



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}, A. Lapkin^{a,c,*}

^a Centre Tecnològic de la Química de Catalunya, Carrer Marcel·li Domingo S/N, 43007 Tarragona, Spain

^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

ARTICLE INFO

Keywords:

Recyclable catalysts
Continuous flow
Sonogashira
Aryl bromide
Heterogenised catalysts

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 h 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 (Littke and Fu, 2002; Buchwald et al., 2003; Denmark and Sweis, 2004; Farina, 2004; Frisch and Beller, 2005; Gabriele et al., 2008). These coupling processes had a transformative impact on chemicals industries and have been employed in a number of industrial applications (Negishi et al., 2002; Calderazzo et al., 2006) 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 (Torborg and Beller, 2009; Kotha et al., 2013; Siddaraju et al., 2014; Kumbhar and Salunkhe, 2015; Sivanandan et al., 2015). In most cases, the new reaction development was performed under conventional batch synthesis conditions, whereas most chemical companies, especially in the pharmaceutical and specialty chemicals fields, are rapidly developing capability in continuous flow manufacturing (Falß et al., 2016; Chartoire et al., 2016).

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 (Noel and Buchwald, 2011). 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. Fig. 1

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 (Constable et al., 2007). 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) (Newman and Jensen, 2013). 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 (Rossetti and Compagnoni, 2016). As a consequence of these advantages, the use of continuous flow reactors has attracted a considerable interest from the pharmaceutical industry (Roesner and Buchwald, 2016; Vadula and Gonzalez, 2013).

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 (Yang et al., 2016; Tran et al., 2015; Baumann and Baxendale, 2015; Anderson and Buchmeiser, 2012). Yet, carrying out

* Corresponding author at: Centre Tecnològic de la Química de Catalunya, Carrer Marcel·li Domingo S/N, 43007 Tarragona, Spain.
E-mail address: itziar.penafiel@manchester.ac.uk (I. Peñafiel).

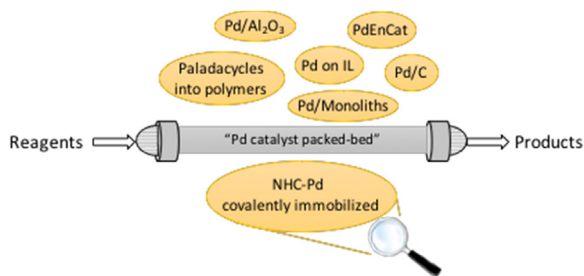


Fig. 1. An illustration of the concept of continuous flow synthesis with the heterogenised Pd catalysts.

palladium-catalysed 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 (Cukalovic et al., 2010), 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 (Reizman et al., 2016; Kataria et al., 2016; Zhang et al., 2015; Shil et al., 2014; Pavia et al., 2013; Muñoz et al., 2012; Mennecke et al., 2008; Baxendale et al., 2006), 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 (Losch et al., 2016; Bao and Tranmer, 2015; Javaid et al., 2011; Solodenko et al., 2004).

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 immobilization of the polymer-tagged palladium catalysts in a stationary solvent for the Sonogashira cross coupling of different aryl bromides and phenyl acetylene (Hillerich and Plenio, 2003). 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 (Fukuyama and Ryu, 2012).

Recently our group has demonstrated the effectiveness of a well-defined Pd complex bearing functionalized N-heterocyclic carbene (NHC) as a ligand (Martínez et al., 2015). 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 (Conley et al., 2014). 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, CaH_2 or P_2O_5 , 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 $^{13}\text{C}\{^1\text{H}\}$ 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 HNO_3 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) $_2$ (Kunste and Siegl, 1976), imidazolium salt ligand (Krinsky et al., 2014) 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 $3@Al_2O_3$

($@Al_2O_3$ 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 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 CH_2Cl_2 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 CH_2Cl_2 . The recovered yield of $3@Al_2O_3$ was 2.36 g. Pd content by ICP: 1.76 wt% (0.162 mmol g^{-1}). Anal. Calcd. for $\text{C}_{42}\text{H}_{64}\text{Cl}_2\text{N}_2\text{O}_6\text{PdS}_2\text{Si}_2@Al_2O_3$ 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 $3@TiO_2$

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 CH_2Cl_2 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 CH_2Cl_2 . The recovered yield of $3@TiO_2$ was 2.5 g. Pd content by ICP: 0.76 wt% (0.143 mmol g^{-1}). Anal. Calcd. for $\text{C}_{50}\text{H}_{80}\text{Cl}_2\text{N}_2\text{O}_6\text{PdS}_2\text{Si}_2@TiO_2$ 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.

Download English Version:

<https://daneshyari.com/en/article/8862575>

Download Persian Version:

<https://daneshyari.com/article/8862575>

[Daneshyari.com](https://daneshyari.com)