

Successful application of microstructured continuous reactor in the palladium catalysed aromatic amination

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Received 7 December 2004; received in revised form 15 March 2005; accepted 15 March 2005

Available online 15 June 2005

Abstract

Micro reactor technology was successfully applied in the palladium catalysed C–N cross-coupling reaction between 4-bromotoluene and piperidine. Excellent conversions and selectivities were obtained without any by-product formation in continuous reactor. © 2005 Elsevier B.V. All rights reserved.

Keywords: Amination; Palladium; Organic chemistry; Catalysis micro reactor and continuous reactor

Micro reactors have proven to be highly valuable tools in organic chemistry [1]. Among further advantages of this technology are a large flexibility of operating conditions with efficient heat transfer, optimized mixing and high reaction control. Micro reactors are available in several designs and models, but only few examples of pilot plant implementation are reported [2]. Cellular Process Chemistry GmbH Company has recently developed a continuous bench top micro reactor, with pumping and heating systems fully integrated, appropriate to process optimization and production (gram to kilogram). During the course of our studies, we focussed on the palladium catalyzed cross-coupling reaction between 4-bromotoluene and piperidine. We were particularly interested in applying this micro reactor technology to palladium catalyzed amination developed by Hartwig and Buchwald [3]. Interest in palladium-catalyzed C–N coupling reaction has grown constantly during the last few years [3]. Since 1998, major advances have been described by a number of research groups. However the lack of a general palladium-based catalyst for aryl halide substitution reac-

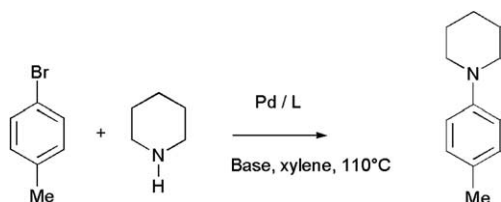
tions, as well as the elevated temperature often required, have prompted research groups to search for new more active catalysts. Thus catalysts based on bulky electron-rich diarylphosphanes discovered by Buchwald have proven to be particularly mild and versatile [4]. Many compounds in the drug development pipelines have bond connections, carbon–nitrogen or others, that can be made with a palladium-catalyzed coupling reaction.

In this paper we wish to report our preliminary results concerning the usefulness and advantages of a micro reactor towards a classical batch reactor for our synthesis application.

Initially we focussed on the direct coupling between 4-bromotoluene and piperidine in a standard batch reactor (Scheme 1). The reaction was carried out in xylene at 110 °C using 1.4 equiv of base and 0.2% molar of catalyst ($\text{Pd}(\text{OAc})_2 + 3$ DavePhos [5]) and 1.05 equiv of piperidine versus 4-bromotoluene. A common industrial base, sodium *tert*-amylate, was chosen because of its high solubility in non polar organic solvents. The reaction reached completion in less than 20 min and allowed the selective formation of *N*-(4-tolyl)-piperidine without any side-product formation.

We have then turned our attention to transferring the reaction to continuous micro reactors. Reactions

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Scheme 1. Amination reaction of *p*-bromotoluene with piperidine using Pd/L catalyst.

were performed in a CPC-GmbH micro reactor made up a 2 mL mixing area (CYTOS™) and a 17 mL reaction plate (RESIDOS™). In this configuration, the addition of other RESIDOS™ could improve the productivity (Fig. 1). Indeed the choice of volume and flow rate has a crucial impact on the residence time thus increasing from seconds to several hours.

The micro reactor hydrodynamic properties were first determined with a residence time distribution analysis (RTD). A positive injection step of the inert tracer (dodecane) displayed a typical RTD profile from which the Péclet dimension number (Pe) was calculated.

$$Pe = \frac{u \cdot L}{D_{ax}} \approx \frac{2 \cdot V_s^2}{\sigma^2} \quad (1)$$

This number is defined by the product of linear velocity (u) and length (L) per axial dispersion (D_{ax}). It is also an approximation of the reactor volume (V_s) per signal outlet variance (σ^2) and is related to flow (convection) versus dispersion (conduction). We found a high Péclet number (300) which denotes a low axial dispersion during elution and then reasonably allows to consider the micro reactor as a plug flow reactor (Fig. 2).

First of all, reservoir A was filled with reagents solution (4-bromotoluene, piperidine, base in xylene and dodecane as an internal standard for gas chromatography analysis) and reservoir B with catalytic solution (palladium acetate and ligand in xylene). Both of the solutions were then simultaneously injected in the

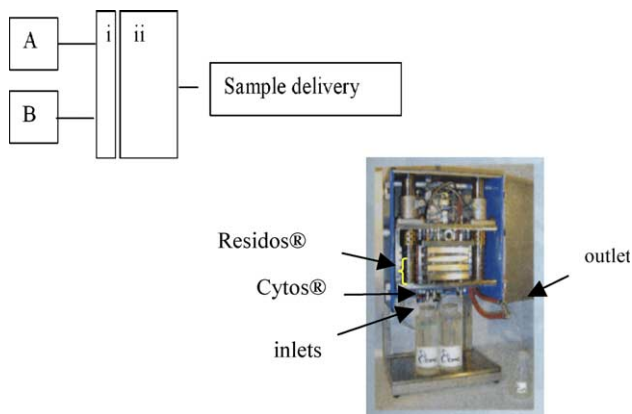


Fig. 1. A and B reagent's reservoir; (i) CYTOS® and (ii) RESIDOS® modules.

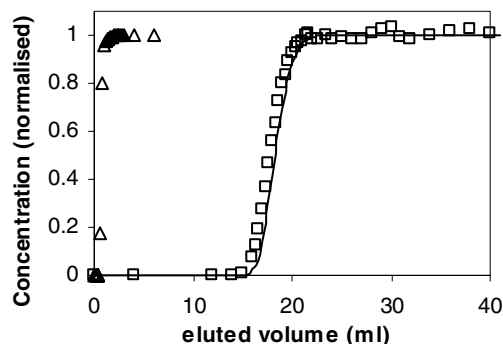


Fig. 2. Inlet (Δ) and outlet (\square) signal; $Q = 1$ mL/min, $V = 17$ mL, inert tracer: dodecane and solvent: xylene.

CYTOS™ reaction area and mixed together in the heated RESIDOS™. Samplings from the outlet solution were regularly collected, immediately cooled at room temperature and analyzed by gas chromatography. Sodium bromide being formed during the reaction process, the outlet solution consisted in a slurry solution. However no clogging could be noticed during all our studies. This confirmed the compatibility of these continuous micro reactors with heterogeneous reactions.

We have first investigated the influence of the temperature. An experiment was realized at room temperature using 1 mL of each solution. Nevertheless, after 3 days of residence time, no coupling reaction could occur (Table 1, entry 6). We have then conducted a set of experiments at 110 °C using two operating conditions described as follow:

1. Reagent and catalyst solution 1 mL/min, residence time 7.5 min and molar concentrations: [4-bromotoluene] = 0.298 mol/L, [piperidine] = 0.30 mol/L, [base] = 0.417 mol/L, [internal standard] = 0.05 mol/L and [Pd] = 0.545 mmol/L (0.18% molar).

2. Reagent solution 1 mL/min and catalyst solution 0.5 mL/min, residence time 11.3 min and molar concentrations: [4-bromotoluene] = 0.397 mol/L, [piperidine] = 0.404 mol/L, [base] = 0.556 mol/L, [internal

Table 1
Selected results using continuous micro reactor

Entry	Eluted volume (test time, min)	Residence time (min)	Conversion (%) ^b	Selectivity (%)
1 ^c	24 (12)	7.5	100	>99
2 ^c	35 (29)	7.5	99	>99
3 ^d	22.5 (44)	11.3	100	>99
4 ^d	27 (1 h)	11.3	100	>99
5 ^a	No	17	100	>99
6		3 days	0	0

^a Batch test experimental condition [4-bromotoluene] and [piperidine] = 0.69 mol/L, [Base] = 0.92 mol/L and [Pd] = 1.4 mmol/L (0.2% molar), temperature = 110 °C.

^b GC analysis.

^c Operating conditions 1.

^d Operating conditions 2.

standard] = 0.05 mol/L and [Pd] = 0.36 mmol/L (0.09% molar).

Whatever the conditions were, in terms of conversion and selectivity, the micro reactor performances were closely identical to those obtained in the batch reactor (Table 1, entries 1–4 and 5). Reactions reached completion with low residence time and no by-product resulting of a reduction C–Br to C–H and an aryne processes was detected. Due to short residence time, no catalyst decomposition was observed (no Pd colloids) and slightly orange-yellow final solution was obtained.

This micro reactor allowed a high productivity in *N*-(4-tolyl)-piperidine (150 g per day). Moreover the addition of two RESIDOS[®] modules can increase volume (47 mL) and thus productivity to 400 g per day.

In conclusion, we have demonstrated that it is possible to carry out palladium-catalyzed cross-coupling amination reaction in a continuous plug-flow reactor. This technology presents many advantages: an easy increase of productivity by additional reactors, easy extrapolation, low reactor volume, low time to get a stationary mode. Otherwise, numbering up micro reactor advantageously replaces scale up, for example a micro structured reactor obtained by addition of 10 CYTOS[®] and RESIDOS[®] in parallel was enough for a production of 1.3 ton per year (0.36 t/h/m³). Further applications of this micro reactor technology to a wide range of other catalytic reactions are currently in progress in our laboratories.

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