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Larock heteroannulation of 2-bromoanilines with internal alkynes via ligand and salt free Pd/C catalysed reaction

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ABSTRACT

An alternative to the use of ligands and homogeneous catalysis to promote the synthesis of 2,3-disubstituted indoles starting from 2-bromoanilines is described for the first time. This reaction could be achieved through a Larock heteroannulation via a ligand free heterogeneous catalysis.

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Discovered more than one century ago, indole nucleus still receives great attention. Initially associated with the development of efficient medicines,¹ then with agrochemicals and functionals materials,² the indole ring continues to play an important role in a wide variety of synthetic methodologies^{3–9} leading to total syntheses. In the continuing search for more economical, efficient and selective procedures, the palladium-catalysed indolisation discovered by Larock has emerged as a powerful tool (Scheme 1).^{10,11} This approach is highly versatile allowing the coupling of iodoanilines with internal alkynes to afford, in a single step, 2,3-disubstituted indoles.

While effective, this methodology suffered from drawbacks linked to the use of homogeneous catalysts which are generally combined with additives (salt and ligands) to maintain high activity. To avoid such limitations, we developed the first heterogenous-ly Pd-catalysed ligand and salt free Larock heteroannulation using both readily available catalysts¹² (Pd/C and/or Pd/NaY) as well as more elaborate hybrid materials¹³ (Pd/SBA-15).

This approach led to an enhanced activity with higher product yields than those achieved under homogeneous conditions. Despite this amelioration, our methodology was limited to the use of the expensive and relatively unstable aryl iodides, which constituted a significant limitation to any industrial application of this technique. Herein, we report our effort to extend the Larock indole synthesis to the less expensive and more robust 2-bromoanilines.

Initially, we evaluated the coupling of 2-bromoaniline with triethyl(phenylethynyl)silane under Larock's original conditions. As expected, no reaction occurred.¹¹ Indeed, Lu and co-workers reported that the coupling of 2-bromoanilines with internal alkynes required electron-rich palladium complexes,¹¹ which they achieved by using the bulky and electron-rich ferrocenyl phosphine ligands (DtBPF) at 10 mol % loading associated with Pd(OAc)₂.¹⁴ This protocol was recently optimised by Cui et al. who replaced the costly phosphine ligand by a low-priced phenylurea.¹⁵

Encouraged by our initial success in the heterogeneously Pdcatalysed Larock heteroannulation, we evaluated the Pd/C catalyst. Surprisingly, using only 2 mol % Pd/C under previously optimised reaction conditions (3 equiv Na₂CO₃, DMF, 120 °C), the 2-bromoaniline was fully converted to 3-phenyl-2-(triethylsilyl)-1*H*-indole with 85% isolated yield.¹⁶



Scheme 1. Larock indole synthesis.

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Table 1

Larock heteroannulation for 2,3-disubstituted indoles via ligand free Pd/C catalysed coupling of internal alkynes with 2-bromoanilines^a





^a Reaction conditions: 1 mmol 2-bromoaniline, 3 mmol alkyne, 2 mol % Pd/C, 3 equiv Na₂CO₃, 2 mL DMF, 120 °C.

^b 1 mol % Pd/C was used.

^c Isolated yield after flash chromatography on silica.

 d Isolated product after $-Si(Et)_{3}$ hydrolysis by HCl 1 M.

The study was expanded to a variety of substituted 2-bromoanilines and alkynes (Table 1). Whatever the nature of the substrate, indoles were obtained in good to high yields (60–95%) demonstrating the efficiency, the selectivity and the versatility of the methodology. Indeed, no side reactions, such as multiple insertions or amination/dimerisation of the substrates, were observed, as had been reported for other systems.¹¹ The reaction could also be achieved using lower catalyst loadings and longer reaction times (e.g., with 1 mol % Pd/C, as in Table 1, entry 1).

Diphenylacetylene is a more challenging substrate, as it has the tendency to give numerous oligomerisation side products.^{10,17} Working at 120 °C led to very low conversion (10%) even after 48 h, but at 140 °C various 2,3-diphenylindoles were obtained in good to high yields (Table 2). 2-Bromo or 4-methyl-2-bromoaniline was fully converted to the corresponding indoles in high 70% isolated yields (entries 1 and 2). The mixed dihalide 4-chloro-2-bromoaniline underwent partial deshalogenation but nevertheless was converted to the target 5-chloro-2,3-diphenylindole in 55% isolated yield (entry 3). The only limitation observed is related to

Table 2

Larock heteroannulation for 2,3-diphenylindoles via ligand free Pd/C catalysed coupling of diphenylacetylene with 2-bromoanilines^a



^a Reaction conditions: 1 mmol 2-bromoaniline, 3 mmol alkyne, 2 mol % Pd/C, 3 equiv Na₂CO₃, 2 mL DMF, 140 °C.

^b Determined by GC with an internal standard (biphenyl, Δ_{rel} = ±5%).

^c Isolated yield after flash chromatography on silica.

the use of highly desactivated 2,6-bromoaniline that resulted in a very low reaction rate as after 10 d only 50% of the starting aniline was converted.

In summary, we developed for the first time a regioselective indole synthesis from 2-bromanilines and internal alkynes catalysed by commercially available Pd/C catalyst without adding any ligand or salt. The new protocol led to useful and high isolated yields (55– 95%) whatever the alkynes or bromoanilines engaged. We believe that this highly practical procedure is very competitive with respect to existing ones, particularly in the chemical industries where economical considerations are concerned.

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Supplementary data

Supplementary data (general information, typical experimental procedure for the Larock heteroannulation, physical properties of isolated compounds, copy of ¹H and ¹³C NMR spectra and copy of MS spectra are available) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.044.

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- 16. Pd/C (10 wt % on dry basis) was purchased from Aldrich Chemical (E101 NE/W) and is characterised by a low degree of reduction (XPS analyses) and high water content (52%). Typical experimental procedure for the larock heteroannulation: aryl bromide (1 mmol), alkyne (3 mmol), Na₂CO₃ (3 mmol), Pd/C (2 mo 1%) and DMF (2 mL) were introduced in a sealed tube. The reactor was placed under stirring in a preheated oil bath at 120 °C or 140 °C after being flushed by argon. 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 then washed with Na₂CO₃ (2 × 40 mL) and brine (40 mL). The organic layer was dried over Na₂SO₄ and the solvent was removed under reduced pressure. If necessary (for the silylated compounds), the crude product could be fully deprotected by treatment with HCl 1 M before being purified by flash chromatography on silica.
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