

Recyclable supported Pd-NHC catalytic systems for the copper-free Sonogashira cross-coupling in flow

I. Peñafiel,^{a,c} A. Martínez-Lombardia,^b C. Godard,^b C. Claver^{a,b} and A. Lapkin^{*c}

[a] Centre Tecnològic de la Química de Catalunya. Carrer Marcel·li Domingo S/N 43007 Tarragona, Spain; e-mail: itziar.penafiel@manchester.ac.uk;

[b] Departament de Química Física i Inorgànica. Universitat Rovira i Virgili. Carrer Marcel·li Domingo S/N 43007 Tarragona, Spain

[c] Department of Chemical Engineering and Biotechnology. University of Cambridge. Philippa Fawcett Drive, Cambridge CB3 0AS, UK.

Abstract: A new family of well-defined NHC-Pd complexes immobilised onto silica, alumina and titania is reported. The catalysts display activity and recyclability in the Sonogashira cross-coupling reactions under batch and continuous flow conditions. Under batch conditions the new catalytic systems were recycled up to four times with yields over 80%. These catalysts have a broad substrate scope of different aryl bromides and alkynes. The titania-supported catalysts show good conversions under continuous flow conditions at least over 8 hours on stream using MeOH as solvent.

1. Introduction

Palladium catalysed cross-coupling reactions are very important synthetic methodologies for the formation of carbon–carbon and carbon–heteroatom bonds, recognised by a Noble prize in Chemistry in 2010.^[1–6] These coupling processes had a transformative impact on chemicals industries and have been employed in a number of industrial applications^[7, 8] as well as reported in numerous publications on the syntheses of complex organic molecules and materials, such as natural products, fine chemicals, drugs, agrochemicals and polymers.^[9–13] In most cases, the new reaction development was performed under conventional batch synthesis conditions, whereas most chemical companies, especially in the pharmaceutical and speciality chemicals fields, are rapidly developing capability in continuous flow manufacturing.^[14, 15]

The use of Pd-based catalysts under flow conditions represents specific challenges of production of solids and leaching of Pd into the products, which complicate the development of generic, efficient manufacturing protocols.^[16] Therefore, the design of robust and more efficient catalysts with high turnover numbers (TON), high turnover frequencies (TOF) and low leaching has become an important target in this field. In this context, the use of recyclable immobilised homogeneous catalysts, which exhibit high activity and selectivity as well as low leaching, could provide a generic solution.

Continuous processing has been placed in the top 10 of green engineering research areas by pharmaceutical industry, since it offers new opportunities for developing more efficient chemical processes due to several advantages.^[17] Specifically, *better process economics* (lower cost of production via reduced inventory, footprint, waste, emissions and energy consumption); *better product quality* (improved quality and consistency compared to batch operations, intensive operating conditions at elevated temperatures and pressures, precise control of temperature, pressure and heat transfer); *safety* (via smaller reactor volumes and holdup volumes of potentially hazardous reagents or solvents); *lower environmental impact* (the reaction can be run neat in a flow reactor or at least more concentrated involving a potential reduction of solvent volume).^[18] Moreover, continuous-flow processes are usually more reproducible due to precise control of the reaction parameters, and allow faster development of the scaled-up processes, significantly reducing the time to market.^[19] As a consequence of these advantages, the use of continuous flow reactors has attracted a considerable interest from the pharmaceutical industry.^[20, 21]

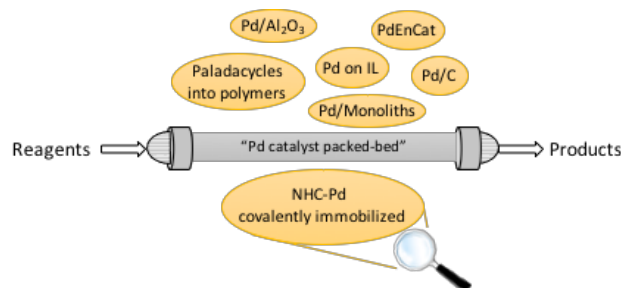


Fig 1. An illustration of the concept of continuous flow synthesis with the heterogenised Pd catalysts.

Since the turn of the century, continuous flow methodology has been employed to carry out many important synthetic transformations, including catalytic reactions mediated by homogeneous and heterogeneous catalysts.^[22–25] Yet, carrying out palladium-catalyzed C–C cross-coupling reactions in flow has proven to be challenging, due to the large amount of inorganic salts generated as by-products during the process,^[26] that usually cause clogging of the narrow-bore continuous flow reactors. Although

several approaches have been developed for metal-catalysed C-C cross coupling reactions in flow,^[27-34] the number of examples concerning specifically the Sonogashira reaction using flow methodology and a recyclable catalyst, is very small and among those most involve the use of aryl iodides as substrates.^[35-38]

Concerning the use of aryl bromides as substrates for Sonogashira coupling under flow, a small number of examples, involving quite different strategies for catalyst immobilization, are reported in the literature and only two that employ a recyclable catalyst. In 2003 Plenio reported the immobilisation of the polymer-tagged palladium catalysts in a stationary solvent for the Sonogashira cross coupling of different aryl bromides and phenyl acetylene.^[39] More recently, the use of the recyclable solution of ionic liquids containing homogeneous Pd catalysts, reported by Ryu and co-workers, led to the production of a matrix metalloproteinase inhibitor on a 100-gram scale.^[40]

Recently our group has demonstrated the effectiveness of a well-defined Pd complex bearing functionalized N-heterocyclic carbene (NHC) as a ligand.^[41] The silica covalently immobilized catalytic system was evaluated in Suzuki-Miyaura conditions for the coupling of different boronic acids and aryl bromides and the final product was obtained at constant conversion during two hours on stream. In 2014, Thieuleux and co-workers observed interactions between alkyl moieties present in the NHC ligands and bulk silica signals by solid NMR, suggesting that surface interactions could be a general phenomenon for materials that have flexible linkers.^[42] Encouraged by these observations, we continued work on developing good linkers to heterogenize homogeneous catalysts for applications in flow synthesis of pharmaceuticals and report here new results on the low leaching catalysts suitable for continuous flow operation.

2. Material and Methods

Reactions were carried out using standard bench-top techniques unless the use of a Schlenk flask is specified, in which case Schlenk-line inert atmosphere techniques were used. Where stirring of the reaction mixture is indicated, magnetic stirring using a Teflon-coated stir bar was employed throughout. Commercially supplied compounds were used without further purification. Dry solvents were prepared by distillation from Na/benzophenone, CaH₂ or P₂O₅, or collected from a Braun SPS800 solvent purification system. Photochemical reactions were performed using a Philips HPL-N 125 W high-pressure mercury lamp, which can be purchased at most commercial lighting stores. NMR spectra were obtained at the Servei de Recursos Científics i Tècnics (SRCT), URV, with Varian (Agilent) Mercury VX400 or NMR System400 400 MHz spectrometers and calibrated to residual solvent peaks. Chemical shifts for ¹H and ¹³C{¹H} NMR spectra are reported relative to TMS. ICP analysis was conducted at the SCRT using an ICP-OES Spectro Arcos instrument. Samples were digested in concentrated HNO₃ under microwave irradiation before being diluted for analysis. HR-MS (ESI-TOF) analysis was performed at the SCRT, on an Agilent Time-of-Flight 6210 spectrometer. GC-MS analysis was conducted on Agilent 6850 instruments, fitted with HP-5 capillary columns. Elemental analyses were performed at Centro de microanálisis elemental at Universidad Complutense de Madrid. Silica, titania and γ -alumina used for catalyst immobilization were dried for 1 h at 80 °C, 10⁻³ bar prior to use. Pd(acac)₂,^[43] imidazolium salt ligand^[44] and pre-catalyst were prepared according to literature procedures.

2.1. Synthesis of the supported catalysts

2.1.1. One-pot procedure for preparation of 3@Al₂O₃ (@Al₂O₃ makes reference to the support onto which the metal complex **3** is immobilised). A flame-dried Schlenk flask was charged with **1** (200 mg, 0.441 mmol, 1.0 equiv.), 3-mercaptopropyl(triethoxy)silane (225 μ L, 0.887 mmol, 2.0 equiv.) and DMPA (22 mg, 0.09 mmol, 0.20 equiv.), followed by freshly-dried EtOH (1.5 mL). The reaction mixture was then stirred and irradiated with a 125 W high-pressure mercury lamp (8 cm of separation between the bulb and flask) for 24 h. The solvent was removed under reduced pressure, and the residue was re-dissolved in CH₂Cl₂ and evaporated again in order to fully remove the EtOH. Next, Pd(acac)₂ (134 mg, 0.441 mmol, 1.0 equiv.) was added along with 1,2-DCE (5 mL). After the reaction mixture was heated at 75 °C with stirring for 2 days and then allowed to cool, it was slowly transferred *via* cannula to another Schlenk flask containing a stirred (400 rpm) suspension of previously dried 60 mesh alumina (2.0 g) in 1,2-DCE (5 mL). This suspension was stirred at 250 rpm for 30 min at ambient temperature, then the temperature was increased to 75 °C and stirring was continued for 24 h. During this time all of the yellow colour in the supernatant was transferred to the alumina. Finally, the material was hot-filtered and washed with copious amounts of CH₂Cl₂. The recovered yield of **3@Al₂O₃** was 2.36 g. Pd content by ICP: 1.76 wt% (0.162 mmol g⁻¹). Anal. Calcd. for C₄₂H₆₄ClN₂O₆PdS₂Si₂@Al₂O₃ based on Pd loading: C, 12.5; H, 1.61; N, 0.70; S, 1.60. Found: C, 9.55; H, 1.93; N, 0.67; S, 1.18.

2.1.2. One-pot procedure for preparation of 3@TiO₂. A flame-dried Schlenk flask was charged with **1** (213 mg, 0.377 mmol, 1.0 equiv.), 3-mercaptopropyl(triethoxy)silane (190 μ L, 0.754 mmol, 2.0 equiv.) and DMPA (19 mg, 0.08 mmol, 0.20 equiv.), followed by freshly-dried EtOH (1.5 mL). The reaction mixture was then stirred and irradiated with a 125 W high-pressure mercury lamp (8 cm of separation between the bulb and flask) for 24 h. The solvent was removed under reduced pressure, and the residue was re-dissolved in CH₂Cl₂ and evaporated again in order to fully remove the EtOH. Next, Pd(acac)₂ (115 mg, 0.377 mmol, 1.0 equiv.) was added along with 1,2-DCE (5 mL). After the reaction mixture was heated at 75 °C with stirring for 2 days and then allowed to cool, it was slowly transferred *via* cannula to another Schlenk flask containing a stirred (400 rpm) suspension of previously dried 60 mesh silica (1.71 g) in 1,2-DCE (3 mL). This suspension was stirred at 250 rpm for 30 min at ambient temperature, then the temperature was increased to 75 °C and stirring was continued for 24 h. During this time all of the yellow colour in the supernatant was transferred to the titania. Finally, the material was hot-filtered and washed with copious amounts of CH₂Cl₂. The recovered yield of **3@TiO₂** was 2.5 g. Pd content by ICP: 0.76 wt% (0.143 mmol g⁻¹). Anal. Calcd. for C₅₀H₈₀ClN₂O₆PdS₂Si₂@TiO₂ based on Pd loading: C, 9.91; H, 1.33; N, 0.46; S, 1.06. Found: C, 8.87; H, 1.94; N, 0.58; S, 0.97.

2.2. General procedure for catalytic Sonogashira reaction. A small Schlenk flask or 5 mL screw topped vial was charged with the catalyst, base, alkyne and the aryl halide (if solid). The flask or vial was capped with a septum or septum cap and flushed with N₂, and then the aryl halide was added *via* microsyringe if liquid. Solvent was added *via* syringe (2 mL organic solvent) and, in the case of the Schlenk flask runs, the septum was replaced by a glass stopper. The reaction mixture was then stirred at 400 rpm and heated at the indicated temperature. After the indicated reaction time, the vessel was cooled in an ice bath. Next, the mixture of reaction was filtered through a small plug of silica. In the case of the biphasic aqueous runs, the aqueous layer was then extracted with toluene (2 \times 0.5 mL) and the extracts were filtered through the same silica plug. The silica

plug was washed with toluene (1 mL). The product mixture was analyzed by GC at this stage, and then it was evaporated under reduced pressure and purified by silica gel chromatography using hexane/EtOAc as eluent.

2.3. General procedure for recycling of the supported catalysts for Sonogashira reaction. In the cases where catalyst recycling was performed, an internal standard (undecane) was added after cooling the reaction mixture in an ice bath; the supported catalyst was separated from the organic phase by decantation. The supported catalyst was then successively washed with water, EtOH and Et₂O, then dried under vacuum and directly reused in the next cycle.

2.4. Coupling products obtained by Sonogashira reactions

1-(4-(phenylethynyl)phenyl)ethanone (4a)^[45]

Yellow solid. Chromatographed with 10:1 *n*-hexane/EtOAc. ¹H NMR (400 MHz, CDCl₃): 2.61 (s, 3H), 7.37 (m, 3H), 7.56 (m, 2H), 7.62 (dd, 2H, *J* = 1.9, 6.7 Hz), 7.94 (dd, 2H, *J* = 2.0, 6.7 Hz); HR-MS: *m/z* = 220.0900, calcd. for C₁₆H₁₂O [M⁺]: 220.0888.

1-(4-((4-methoxyphenyl)ethynyl)phenyl)ethanone (4b)^[46]

White solid. Chromatographed with 10:2 *n*-hexane/EtOAc. ¹H NMR (400 MHz, CDCl₃): 2.60 (s, 3H), 3.83 (s, 3H), 6.90 (d, 2H, *J* = 8.9 Hz), 7.49 (d, 2H, *J* = 8.9 Hz), 7.58 (d, 2H, *J* = 8.5 Hz), 7.93 (d, 2H, *J* = 8.5 Hz). HR-MS: *m/z* = 250.0999, calcd. for C₁₇H₁₄O₂ [M⁺]: 250.0994.

4-((4-Aminophenyl)ethynyl)acetophenones (4c)^[47]

Yellow oil. Chromatographed with 10:1 *n*-hexane/EtOAc. ¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 3.86 (bs, 2H), 2.58 (s, 3H); HR-MS: *m/z* = 235.1000, calcd. for C₁₆H₁₃NO [M⁺]: 235.0997.

1-(4-*o*-Tolylethynylphenyl)ethanone (4d)^[48]

Yellow oil. Chromatographed with 10:1 *n*-hexane/EtOAc. ¹H NMR (400 MHz, CDCl₃): δ 2.53 (s, 3H), 2.62 (s, 3H), 7.16–7.28 (m, 3H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 2H); HR-MS: *m/z* = 234.1042, calcd. for C₁₇H₁₄O [M⁺]: 234.1045.

2.5. General procedure for Sonogashira reaction mediated by the supported catalysts under continuous flow conditions. Catalytic activity and stability of the catalyst **3@Al₂O₃** and **3@TiO₂** were studied under flow conditions using two HPLC pumps and a packed-bed reactor. The rig is shown schematically in Fig. 2.

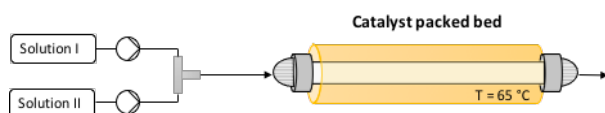


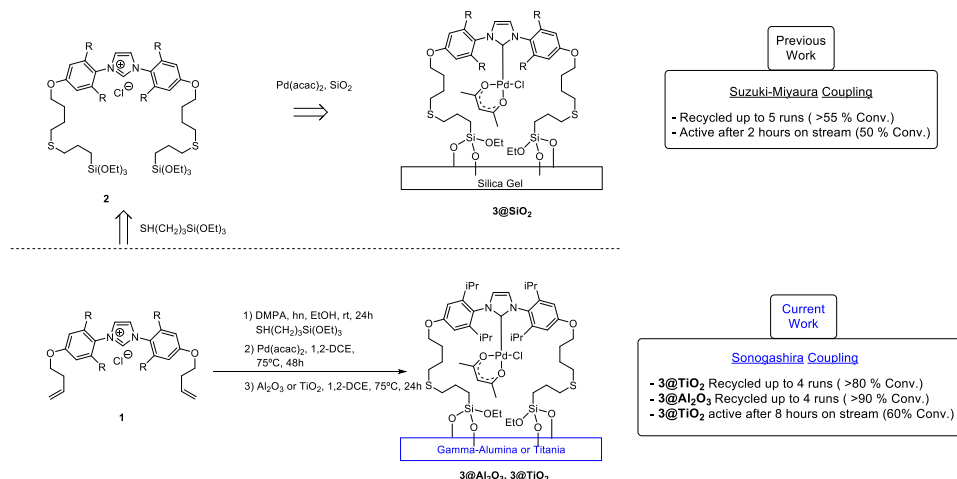
Fig. 2 Scheme of a continuous flow reactor using a syringe pump (Harvard) and an OmniFit reactor column.

Two solutions with the reagents were prepared: Solution I consisted of a 0.2 M solution of 4-bromoacetophenone and solution II contained 0.3 M of phenylacetylene and 0.4 M of base (Cs₂CO₃) in the appropriate solvent. $\mu_1 = \mu_2 = 0.2 \text{ mL min}^{-1}$, the total flow rate was 0.40 mL/min. The merged flow was then introduced to the inlet of the packed-bed column assembly (borosilicate glass with PTFE end pieces, 6.6 mm ID x 100 mm length, OmniFit). The column was packed with the desired amount of catalyst and an extra amount of silica is added to prove the length of the catalytic bed of 2.33 cm, which corresponds to the packed bed volume of 0.797 mL. Volume of void in the catalytic bed in the approximation of close random packing of ideal spheres is 0.298 mL (void fraction is approx. 0.375, porosity of the support is neglected). Aliquots were analysed using GC, mesitylene was used as the internal standard.

3. Results and Discussion

3.1. Pd NHC catalytic systems preparation and characterization

The synthetic route used for the functionalisation and immobilisation of imidazolium **1** in the three inorganic solid supports, and the obtained catalytic and recyclability results are summarized in Scheme 1. The γ -Al₂O₃ and TiO₂-supported Pd-NHCs (**3@Al₂O₃** and **3@TiO₂** respectively) were prepared following the methodology previously described.^[42] In the case of the **3@SiO₂** a sequential one-pot reaction involves the functionalization of the imidazolium salt **1** with triethoxysilyl groups, coordination of this heterogenised compound **2** to Pd and the subsequent immobilization of the resulting Pd-NHC complex **3** onto γ -Al₂O₃ and TiO₂. The acronym “**NumberOfCompound@InorganicSupport**” makes reference to the covalently immobilized metal complex onto different inorganic supports.



Scheme 1. An overview of the previous and current work.

Characterization of these new catalytic species was completed by N₂-sorption measurements, thermogravimetric analysis (TGA) and elemental analysis, and the amount of palladium was determined by inductively coupled plasma of the dissolved solids. Some analytical data are summarized in Table 1. The nitrogen adsorption-desorption isotherms of **3@SiO₂**, **3@Al₂O₃**, and **3@TiO₂** at 77 K are shown in Fig. 3. For the three catalytic systems, a significant reduction in pore diameters and BET surface areas compared with those of the parent supports [given in brackets] was observed, Table 1. These reductions are in excess of 100 m² g⁻¹ for the **3@SiO₂** and the **3@Al₂O₃**, and around 10 m² g⁻¹ for the titania-supported catalyst. These reductions are interpreted as indicators of successful grafting of the precursor **3** onto the different supports as well as partial filling of the pores, thus corresponding to distribution of the catalyst within the pore structure of the supports, rather than on the external surface.

Table 1. Selected analytical and textural data of supported catalytic systems **3@Al₂O₃** and **3@TiO₂**.

	TGA ^[a] (%)	Pd (%)	S _{BET} (m ² g ⁻¹)	S _{BET} ^[b] (m ² g ⁻¹)	Ø _{pore} (nm)
3@SiO₂	92.6	2.52	389	473	3.6 [6.1]
3@Al₂O₃	85.4	1.76	124	208	6.9 [7.1]
3@TiO₂	95.9	0.76	43	51	15.7 [20.3]

^[a] Residual mass measured in the TGA analysis. ^[b] S_{BET} for the corresponding parent supports.

The three supported catalytic systems are mesoporous materials. However, significant differences in their porosity were observed depending on the support; for the **3@Al₂O₃** the 6.9 nm pore diameter was found while the titania-supported system **3@TiO₂** exhibited the largest pore diameter, 15.7 nm, and the **3@SiO₂** possesses the smallest pores, 3.6 nm. The BET surface areas for the **3@SiO₂** and the **3@Al₂O₃** catalysts are relatively high, ranging from 124 to 389 m² g⁻¹, with type IV isotherms, while the **3@TiO₂** has a low surface area of 43 m² g⁻¹ and exhibited a type II isotherm according to IUPAC classification, Fig. 3. For these mesoporous catalytic systems, the contribution of micropores is negligible, most of the pores being in the range of mesopores.

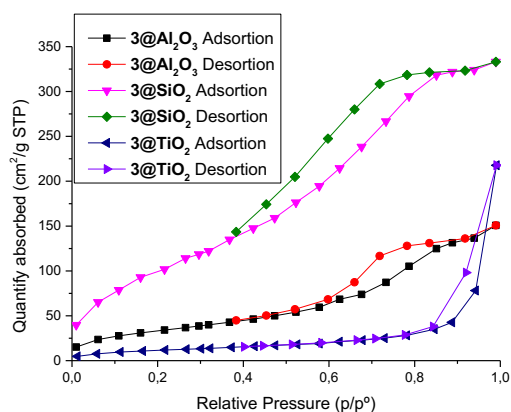


Fig. 3 N₂ sorption isotherm of 3@SiO₂, 3@Al₂O₃ and 3@TiO₂.

The TGA profiles of the three supported catalytic systems (reported in ESI) show the first weight loss of less than 3% below 200 °C due to desorption of water and the remaining uncondensed ethoxy groups. This is followed by the second, more significant, weight loss in the 250-500 °C range, assigned to decomposition of the NHC ligand. The ICP analysis gives data on the actual Pd loading for each supported catalytic systems, Table 1. This Pd loading was higher for the 3@Al₂O₃ and the 3@SiO₂ systems than that for the titania-supported catalyst 3@TiO₂.

3.2. Catalytic activity and recyclability under batch conditions

In view of successful previous results for the Suzuki-Miyaura reaction using the silica supported system, we considered of interest to explore the activity, recovery and reuse of these catalytic systems in Sonogashira coupling reaction, which offers a convenient access to substituted alkynes.^[49] First, screening of the reaction conditions was performed. It was observed that the Sonogashira coupling between 4-bromoacetophenone and phenylacetylene was efficiently carried out in the presence of 1 mol% of Pd in DMF as solvent and cesium carbonate as a base (see ESI). Reactions were performed without the use of CuI as co-catalyst, which constitutes an advantage from the point of view of green chemistry, since it reduces the waste generated.

Once the conditions were optimised, the reaction was carried out with four recycles for each catalyst, see results in Fig. 4. In the first run, the silica supported catalyst 3@SiO₂ has shown an 81% conversion with total selectivity towards the cross-coupling product. However, this system exhibited a constant loss of activity in consecutive runs, with the decrease in conversion from 81 to 60% in the fourth run. In contrast, when the titania-supported catalyst 3@TiO₂ was used, up to 90% conversion was achieved in the first two runs, before decreasing gradually to 75% in the fourth run. This decrease in catalytic activity could be associated with handling of the samples during the recycling, since the catalyst is washed with water, EtOH and Et₂O before been used in the next cycle. The alumina supported catalyst, 3@Al₂O₃, provided conversions above 90% during first two runs, after which the conversion decreased moderately (86%) and remained constant during the following two runs. It was therefore concluded that the alumina supported catalyst 3@Al₂O₃ was more robust under these reaction conditions.

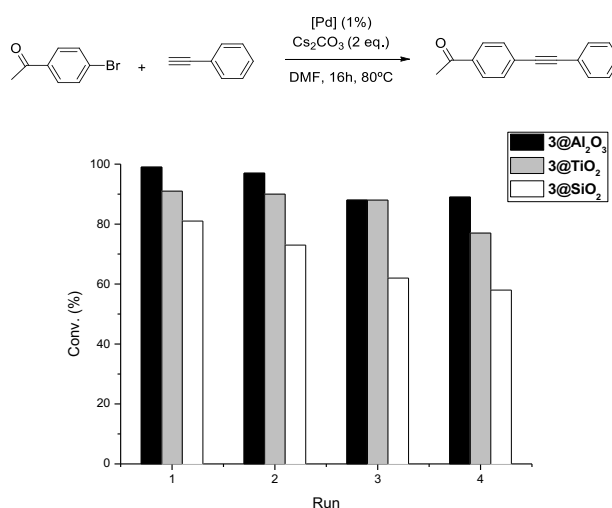
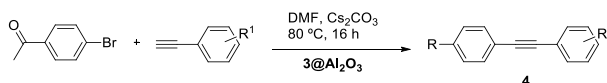


Fig. 4 Performance of the supported catalysts 3@SiO₂, 3@Al₂O₃ and 3@TiO₂ under anhydrous conditions for the Sonogashira coupling of 4-bromoacetophenone with phenylacetylene.

The scope of the Sonogashira reaction was examined for various alkynes and the results obtained with the 3@Al₂O₃ catalyst are shown in Fig. 5. The coupling product of 4-acetophenone with phenylacetylene led to the corresponding coupling product with a 94% isolated yield, **4a**. Good-to-excellent yields of the coupling products for the electron-rich alkynes were obtained, Fig. 5, compounds **4b** and **4c**, respectively, and the *ortho*-substitution in the alkyne was widely tolerated providing the final product **4d** with excellent yield. Thus, the pre-catalyst 3@Al₂O₃ allows the coupling of arylbromide with *ortho*-substituted and electron rich aromatic alkynes.



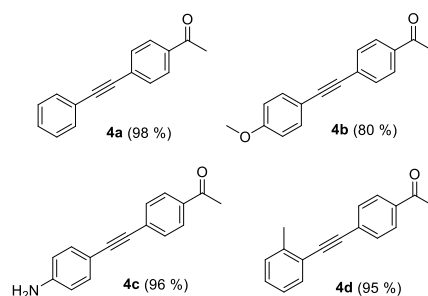


Fig. 5 Sonogashira reaction alkynes scope. ^[a]Conditions: 1 mmol ArBr, 1.5 mmol alkyne, 2.0 mmol Cs₂CO₃, 4 mL DMF anh., 80 °C, 12 h.

3.3. Catalytic activity and recyclability under continuous flow conditions

Although conversions obtained for the four recycling runs in the batch mode were slightly lower than those already reported in the literature for the similar recyclable catalytic systems,^[50] we considered the titania- and the alumina-supported catalysts as promising candidates for performing Sonogashira reaction in flow. The continuous flow process was run in dry MeOH to maximise the solubilisation of the salts formed in the course of the reaction. It is noteworthy that this change of solvent from toluene and DMF to MeOH represents a further step towards a cleaner process.

The two immobilised catalytic systems were tested in the Sonogashira coupling between 4-bromoacetophenone and phenylacetylene in flow. The results are summarised in Fig. 6. Two solutions with the reagents were prepared. Solution I consisted of a 0.2 M solution of 4-bromoacetophenone and solution II was 0.3 M phenylacetylene and 0.4 M base (Cs₂CO₃). The flow rates of the two solutions were equal, $\mu_1 = \mu_2 = 0.2 \text{ mL min}^{-1}$, thus with the total flow rate of 0.40 mL min^{-1} . The merged flow was introduced to the inlet of the packed-bed column assembly. The column was packed with a catalyst providing the length of the catalytic bed of 2.3 cm, which corresponds to the packed bed volume of 0.787 mL. Volume of void in the catalytic bed in the approximation of close random packing of ideal spheres is 0.295 mL (void fraction is approx. 0.375; porosity of the support neglected), giving theoretical space time of approx. 3 min. Aliquots were analysed using GC with mesitylene as an internal standard.

An initial induction period was observed for both catalysts, which could indicate the possible generation of palladium nanoclusters,^[51-53] though no catalyst decomposition was apparent during the experiments. The steady state was reached after 70 minutes of reaction for the **3@Al₂O₃** catalyst and after 80 min for the **3@TiO₂** catalyst, with conversions over 92% for both catalysts. High levels of conversion were maintained during the following 70 minutes on stream, and no by-products could be detected by GC. This is one of the very few examples, which provides efficient Sonogashira coupling of an aryl bromide substrate under continuous flow conditions without rapid and substantial loss of activity.

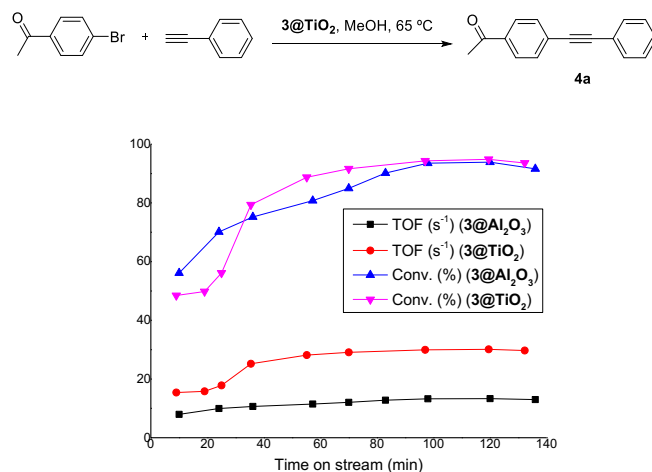


Fig. 6 Conversion and activity of catalysts expressed in terms of TOF in the Sonogashira reaction using **3@Al₂O₃** and **3@TiO₂** supported catalysts

The **3@TiO₂** catalyst exhibited higher TOF, which suggests that more catalytic sites are accessible in this catalyst. At this stage, there is not enough experimental evidence to suggest that specific catalyst-support interactions are responsible for the observed variations in activity between the two catalysts.

Encouraged by these unprecedented results and to test further the catalyst' stability, we decided to run a longer Sonogashira experiment employing the titania-supported catalyst. The catalyst showed an induction period providing a maximum TOF of 25 s^{-1} ,

Fig 7. After approx. four hours on stream the conversion began to decrease gradually. Consequently, after 8 hours on stream the final conversion was in the range of 52 - 54% and the catalytic activity (expressed in s^{-1} , TOF) dropped from 24 to $16 s^{-1}$, suggesting catalyst's degradation. However, leaching characterised by ICP after 8 hours on stream was lower than expected, 2.6% loss of Pd. In spite of the loss of activity shown after the first four hours on stream, these results are competitive in comparison with the two similar examples in the literature^[39,40] since this titania-supported catalyst exhibits activity for longer reaction times containing a lower amount of metal.

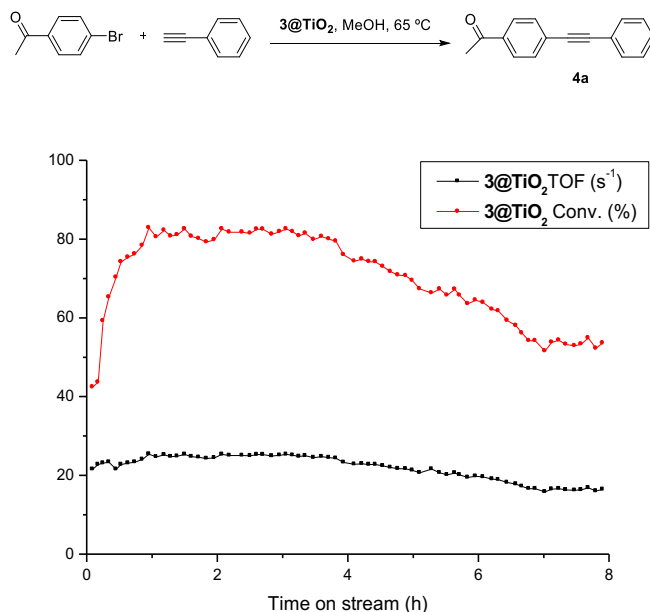


Figure 7. Conversion and TOF obtained for Sonogashira reaction under flow conditions.

In order to determine the cause for the decrease of activity the experiment was repeated and ICP measurements were performed for different fractions of the solid from the glass reactor column: at the beginning, middle and the end of the column. It was found that the amount of Pd in the first fraction was only slightly lower than in the other two (less than 0.3 wt% for the first fraction, less than 0.4 wt% for the other two fractions). On the one hand this may be interpreted as a gradual transformation of the molecular catalyst into Pd clusters, which slowly move through the support and could be carried with the reaction solution out of the reactor. However, the observed gradient of Pd concentration in the solid is too low for this to be of any significance. We were unable to confirm formation of Pd nanoparticles, since the low Pd loading did not allow precise measurements by XPS and TEM. In an earlier study of Heck coupling in flow some of us have observed gradual loss of Pd from a carbon-supported nanoparticle catalyst and a method of avoiding the loss of Pd from the reactor was suggested by periodically switching the direction of flow in such a system.^[54] In the system studied here, we were unable to categorically identify the mechanism of catalyst deactivation. The specific nature of deactivation of this catalytic system deserves further study, given its promising performance: The results obtained with the 3@TiO₂ catalyst under continuous flow conditions are superior to any other reported examples of the Sonogashira transformation of an aryl bromide using a heterogenised molecular palladium catalyst. These advantages make the process highly valuable from the synthetic and environmental points of view.

The study of the influence of the support worth paying further attention. Although a large number of reports concerning the synthesis and the effect of the support on the activity of metal nanoparticles as catalysts reveal that the support represents a relevant parameter for the design and development of recyclable catalysts,^[55, 56] there is hardly any information about the influence of the support in the case of well-defined complexes and the exact mechanism and parameters controlling the incorporation of organic ligands remain unclear. Recently, Thieuleux and co-workers developed materials that contained imidazolium units in the mesopores of silica to obtain molecularly-defined heterogeneous catalysts containing NHC ligands. They observed by ¹H-²⁹Si HETCOR that metal-NHC complexes functionalized with flexible chains fold onto the silica and would promote interactions between the metal and the surface siloxane bridges. These facts turn well-defined organometallic complexes into interesting candidates to being immobilized and to interact with solid supports in a cooperative manner.

4. Conclusions

A new family of well-defined NHC-Pd complexes immobilised onto silica, alumina and titania is reported. The developed catalysts are demonstrated as efficient catalysts for Sonogashira cross-coupling reactions under batch and continuous flow conditions.

Under batch conditions, Sonogashira coupling reaction between phenylacetylene and aryl bromides was best performed in the presence of the alumina supported catalyst **3@Al₂O₃**, which could be reused up to four times with yields over 80%. The application of these easily separable and recyclable heterogeneous catalysts allows cleaner work-up and avoids time-consuming tedious homogeneous catalyst purification.

For the continuous flow processes, both catalytic systems, using supports that are less common in the world of flow chemistry, demonstrated good activity with conversions up to 80% during at least two hours on stream and small loss of active metal. Indeed, the **3@TiO₂** system was active for the Sonogashira reaction after at least 8 hours on stream. Although deactivation of the catalytic system is evident, the system provides constant conversion up to 50% during 8 hours constituting the first efficient NHC-Pd catalysts for the Sonogashira cross coupling of aryl bromides under continuous flow conditions.

5. Acknowledgements

The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (EC FP7) Grant Agreement n. [NMP2-SL-2012-280827]. The authors are grateful to TECSPR14-1-0045; TECNIOspring programme, the Agency for Business Competitiveness of the Government of Catalonia, ACCIÓ, the Generalitat de Catalunya (2014SGR670), and the Spanish Ministerio de Economía y Competitividad (CTQ2016-75016-R) for financial support.

Keywords: Recyclable catalysts • continuous flow • Sonogashira • Aryl bromide • Heterogenised catalysts

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Recyclable supported Pd-NHC catalytic systems for the copper-free Sonogashira cross-coupling in flow

I. Peñafiel,^{*a,c} A. Martínez-Lombardia,^b C. Godard,^b C. Claver^{a,b} and A. Lapkin^{*c}

[a] Centre Tecnològic de la Química de Catalunya. Carrer Marcel·li Domingo S/N 43007 Tarragona, Spain; e-mail:

itzjar.penafiel@manchester.ac.uk;

[b] Departament de Química Física i Inorgànica. Universitat Rovira i Virgili. Carrer Marcel·li Domingo S/N 43007 Tarragona, Spain

[c] Chemical Engineering and Biotechnology Department. University of Cambridge. Philippa Fawcett Drive, Cambridge CB3 0AS, UK.

Supporting Information

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General Considerations

Reactions were carried out using standard bench-top techniques unless the use of a Schlenk flask is specified, in which case Schlenk-line inert atmosphere techniques were used. Where stirring of the reaction mixture is indicated, magnetic stirring using a Teflon-coated stir bar was employed throughout. Commercially supplied compounds were used without further purification. Dry solvents were prepared by distillation from Na/benzophenone, CaH₂ or P₂O₅, or collected from a Braun SPS800 solvent purification system. Photochemical reactions were performed using a Philips HPL-N 125 W high-pressure mercury lamp, which can be purchased at most commercial lighting stores. NMR spectra were obtained at the Servei de Recursos Científics i Tècnics (SRCT), URV, with Varian (Agilent) Mercury VX400 or NMR System400 400 MHz spectrometers and calibrated to residual solvent peaks. Chemical and shifts for ¹H and ¹³C{¹H} NMR spectra are reported relative to TMS. ICP analyses were conducted at the SCRT using an ICP-OES Spectro Arcos instrument. Samples were digested in concentrated HNO₃ under microwave irradiation before being diluted for analysis. HR-MS (ESI-TOF) analyses were also performed at the SCRT, on an Agilent Time-of-Flight 6210 spectrometer. GC-MS analyses were conducted on Agilent 6850 instruments, fitted with HP-5 capillary columns. Elemental analyses were performed at Centro de microanálisis elemental at Universidad Complutense de Madrid. Other than solvents, reagents obtained from commercial sources were used without further purification. Silica, titania and γ-alumina used for catalyst immobilization were dried for 1 h at 80 °C, 10⁻³ bar prior to use. Pd(acac)₂,¹ imidazolium salt ligands² and precatalyst were prepared according to literature procedures.

Synthesis of supported catalysts

One-pot procedure for preparation of 3@Al₂O₃. A flame-dried Schlenk flask was charged with **1** (200 mg, 0.441 mmol, 1.0 equiv.), 3-mercaptopropyl(triethoxy)silane (225 μL, 0.887 mmol, 2.0 equiv.) and DMPA (22 mg, 0.09 mmol, 0.20 equiv.), followed by freshly-dried EtOH (1.5 mL). The reaction mixture was then stirred and irradiated with a 125 W high-pressure mercury lamp (8 cm of separation between the bulb and flask) for 24 h. The solvent was removed under reduced pressure, and the residue was re-dissolved in CH₂Cl₂ and evaporated again in order to fully remove the EtOH. Next, Pd(acac)₂ (134 mg, 0.441 mmol, 1.0 equiv.) was added along with 1,2-DCE (5 mL). After the reaction mixture was heated at 75 °C with stirring for 2 days and then allowed to cool, it was slowly transferred *via* cannula to another Schlenk flask containing a stirred (400 rpm) suspension of previously dried 60 mesh silica (2.0 g) in 1,2-DCE (5 mL). This suspension was stirred at 250 rpm for 30 min at ambient temperature, then the temperature was increased to 75 °C and stirring was continued for 24 h. During this time all of the yellow colour in the supernatant was transferred to the alumina. Finally, the material was hot-filtered and washed with copious amounts of CH₂Cl₂. The recovered yield of **3@Al₂O₃** was 2.36 g. Pd content by ICP: 1.76 wt% (0.162 mmol/g). Anal. Calcd. for C₄₂H₆₄ClN₂O₆PdS₂Si₂@Al₂O₃ based on Pd loading: C, 12.5; H, 1.61; N, 0.70; S, 1.60. Found: C, 9.55; H, 1.93; N, 0.67; S, 1.18.

One-pot procedure for preparation of 3@TiO₂. A flame-dried Schlenk flask was charged with **1** (213 mg, 0.377 mmol, 1.0 equiv.), 3-mercaptopropyl(triethoxy)silane (190 μL, 0.754 mmol, 2.0 equiv.) and DMPA (19 mg, 0.08 mmol, 0.20 equiv.), followed by freshly-dried EtOH (1.5 mL). The reaction mixture was then stirred and irradiated with a 125 W high-pressure mercury lamp (8 cm of separation between the bulb and flask) for 24 h. The solvent was removed under reduced pressure, and the residue was re-dissolved in CH₂Cl₂ and evaporated again in order to fully remove the EtOH. Next, Pd(acac)₂ (115 mg, 0.377 mmol, 1.0 equiv.) was added along with 1,2-DCE (5 mL). After the reaction mixture was heated at 75 °C with stirring for 2 days and then allowed to cool, it was slowly transferred *via* cannula to another Schlenk flask containing a stirred (400 rpm) suspension of previously dried 60 mesh silica (1.71 g) in 1,2-DCE (3 mL). This suspension was stirred at 250 rpm for 30 min at ambient temperature, then the temperature was increased to 75 °C and stirring was continued for 24 h. During this time all of the yellow color in the supernatant was transferred to the silica. Finally, the material was hot-filtered and washed with copious amounts of CH₂Cl₂. The recovered yield of **3@TiO₂** was 2.5 g. Pd content by ICP: 0.76 wt% (0.143 mmol / g). Anal. Calcd. for C₅₀H₈₀ClN₂O₆PdS₂Si₂@TiO₂ based on Pd loading: C, 9.91; H, 1.33; N, 0.46; S, 1.06. Found: C, 8.87; H, 1.94; N, 0.58; S, 0.97.

TGA Graphics of 3@SiO₂, 3@Al₂O₃ and 3@TiO₂

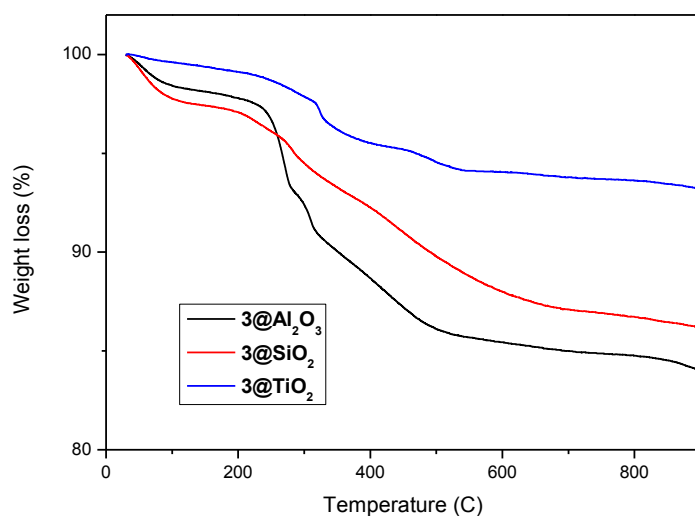


Figure S1. TGA of 3@immobilised catalytic systems (10 °C min⁻¹ in air)

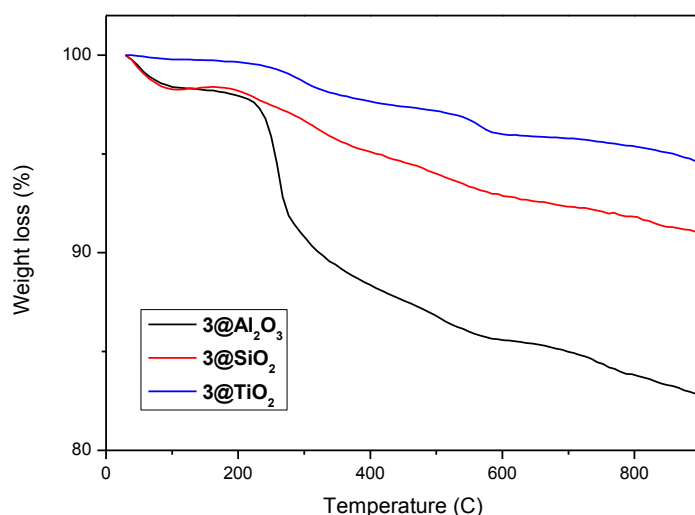


Figure S2. TGA of 3@immobilised catalytic systems (10 °C min⁻¹ in N₂)

Performance of the supported catalysts in Sonogashira reaction

General procedure for catalytic Sonogashira reaction runs. A small Schlenk flask or 5 mL screw topped vial was charged with the catalyst, base, alkyne and the aryl halide (if solid). The flask or vial was capped with a septum or septum cap and flushed with N₂, and then the aryl halide was added *via* microsyringe if liquid. Solvent was added *via* syringe (2 mL organic solvent) and, in the case of the Schlenk flask runs, the septum was replaced by a glass stopper. The reaction mixture was then stirred at 400 rpm and heated at the indicated temperature. After the indicated reaction time, the vessel was cooled in an ice bath. Next, the mixture of reaction was filtered through a small plug of silica. In the case of the biphasic aqueous runs, the aqueous layer was then extracted with toluene (2×0.5 mL) and the extracts were filtered through the same silica plug. The silica plug was when washed with toluene (1 mL). The product mixture was analyzed by GC at this stage, and then it was evaporated under reduced pressure and purified by silica gel chromatography using hexane/EtOAc as eluent.

Optimization of reaction conditions for supported catalysts in the Sonogashira reaction.

The substrate pair 4-bromoacetophenone and phenyl acetylene were chosen for the optimization runs. Upon analysis of the product mixtures from the optimization runs, no by-products were detected in measurable quantities unless indicated otherwise (trace quantities of both homocoupling products were observed in some cases).

Reactions were carried out as above, except that undecane (106 μ L, 0.5 mmol, 1.0 equiv.) was added as a GC-FID internal standard prior to extraction of the product mixture. The GC-FID method used consisted of: Column; Agilent HP-5, 30 m \times 250 μ m. Inlet; temp. = 250 $^{\circ}$ C, pressure = 100.0 kPa, 16:1 split, total flow = 25.0 mL/min, helium carrier. Detector; temp. = 275 $^{\circ}$ C, hydrogen flow = 40.0 mL/min, air flow 450.0 mL/min, makeup flow (helium) = 45.0 mL/min. Oven; initial temp. = 45 $^{\circ}$ C (5 min), ramp = 10 $^{\circ}$ C/min to 250 $^{\circ}$ C, hold at 250 $^{\circ}$ C for 5 min.

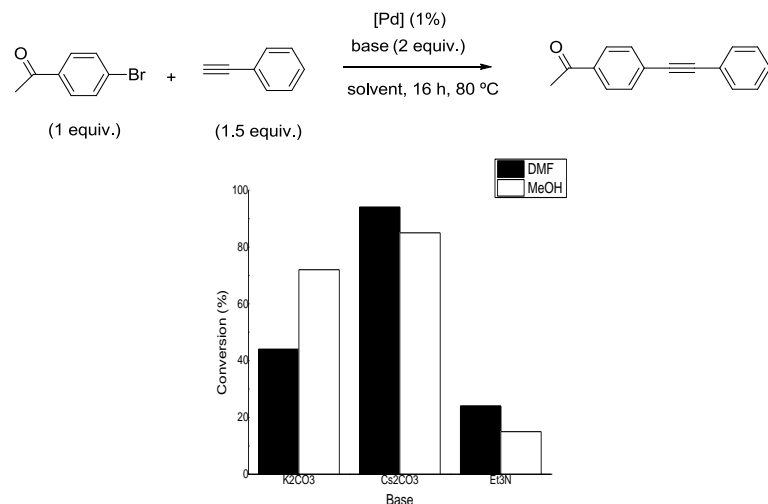


Figure 5. Optimization of base and solvent for the Sonogashira reaction employing the Al₂O₃ supported catalyst **3@Al₂O₃**. Conversions calculated by GC employing undecane as internal standard

General procedure for recycling of the supported catalysts for Sonogashira reaction. In the cases where catalyst recycling was performed, an internal standard (undecane) was added after cooling the reaction mixture in an ice bath; the supported catalyst was separated from the organic phase by decantation. The supported catalyst was then successively washed with water, EtOH and Et₂O, then dried under vacuum and directly reused in the next cycle.

General procedure for Sonogashira reaction mediated by the supported catalysts under continuous flow conditions.

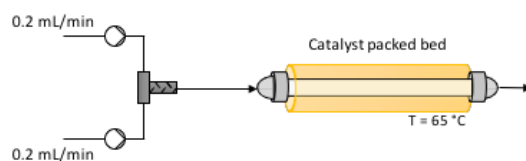
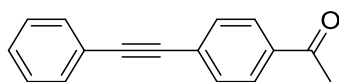


Fig. S3 Scheme of a continuous flow reactor using a Vapourtec pumping and reactor modules.

Catalytic activity and stability of the catalyst **3@Al₂O₃** and **3@TiO₂** were studied under flow conditions using a two syringe pump and a packed-bed reactor. The rig is shown schematically in Fig. 9.

Two solutions with the reagents were prepared: Solution I consisted in a 0.2 M solution of 4-bromoacetophenone and solution II contained 0.3 M of phenylacetylene and 0.4 M of base (Cs₂CO₃). $\mu_1 = \mu_2 = 0.2$ mL/min, the total flow rate was 0.40 mL/min. The merged flow was then introduced to the inlet of the packed-bed column assembly (borosilicate glass with PTFE end pieces, 6.6 mm ID \times 100 mm length, OmniFit). The column was packed with a catalyst providing the length of the catalytic bed of 2.33 cm, which corresponds to the packed bed volume of 0.797 mL. Volume of void in the catalytic bed in the approximation of close random packing of ideal spheres is 0.298 mL (void fraction is about 0.375, porosity of the support is neglected). The mean residence time in the packed bed was calculated to be 7.97 min calculated from residence time distribution curves measured for the QuadraSil-AP. Aliquots were analysed using GC, mesitylene was used as the internal standard.

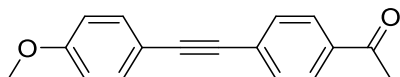
Coupling products obtained by Sonogashira reactions



1-(4-(phenylethynyl)phenyl)ethanone (4a)

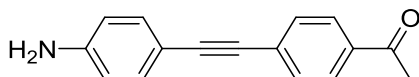
Yellow solid. Chromatographed with 10:1 *n*-hexane/EtOAc.

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 2.62 (s, 3H), 7.36-7.39 (m, 3H), 7.54-7.57 (m, 2H), 7.60-7.63 (m, 2H), 7.95 (d, 2H, $J = 8.0$ Hz); HR-MS: $m/z = 220.0900$, calcd. for $\text{C}_{16}\text{H}_{12}\text{O}$ [M^+]: 220.0888. NMR and MS peaks match literature values.³



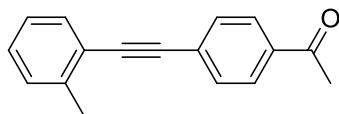
1-(4-(4-methoxyphenyl)ethynyl)phenyl)ethanone (4b)

White solid. Chromatographed with 10:2 *n*-hexane/EtOAc. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 2.59 (s, 3H), 3.81 (s, 3H), 6.88 (d, 2H, $J = 8.8$ Hz), 7.48 (d, 2H, $J = 9.2$ Hz), 7.56 (d, 2H, $J = 8.8$ Hz), 7.91 (d, 2H, $J = 8.8$ Hz); HR-MS: $m/z = 250.0999$, calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_2$ [M^+]: 250.0994. NMR and MS peaks match literature values.⁴



4-(4-(4-Aminophenyl)ethynyl)acetophenones (4c)

Yellow oil. Chromatographed with 10:1 *n*-hexane/EtOAc. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 2.60 (s, 3H), 7.64 (d, 2H, $J = 8.0$ Hz), 7.35 (d, 2H, $J = 8.0$ Hz), 7.55 (d, 2H, $J = 8.0$ Hz), 7.91 (d, 2H, $J = 8.0$ Hz); HR-MS: $m/z = 235.1000$, calcd. for $\text{C}_{16}\text{H}_{13}\text{NO}$ [M^+]: 235.0997. NMR and MS peaks match literature values.⁵

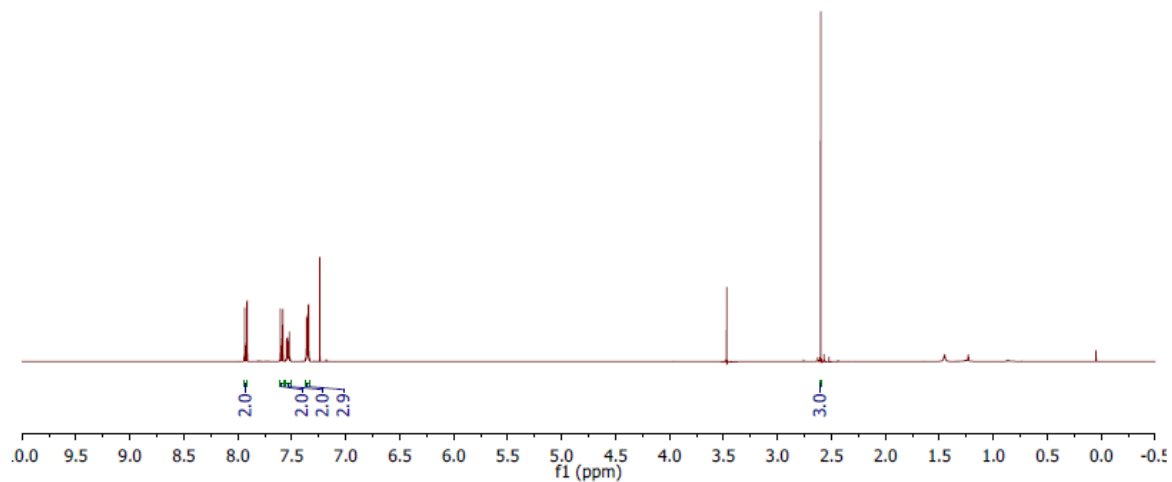


1-(4-o-Tolyethynylphenyl)ethanone (4d)

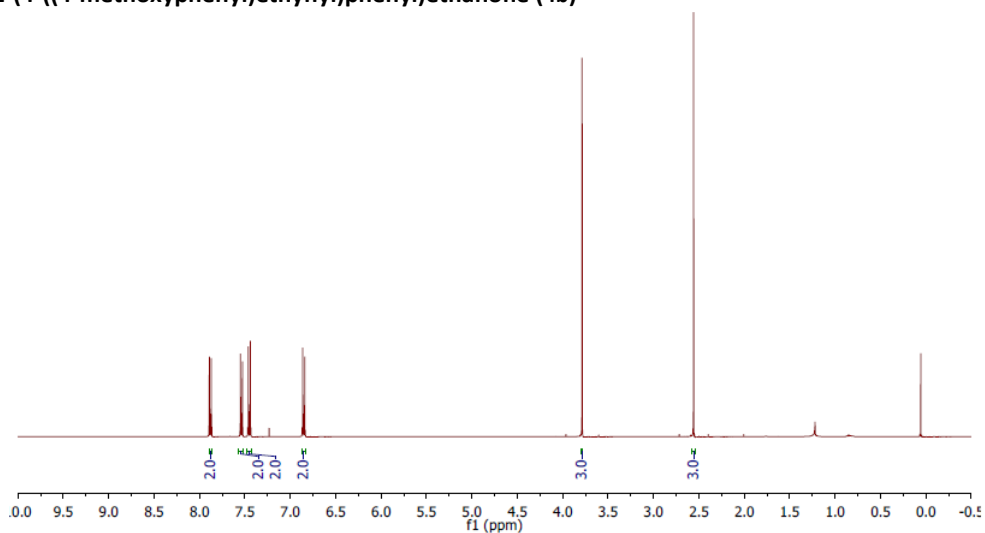
Yellow oil. Chromatographed with 10:1 *n*-hexane/EtOAc. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 2.53 (s, 3H), 2.62 (s, 3H), 7.18-7.27 (m, 3H), 7.51 (d, 2H, $J = 8.4$ Hz), 7.61 (d, 2H, $J = 8.4$ Hz), 7.94 (d, 2H, $J = 8.8$ Hz); HR-MS: $m/z = 234.1042$, calcd. for $\text{C}_{17}\text{H}_{14}\text{O}$ [M^+]: 234.1045. NMR and MS peaks match literature values.⁶

NMR Spectra of synthesized compounds

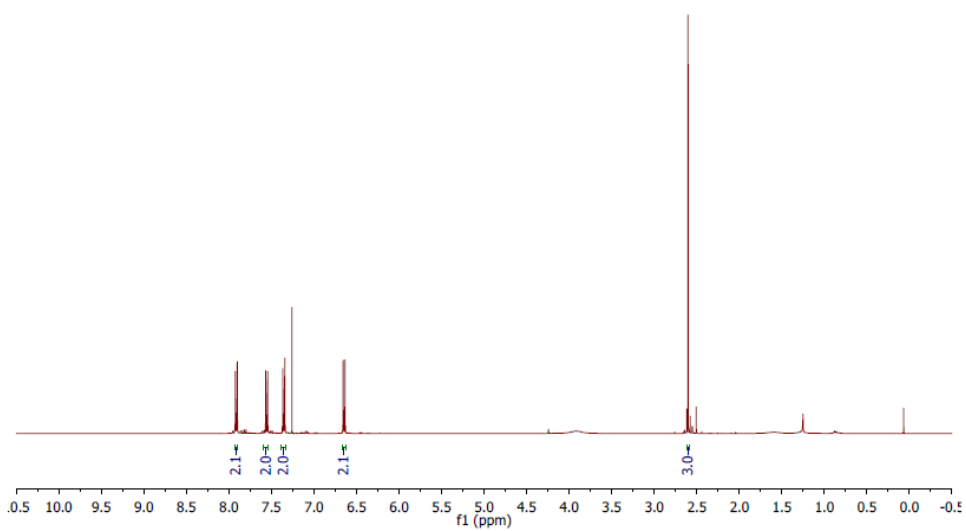
1-(4-(phenylethynyl)phenyl)ethanone (4a)



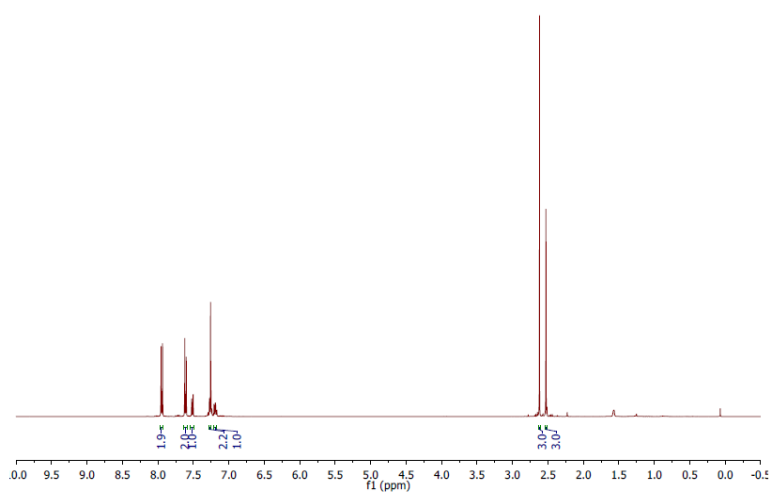
1-(4-((4-methoxyphenyl)ethynyl)phenyl)ethanone (4b)



4-((4-Aminophenyl)ethynyl)acetophenones (4c)



1-(4-o-Tolylethynylphenyl)ethanone (4d)



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