Supplementary Material (ESI) for Chemical Communications

Supplementary Information

Efficient batch and continuous flow Suzuki cross-coupling reactions under mild conditions, catalysed by polyurea-encapsulated palladium(II) acetate and tetra-*n*-butylammonium salts

[PdEnCat]™ 40 [0.4 mmol/g $Pd(OAc)_2$ content, 4.6% w/w Pd] was supplied by Avecia <encat@avecia.com>.and is available through Sigma-Aldrich. www.sigmaaldrich.com/Area_of_Interest/Chemistry/Drug_Discovery/Product_Highlights/Pd_EnCat.html. The [PdEnCat] ™ 40 columns [5 cm (*l*) × 0.45 cm (ID)] were supplied by AstraZeneca. The columns were packed at 2500 psi (~172 bar) with *ca.* 0.48 g of PdEnCat™ 40 and were heated to the specified temperature in a water bath. Bromobenzene, iodobenzene, *p*-tolylboronic acid, $^{n}Bu_4NOAc$ and $^{n}Bu_4NOH$ (1M solution in methanol) were purchased from Aldrich. $^{n}Bu_4NOMe$ (20% w/v solution in methanol) and $^{n}Bu_4NF$ (1M solution in THF) were sourced from Fluka and Lancaster, respectively. Liquid carbon dioxide (99.9995%) was supplied by Messer, dried and deoxygenated by passing over Oxisorb™ catalyst prior to use. HPLC grade methanol and toluene were degassed prior to use.

Representative procedure 1; Batch mode Suzuki reaction of bromobenzene and *p*-tolylboronic acid using [PdEnCat]™ 40 in toluene-methanol: A 20 cm^3 sealed tube charged with [PdEnCat]™ 40 [0.4 mmol/g $Pd(OAc)_2$ content, 4.6% w/w Pd], bromobenzene (1 mmol), *p*-tolylboronic acid (1 mmol), $^{n}Bu_4NX$ (1 mmol) and toluene-methanol (9:1, 10 cm^3) was placed in an oil bath, preheated to the specified temperature. After stirring for the specified length of time, the reaction mixture was cooled to room temperature. The isolated yield of 4-methylbiphenyl was determined after flash chromatography of the concentrated reaction mixture with light petroleum (30-40) as the eluent. The GC yield of the Suzuki cross-coupled product (R_t = 17.9 min) was determined by analysis of the crude reaction mixture after addition of mesitylene (*ca.* 0.5 mmol) as the internal standard (R_t = 8.7 min) (and dilution with CH_2Cl_2 to a volume of 50 cm^3) [GC method: Hewlett-Packard GC 5890; SGE BP5 capillary column (*l* = 25 m, ID = 0.32 mm, film thickness: 0.5 μm); FID detector; method: 50 ^{o}C for 5 min, temperature increase at 10 ^{o}C/min for 20 min, 250 ^{o}C for 3

min)]. ICP-MS analysis of selected Suzuki products indicated Pd levels between 1-13 ppm. Low leaching of Pd catalyst into the reaction solution was confirmed by the fact that hot filtration to remove the catalyst effectively stops the process.[1, 2] In very difficult cases one can envisage using scavenger resins to remove any contaminating metal residues. This would be especially attractive in the continuous flow mode.

Representative procedure 2; Batch mode Suzuki reaction of bromobenzene and *p*-tolylboronic acid using [PdEnCat]™ 40 in scCO$_2$: [PdEnCat]™ 40 [0.4 mmol/g Pd(OAc)$_2$ content, 4.6% w/w Pd], bromobenzene (1 mmol), *p*-tolylboronic acid (1 mmol) and ^{n}Bu$_4$NX (1 mmol) were placed in a 10 cm^3 pressure cell equipped with inlet and outlet fittings, a thermocouple, a sapphire window and a magnetic stirrer. The cell was connected to a CO_2 compressor (NWA PM 101 compressor pump) and charged with CO_2 (previously dried and deoxygenated by passing CO_2 over activated Oxisorb catalyst) to a pressure of *ca.* 700 psi.[3] The cell was heated to the said temperature and the pressure was adjusted to that specified by addition of more CO_2. Upon completion of reaction, the cell was allowed to cool to ambient temperatures. The contents of the cell were vented into CH_2Cl_2 (20 cm^3). Once atmospheric pressure was reached, the cell was opened and washed with CH_2Cl_2 (2 × 10 cm^3). The organic fractions were combined, mesitylene (*ca.* 0.5 mmol) was added and the solution was diluted with CH_2Cl_2 to a volume of 50 cm^3. The yield of 4-methylbiphenyl was then determined by GC analysis (GC method: see representative procedure 1).

Representative procedure 3; Continuous flow Suzuki reaction of iodobenzene and *p*-tolylboronic acid using [PdEnCat]™ 40 in toluene-methanol: The [PdEnCat] column supplied by Astra Zeneca was placed in a water bath (heated at the specified temperature). The column was allowed to equilibrate for 40 min by passing toluene-methanol (9:1, v:v) through it at a flow rate of 0.2 cm^3/min with the aid of an HPLC pump. A stock solution [0.05 M; containing iodobenzene (1 mmol), *p*-tolylboronic acid (1 mmol) and ^{n}Bu$_4$NX (1 mmol) in toluene-methanol (20 cm^3) (9:1, v:v)] was then pumped through the [PdEnCat] column at 0.2 cm^3/min. Collection of the reaction mixture took place as soon as it was detected emerging from the [PdEnCat] column. When addition of the stock solution was complete, a 0.4 cm^3 aliquot of the collected reaction mixture was taken aside for GC analysis; mesitylene

(0.25 mmol) was added as an internal standard (GC method: see representative procedure 1). The remaining reaction mixture was cycled through the [PdEnCat] column for further reaction.

It was found that the cross coupling reactions carried out under continuous flow conditions on two consecutive days using the same [PdEnCat] column in the presence of Bu_4NOMe as base afforded quantitative yields of 4-methylbiphenyl, thus demonstrating that full catalytic activity was maintained even after multiple passes through the column.

Reference:

1. C. Ramarao, S. V. Ley, S. C. Smith, I. M. Shirley and N. DeAlmeida, *Chem. Commun*., 2002, 1132.

2. S. V. Ley, C. Ramarao, R. S. Gordon, A. B. Holmes, A. J. Morrison, I. F. McConvey, I. M. Shirley, S. C. Smith and M. D. Smith, *Chem. Commun*., 2002, 1134.

3. A. I. Cooper, W. P. Hems and A. B. Holmes, *Macromolecules*, 1999, **32**, 2156.