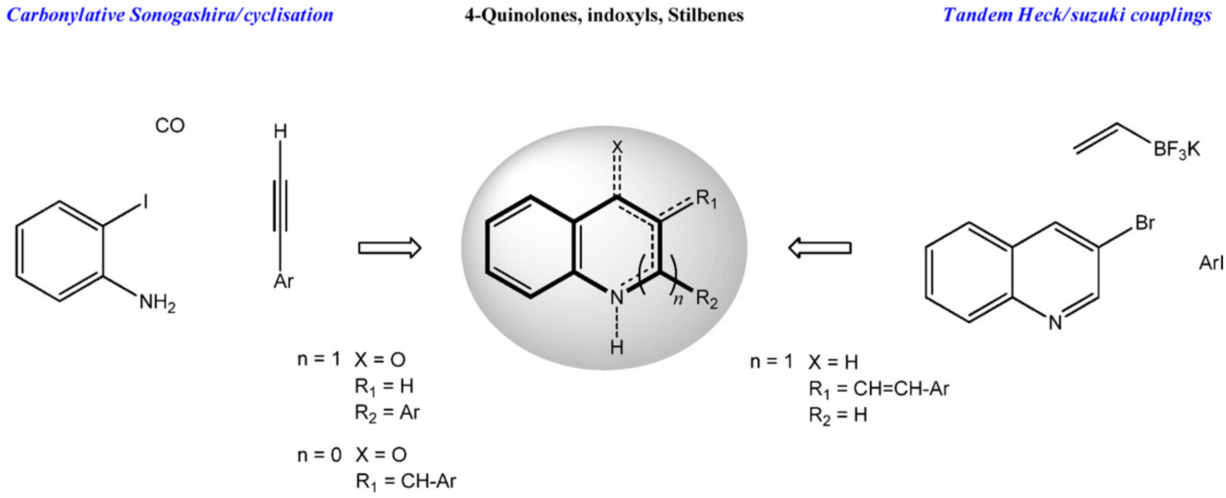


Fig. 5. Preparation of 4-quinolones, indoxyls and stilbenes *via* multi-component reactions.

able substrates for this transformation. While the "hot filtration" test established soluble palladium as the true active species (typically, 4 ppm palladium was detected in the solution during reaction that was associated to almost full redeposition on the support. See [80] and [64] for detailed discussions), the efficiency and robustness of this catalytic system was further demonstrated by the good recyclability of the Pd/C catalyst, given that base is added for each run, supporting the well accepted concept of "palladium reservoir" associated to such heterogeneous catalysts.

Optimization studies were thus conducted to apply such a methodology toward the one-pot preparation of (*E*)-stilbenes following *in situ* addition of an aryl halide (i.e. 3-bromoquinoline in this study) after the vinylation step. Remarkably, three main parameters were found to control the efficiency of this one-pot procedure:

- Only K_3PO_4 H_2O exhibited a superior behavior to perform both Suzuki and Heck couplings. Although AcOK and K_2CO_3 allowed full conversions for the vinylation step, these latter led to only poor conversions (<15%) for the Heck coupling, despite longer reaction times or large excess of the base.
- The home-made PdO/SiO_2 catalyst (8.9 wt%, prepared by wet impregnation followed by calcination in air flow according to [76,81]) displayed a higher activity than Pd/C or the well-known $[Pd(NH_3)_4]$/NaY, providing full conversion within 24 h and improved isolated yields. That was attributed to the nature of immobilized palladium species on the support, respectively Pd(II) as PdO and Pd(0) particles, and that of the support: non porous *versus* microporous, respectively.
- 1,3-Propanediol (1,3-PDO), a bio-sourced solvent produced from corn syrup or by glycerol hydrogenolysis, was found as a safe and environmentally unusual alternative solvent to the use of NMP.

This uncommon solvent proved its efficiency in the vinylation step especially with aryl iodides. This characteristic allowed us to develop an innovative multi-component approach for this one-pot synthesis, taking advantage of the lower reactivity of aryl bromides in 1,3-PDO toward the Suzuki coupling with potassium vinyltrifluoroborate. Furthermore, this solvent proved its usefulness when *ortho* substituted aryl iodides were used. Indeed, the formation of the undesired symmetrical bis-quinolyl stilbene, produced as a major product with NMP, was thus almost suppressed.

This multi-component procedure highlighting a heterogeneous $\{PdO/SiO_2, K_3PO_4{\cdot}H_2O$, 1,3-PDO$\}$ catalytic system has been successfully applied to a range of aryl iodides. The corresponding quinoline-based stilbenes were obtained in good isolated yields whatever the electron donating or withdrawing nature of substituents as well as the substitution pattern of the aryl iodides (Fig. 6). Furthermore, the PdO/SiO_2 catalyst has demonstrated a very good recyclability as close yields were obtained over 5 cycles (respectively, 63%, 69%, 67%, 70% and 69%. Typically, under the reaction conditions 4 ppm palladium was detected in the reaction mixture).

3.2. Selective carbonylative Sonogashira/cyclization strategy for the preparation of indoxyls or 4-quinolones

4-Quinolones represent an important family of bioactive molecules, mainly as antiviral, antibacterial or antimicrobial agents[82–91] for which various syntheses have been described. Indoxyls, due to the lack of efficient procedure, were only sporadically studied; however, the initial evaluations revealed interesting biological behaviors mainly with antiplasmodic activities [92]. Among the different methods described for the synthesis of 2-substituted-4-quinolones [93–109], the palladium catalyzed carbonylative coupling of 2-iodoanilines with arylacetylenes, initially reported by Torii and co-workers[26,27], appears to be the most versatile. These authors obtained good yields toward the expected compounds using either $[PdCl_2(PPh_3)_2]$ or $[PdCl_2(dppf)]$ (5 mol%) in presence of an excess of diethylamine which plays a key role in the cyclization step (Scheme 6).

However, like other authors [29], we observed that diethylamine tends to give huge amount of undesired by-products upon addition of the starting reactants. In order to suppress these side-reactions, we developed a one-pot *two-step* procedure for the synthesis of 4-quinolones. In this strategy, the non-cyclized intermediate **1** is selectively produced using triethylamine as the base in presence of $[PdCl_2(dppp)]$ as catalyst. At completion, diethylamine is added in the reaction mixture to give the expected 4-quinolone **2** in high selectivity. Even if the role of diethylamine is catalytic, an excess is used to achieve high reaction rates. Noticeably, the reaction conditions are softened compared to Torii's original work as only 1 mol% of Pd complex was used at 80 °C under 5 bar of CO in a less toxic solvent such as toluene. This approach enables the synthesis of 4-quinolones in both good selectivities and yields given that the acetylenic derivative is aromatic (Fig. 7).

While the mechanism regarding the formation of 4-quinolone **2** is clear, diethylamine playing the role of nucleophilic catalyst for the cyclization of **1** toward **2**, that of indoxyl **3** described by Catellani and co-workers [41] remained unexplained given the very close reaction conditions (Scheme 7).

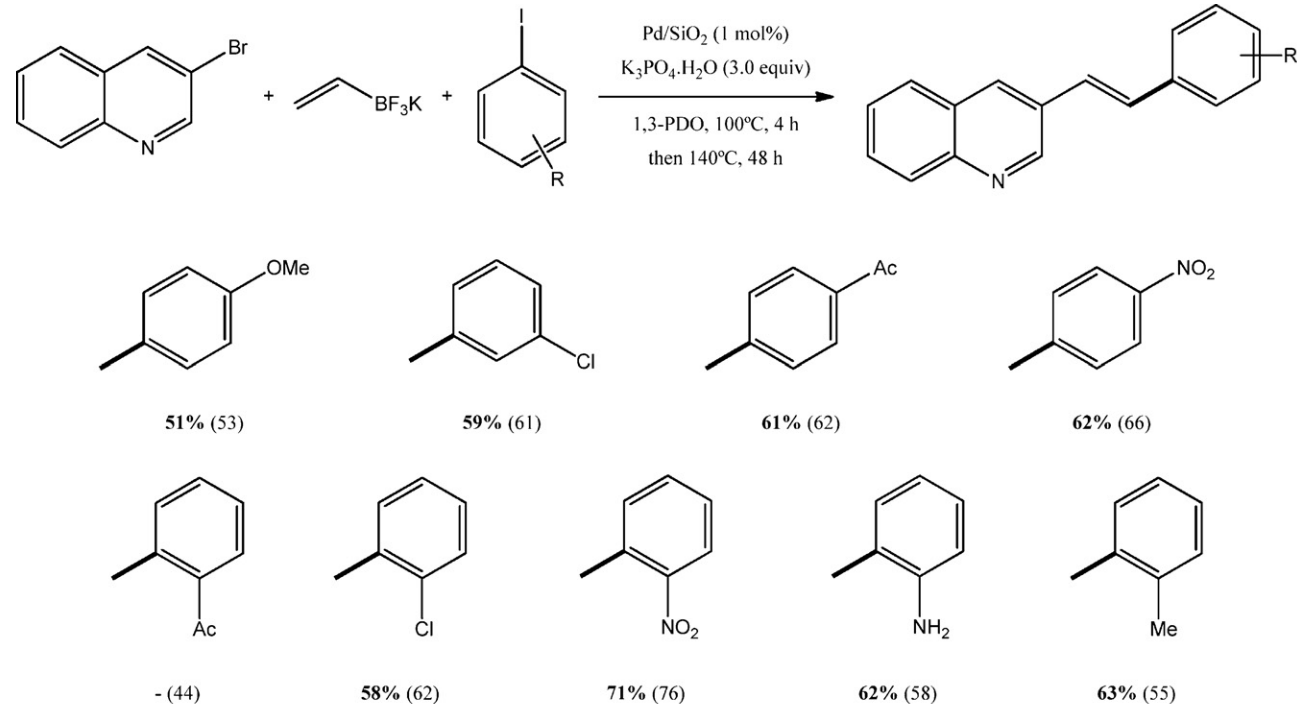
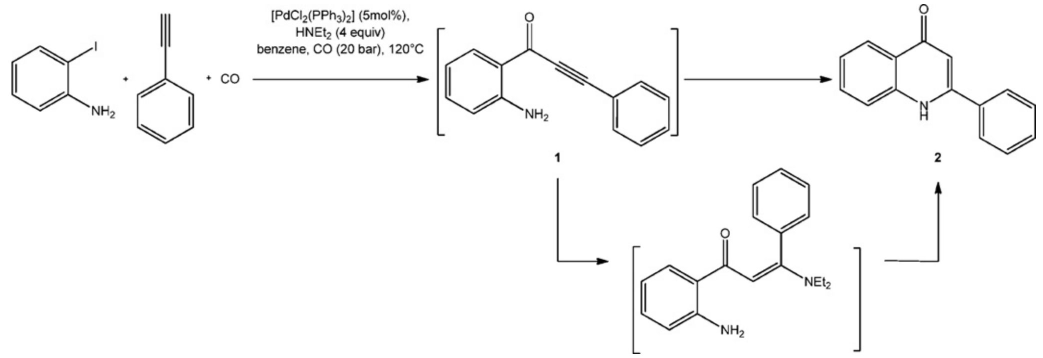


Fig. 6. Multi-component synthesis of (E)-stilbenes in 1,3-PDO through a Suzuki/Heck sequence. Reaction conditions: aryl iodide (3.0 mmol), 3-bromoquinoline (2.0 mmol), potassium vinyltrifluoroborate (3.3 mmol), K_3PO_4 H_2O (9.0 mmol), PdO/SiO_2 8.9 wt% (36.0 mg, 1.0 mol%), 1,3-PDO (3.0 mL). Isolated yield of pure stilbene after flash column chromatography over silica. Values in brackets refer to a tandem procedure (i.e. *in situ* addition of 3-bromoquinoline after the vinylation step).



Scheme 6. Reaction pathway and conditions according to Torii.

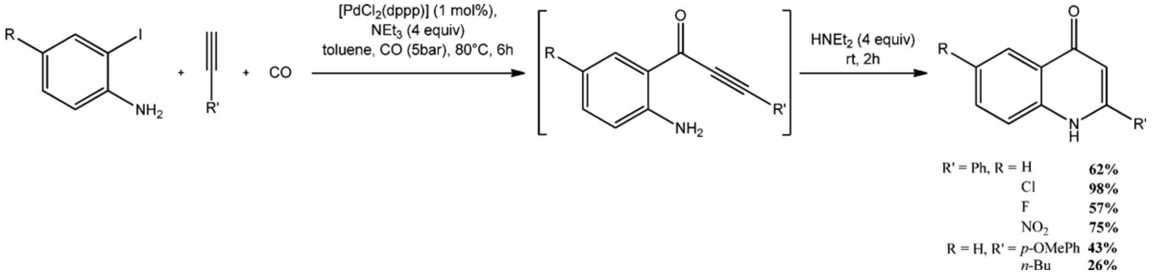
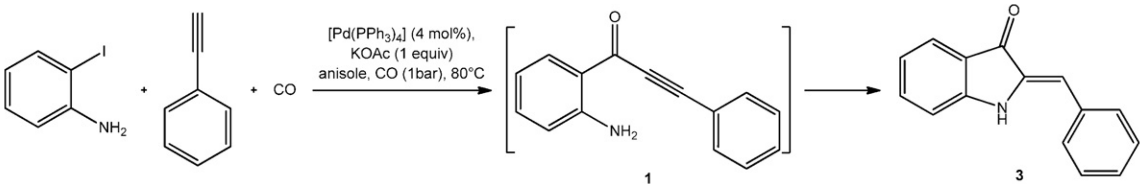


Fig. 7. Optimized homogeneous conditions for the selective synthesis of 4-quinolones. Conditions: 2-iodoaniline (3 mmol), alkyne (1.2 equiv), [$PdCl_2$(dppp)] (1 mol%), NEt_3 (4 equiv), toluene, CO (5 bar), 80 °C, 6 h; then $HNEt_2$ (4 equiv), 20 °C, under air, 2 h.



Scheme 7. Formation of indoxyl and conditions according to Catellani [41].

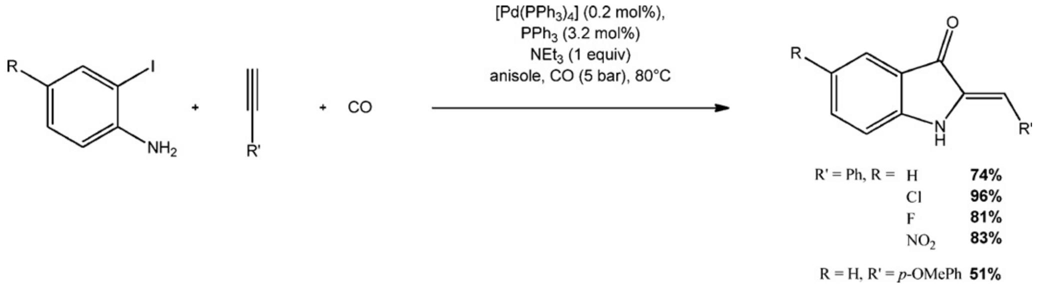


Fig. 8. Optimized homogeneous conditions for the selective synthesis of indoxyls. Conditions: 2-iodoaniline (3 mmol), alkyne (1.2 equiv), $[Pd(PPh_3)_4]$ (0.2 mol%), PPh_3 (3.2 mol%), NEt_3 (1.2 equiv), anisole, 80 °C, CO (5 bar), 3–12 h.

In order to elucidate factors controlling the selectivity toward the 5-membered ring from the intermediate **1**, we performed a broader study varying the nature of the Pd-catalysts, ligands, bases, additives and solvents revealing that the cyclization step toward the indoxyl **3** was catalyzed by "free" phosphine. In this study, the use of $[Pd(PPh_3)_4]$ as the catalyst appeared to be optimal in terms of conversion and selectivity toward the indoxyl compound **3** [77]. Interestingly, with this complex the Pd-loading could be decreased down to 0.2 mol% given that free phosphine was added in the reaction mixture to achieve high cyclization rates. Several indoxyls were thus prepared in good to high isolated yields, mainly as the (Z)-isomer (Fig. 8).

To sum up this study, the formation of indoxyls **3** or 4-quinolones **2** corresponds to two step processes. For both heterocycles, the first step consists in a Pd-catalyzed carbonylative Sonogashira coupling between iodoanilines, alkynes and carbon monoxide to give the intermediate **1**. Then, it follows an organocatalysed cyclization, either by diethylamine toward 4-quinolones **2** or by phosphines to afford indoxyls **3** (Scheme 8). This resulted in two procedures: indoxyls are prepared *via* a one-pot tandem catalysis {[Pd]/[phosphine]} and 4-quinolones **2** through a one-pot multi-catalysis {[Pd] + [amine]} [77].

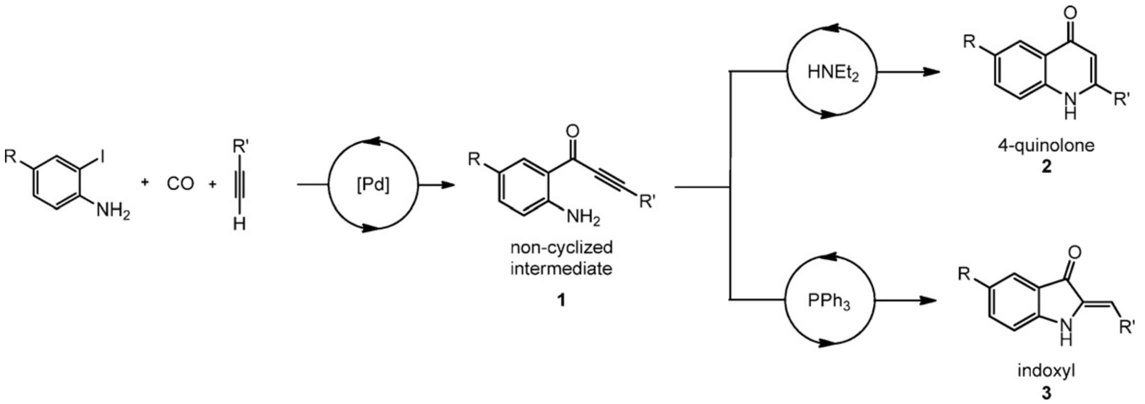
While successful, this methodology still suffers from the need of homogeneous catalysts that are tedious to remove and could result in high palladium and ligand (i.e. phosphine) contamination of final products that is not acceptable when dealing with human and animal health [42]. Accordingly, we underwent studies to develop full heterogeneous one-pot synthesis of indoxyls and 4-quinolones.

In order to achieve this selective synthesis in a heterogeneous fashion, $Pd(PPh_2)_2$@SBA-15 catalyst associated to phosphine catalyst either as homogeneous PPh_3 (Table 3, Method B) or heterogeneous PPh_2@SBA-15 (Table 3, Method C) was used. The later (Fig. 9, left) was prepared *via* a multi-step tethering protocol. Amine hybrid catalyst was also synthesised by grafting of amine on SBA-3 silica [78]. More details on the preparation of those hybrid materials can be found elsewhere [55]. The results thus obtained were compared to those achieved using purely homogeneous catalysts (Table 3, Method A).

As shown in Table 3, 2-benzylidene-indoxyl **3** could be formed in high isolated yield using a semi-heterogeneous catalytic system (Method B). The use of a heterogeneous Pd catalyst enables a decrease in the metal contamination of the crude product from 94 ppm to 28 ppm. However, this Pd content is still too high for a direct use of indoxyl in pharmaceutical applications. This could be related to the stabilization of leached Pd species in solution by soluble triphenylphosphine. To overcome this contamination issue, grafted phosphine PPh_2@SBA-15 was evaluated (Method C). However, the cyclization toward the indoxyl **3** appeared to be slow delivering only 11% yield after 24 h (Table 3, entry 3). Prolonged reaction time gave unfortunately the side-product **4** which was identified as 2-benzyl-*1H*-indole[110] (Table 3, entries 3–6) instead of the expected indoxyl **3**. This product is assumed to be formed by successive reduction/dehydration of the indoxyl **3** (Scheme 9) according previous reports in the literature [111]. Aromatization in the final compound is supposed to be the driving force of the reaction. In line with our previous results [77], replacing triethylamine by another base like *t*-BuOK could help to overcome this difficulty.

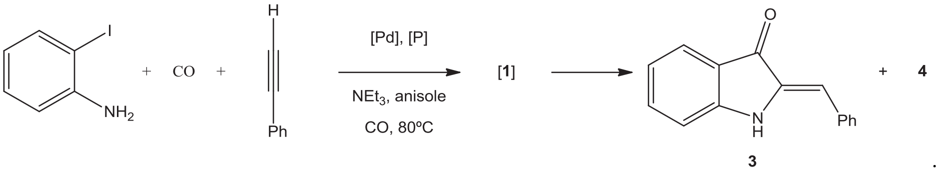
In conclusion, the indoxyl **3** could be efficiently produced through a semi-heterogeneous protocol associating a palladium grafted catalyst and soluble triphenylphosphine which allowed to reduce the palladium contamination of the final product.

Although the two-step procedure enables high selectivities to produce 4-quinolones, it is not convenient for industrial applications to add separately the amine catalyst for reactions conducted under pressure. Therefore, we were interested to develop heterogeneous tandem catalysis rather than a multi-catalysis approach. We evaluated the performances of the Pd(PNP)@SBA-15 catalyst associated either to soluble $HNEt_2$ or NH_2@SBA-15 (Fig. 9, right), both



Scheme 8. Catalytic species involved in the selective formation of 4-quinolones or indoxyls.

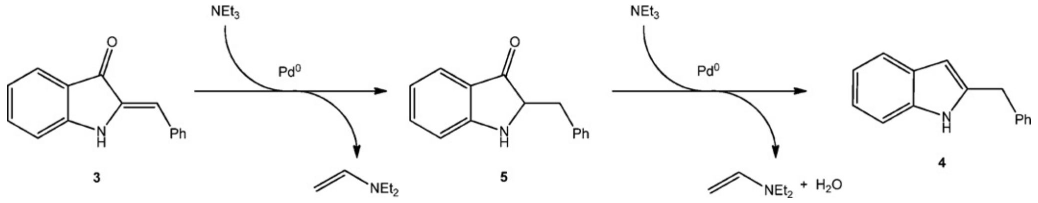
Table 3
Studies toward the heterogeneously catalyzed synthesis of 2-benzylidene-indoxyl **3**.



Entry	Method	Time (h)	GC analysis[a]	Yield[b]	Pd contamination	
			1	3	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		

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), $Pd(PPh_2)_2$@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), $Pd(PPh_2)_2$@SBA-15 (0.1 mol%), PPh_2@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) ($\Delta_{rel} = \pm 5\%$).
[b] When available isolated yields are reported.
[c] Theoretical value, calculated from the amount of Pd used in the reaction.
[d] 94% conversion of 2-iodoaniline was achieved.



Scheme 9. Proposed mechanism for the formation of 2-benzyl-*1H*-indole **4**.

in catalytic amount (1 mol%). The results are compared to those achieved using fully homogeneous multi- or tandem catalysis using [$PdCl_2$(dppp)] (Table 4).

While the homogeneous procedure is very efficient when working with an excess of diethylamine, the use of a catalytic amount requires up to 7 days to achieve a quantitative conversion (Table 4, entries 1 and 2). The reaction time was not modified by using the Pd(PNP)@SBA-15 catalyst (Table 4, entries 3 and 4); however, the metal contamination in the final product could dramatically be decreased with this catalyst. The best performances are observed with the fully heterogeneous catalytic system consisting of a mechanical mixture of the palladium and amine hybrid materials (Table 4, entry 5). Under these conditions, 2-phenyl-4-quinolone **2** is obtained in 61% isolated yield after only 3 days. However, this is only attributed to the enhanced activity of the grafted primary amine compared to diethylamine used as reference in the homogeneous system that is supported by previous experiments [77].

The recyclability of the mixed catalytic materials was then studied over 3 runs following the previously described procedure (Table 5) [78]. Notably, the overall reaction time increased upon recycling. Fine analyses revealed that both steps of the transformation suffer from deactivation: the palladium catalyzed carbonylative Sonogashira increased from 1 to 2 days which is attributed to metal leaching associated with poor redeposition. Similarly, the cyclization of intermediate **1** toward 2-phenyl-4-quinolone **2** increased from 3 to 9 days probably due to the deactivation of grafted amine catalyst by protonation that could not be counter-balanced by using an excess of triethylamine. Nevertheless whatever the level of {Pd(PNP)@SBA-15/NH_2@SBA-3} catalysts mixture deactivation, isolated yields toward the target 2-phenyl-4-quinolone **2** remain stable upon recycling at an average value of 65% given that a longer reaction time is used.

To summarize these studies, one-pot procedures have been developed for the selective syntheses of either 4-quinolones or indoxyls from 2-iodoaniline, phenylacetylene and carbon monoxide. Both homogeneous and heterogeneous pathways have been optimized leading to practical and efficient protocols: a homogeneous two-step multi-catalysis {[$PdCl_2$(dppp)] + $HNEt_2$} or a heterogeneous tandem catalysis {Pd(PNP)@SBA-15/NH_2@SBA-3} to access 4-quinolones; a homogeneous {[$Pd(PPh_3)_4$]/PPh_3} or a semi heterogeneous {$Pd(PPh_2)_2$@SBA-15/PPh_3} catalysis are privileged toward indoxyl derivatives. The choice between homogeneous or heterogeneous catalysis relay to the "user": the first uses commercially available catalysts, while heterogeneous pro-

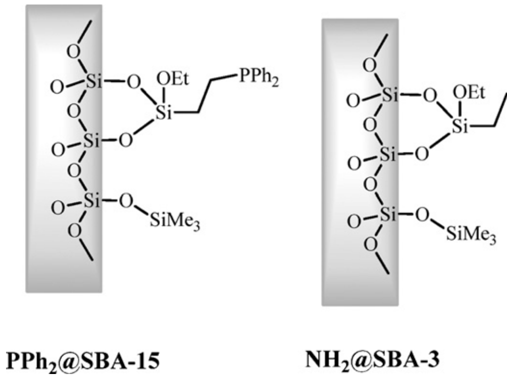
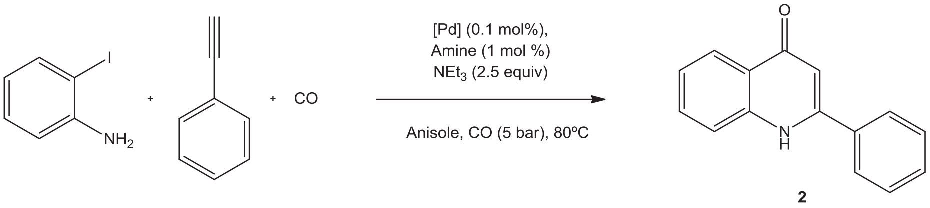


Fig. 9. Phosphine and amine catalysts grafted on SBA type silica. Short-names used throughout the text are reported under the schematic structures.

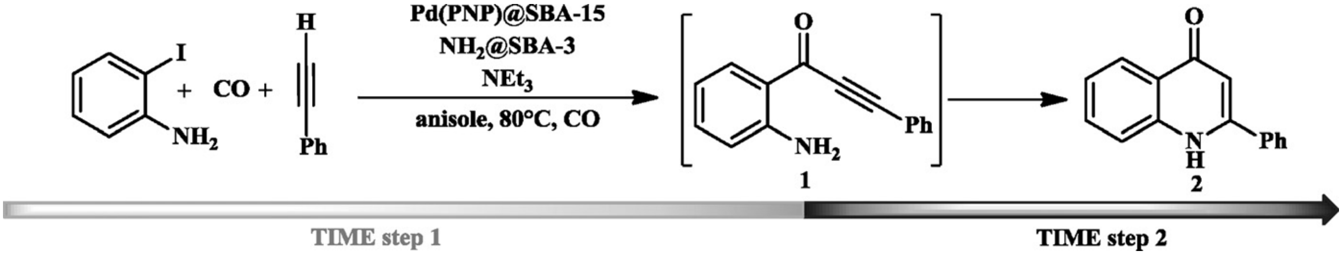
Table 4
Studies toward the heterogeneously catalyzed synthesis of 2-phenyl-4-quinolone **2**.



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	Pd(PNP)@SBA-15 + $HNEt_2$	6	63	n.d.
4	Tandem	Pd(PNP)@SBA-15/$HNEt_2$	7	65	5 ppm
5	Tandem	Pd(PNP)@SBA-15/NH_2@SBA-3	3	61	5 ppm

Reaction conditions: 2-iodoaniline (3 mmol), phenylacetylene (1.2 equiv), [Pd] (0.1 mol%), $HNEt_2$ or NH_2@SBA-3 (1 mol%), triethylamine (2.5 equiv), anisole (5 mL), CO (5 bar), 80 °C.

Table 5
Recycling the {Pd(PNP)@SBA-15/NH2@SBA-3} catalysts mixture for the synthesis of 2-phenyl-4-quinolone **2**.



Run	Time step 1 (days)[a]	Time step 2 (days)[b]	Yield (%)[c]
1	1	3	60
2	1	5	62
3	2	9	72

Reaction conditions: run 1: 2-iodoaniline (6 mmol), phenylacetylene (1.2 equiv), Pd(PNP)@SBA-15 (0.1 mol%), NH_2@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.

[a] Time to full conversion of starting iodoaniline.

[b] Time to full conversion of **1**.

[c] Isolated yield.

tocols required the specific preparation of the catalytic materials. However, the latter resulted in strongly reduced palladium contamination of the final product that could be of interest for pharmaceutical applications.

4. Conclusions

This mini-review featured our recent developments dedicated to the design of innovative Pd-based catalytic procedures for the synthesis and functionalisation of nitrogen-containing heterocycles like indoles and quinolone derivatives, highlighting original and practical improvements. The aim of these developments was to propose to the synthetic chemists, whatever in academic or industrial field, reliable tools, competitive with existing procedures and, when possible, environmentally friendly.

With this goal in mind, depending on the nature of the substrates, the target compounds and the transformations involved, the use of either homogeneous or heterogeneous catalysts, when possible in green solvents, was developed. Thus, the outcome of these studies could be summarized in three main topics:

- the use of green solvents, namely water and 1,3-propanediol, which allowed to perform the direct C-H arylation of (NH)-indoles and the one-pot synthesis of (*E*)-stilbenes, respectively. This improvement is very appreciable given that common procedure used generally polar solvents like DMF, DMAc or NMP that are currently regarded as highly toxic for the environment and should be replaced in industrial applications;
- the design of highly active heterogeneous catalysts, specifically Pd-based hybrid materials grafted onto SBA-15 mesoporous silica. These materials were applied successfully to the selective one-pot synthesis of 4-quinolones and indoxyls. They also proved to be useful for indole syntheses when engaging difficult substrates using our simple and valuable procedure that features a revisited additive-free (no ligand, no salts) Larock indole synthesis. This procedure was initially optimized on 2-iodoanilines using a simple and commercially available Pd/C catalyst, which exceptional reactivity allowed us to expand the scope of this simplified procedure toward 2-bromoanilines;
- the development of selective multi-component reactions, highlighting an easily home-made heterogeneous PdO/SiO_2 catalyst, leading to new procedures that were particularly applied to stilbenes syntheses. Associated to 1,3-propanediol such methodologies featured clearly improved synthetic tools in Heck or Suzuki cross-coupling that are used every days to prepare organic molecules of medicinal interest.

In conclusion, we believe that these operationally simple procedures represent attractive protocols and sensible approaches toward greener chemistry. The scope is probably not limited to the few examples reported herein and we hope that this short review article will stimulate further work in these directions.

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