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

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Suzuki cross-coupling reactions are effected in both conventional organic solvents, under continuous flow conditions at 70 °C, and in batch mode in supercritical carbon dioxide (scCO$_2$), at temperatures as low as 40 °C in the presence of palladium(II) acetate microencapsulated in polyurea [PdEnCat]$^{\text{TM}}$ and tetra-*n*-butylammonium salts.

Recently there has been considerable interest in developing continuous flow heterogeneous catalytic processes in supercritical fluids. Among these the most successful is the heterogeneous hydrogenation process commercialised as a result of the pioneering work by Poliakoff and colleagues.[1,2] In this communication we describe the use of a microencapsulated palladium catalyst in exploratory continuous flow processes in toluene–methanol at 70 °C and in batch mode in supercritical carbon dioxide (scCO$_2$) and toluene–methanol at temperatures as low as 40 °C.

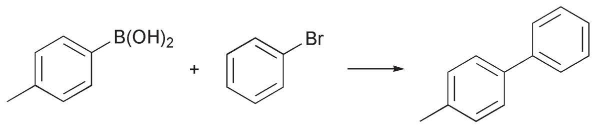
The Suzuki cross-coupling reaction of organoboron reagents with organic halides represents one of the most versatile and straightforward methods for carbon–carbon bond formation. The reaction is largely unaffected by water, tolerating a large range of functionality and yielding non-toxic by-products. Consequently, the Suzuki reaction has been applied in significant and diverse applications not only in academic laboratories but also in industry.[3]

A polyurea-encapsulated Pd(OAc)$_2$ catalyst was discovered in our laboratories.[4] Polyurea was deemed to be a suitable encapsulation matrix by virtue of the ability of the urea functionality to ligate and retain metal species, such as Pd(OAc)$_2$. The microcapsules were prepared by an *in situ* interfacial polymerisation approach. Subsequently, the versatility of the [PdEnCat]$^{\text{TM}}$ catalyst was demonstrated in a range of phosphine-free cross-coupling reactions (carbonylation, Heck, Suzuki and Stille) in organic solvents as well as scCO$_2$.[5] The heterogeneous catalyst can be recovered by a simple filtration and recycled up to four times without deterioration of catalytic activity, thereby presenting the potential for economical manufacturing. The typical procedure for the [PdEnCat]-catalysed cross-coupling reactions entailed elevated temperatures (generally >90 °C) and use of 2.5–3 equivalents of ^{n}Bu$_4$NOAc as the base. As part of a programme concerned with the development of practical and economical processes for industrial applications, it was decided to develop protocols for carrying out these reactions efficiently under mild conditions and with a stoichiometric quantity of base. Conditions for achieving this in both batch and continuous modes in the presence of various tetra-*n*-butylammonium salts (^{n}Bu$_4$NX, X = OAc, OH, OMe and F) are described herein.

Initial investigations centred upon batch-type Suzuki reactions in toluene–methanol (9:1, v:v) in the presence of stoichiometric quantities of ^{n}Bu$_4$NOAc, ^{n}Bu$_4$NOH (1M in MeOH), ^{n}Bu$_4$NOMe (20% w/v in MeOH) and ^{n}Bu$_4$NF (1M in THF). At 110 °C and in the presence of [PdEnCat]$^{\text{TM}}$ 40 [0.4 mmol g^{-1} Pd(OAc)$_2$, 4.6% w/w Pd], all four ^{n}Bu$_4$NX salts (X = OAc, OH, OMe and F) were extremely effective in facilitating the cross-coupling of bromobenzene and *p*-tolylboronic acid, thereby giving rise to 4-methylbiphenyl in near quantitative yields (Table 1, entries 1–4).

At 40 °C, 4-methylbiphenyl could also be obtained in a high yield (85%) with the use of ^{n}Bu$_4$NOH (Table 1, entry 6). Good yields were observed with the use of ^{n}Bu$_4$NOMe and ^{n}Bu$_4$NF at 40 °C (Table 1, entries 7 and 8). The higher yields of 4-methylbiphenyl observed with the use of ^{n}Bu$_4$NX (X = OH, OMe and F) relative to that seen with ^{n}Bu$_4$NOAc may be attributed to the strongly nucleophilic nature of the hydroxide, methoxide and fluoride anions, which facilitates the

Table 1 Batch-mode Suzuki reaction of bromobenzene and *p*-tolylboronic acid catalysed by [PdEnCat] in toluene–methanol[a]



Entry	Method	^{n}Bu$_4$NX	Yield (%)
1	(i)	X = OAc	98[b]
2	(i)	X = OH	98[b]
3	(i)	X = OMe	98[b]
4	(i)	X = F	97[b]
5	(ii)	X = OAc	59[c]
6	(ii)	X = OH	85[c]
7	(ii)	X = OMe	74[c]
8	(ii)	X = F	76[c]

[a] *Reagents and conditions*: [PdEnCat] 40 (4.6% w/w Pd), ^{n}Bu$_4$NX (1 mmol), PhBr (1 mmol), MePhB(OH)$_2$ (1 mmol), MePh–MeOH (9:1, v:v); method (i) 110 °C, 21 h; (ii) 40 °C, 2.5 d. [b] Isolated yields. [c] GC yields. See ESI.

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† Electronic supplementary information (ESI) available: representative procedures for the batch and continuous flow Suzuki reactions. See http://www.rsc.org/suppdata/cc/b4/b418669a/

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transmetallation process. The results show that Suzuki cross-couplings are effected in organic solvent at low temperature and without the need for excess ^{n}Bu$_4$NX salt.

Supercritical carbon dioxide offers a cheaper, non-toxic and environmentally more benign alternative to conventional organic solvents for organic synthesis.[6] There has been considerable interest in hydrogenation[7] and Pd-mediated C–C bond formation reactions in this medium.[8] Our previous studies using [PdEnCat] to catalyse the Suzuki reaction of bromobenzene and *p*-tolylboronic acid were carried out at 100 °C.[5] For potential extension to continuous flow conditions a lower temperature would be preferable. With this in mind batch mode reactions in scCO$_2$ were examined with various additives (Table 2).

At 100 °C (3000 psi), 4-methylbiphenyl was produced in almost quantitative yields in the presence of stoichiometric amounts of ^{n}Bu$_4$NX (X = OAc, OH and OMe) (Table 2, entries 1–3). At 40 °C (1400 psi), the cross-coupled product was obtained in a good yield of 66% with the use of ^{n}Bu$_4$NOMe (Table 2, entry 8). With ^{n}Bu$_4$NOH and ^{n}Bu$_4$NOMe, the hydroxide and methoxide anions are likely to react with CO$_2$ to form the corresponding carbonates, which may function as the active bases for these cross-coupling reactions in scCO$_2$.

In chemical manufacturing processes, the operation costs and labour required for continuous flow processes are generally less than those for batch processes. As it has been shown that [PdEnCat] can be recycled without significant loss of activity and with minimal leaching‡ of Pd from the microcapsules,[4,5] cross-coupling reactions with the immobilised [PdEnCat] catalyst as the stationary phase under continuous flow conditions were investigated.

In the present work, experiments for "proof-of-concept" were carried out by passing a stock reagent solution containing iodobenzene, *p*-tolylboronic acid and ^{n}Bu$_4$NX (X = OAc, OH, OMe and F) through an HPLC column packed with the [PdEnCat] catalyst (Table 3). The cumulative yield of 4-methylbiphenyl was determined using GC.

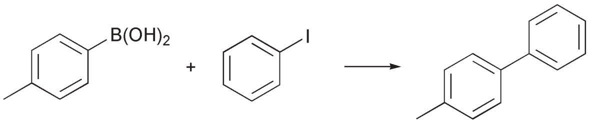
The results of these preliminary results are extremely encouraging. Whilst low to moderate yields of 4-methylbiphenyl were obtained at 55 °C in the presence of ^{n}Bu$_4$NOAc and ^{n}Bu$_4$NF (Table 3, entries 1 and 4), the use of ^{n}Bu$_4$NOH and ^{n}Bu$_4$NOMe gave rise to 4-methylbiphenyl in high yields (70% and 85% respectively) after just three passes through the [PdEnCat] column (Table 3, entries 2 and 3). Most impressive is the performance of ^{n}Bu$_4$NOMe at 70 °C; a quantitative yield of 4-methylbiphenyl was obtained after a single pass through the [PdEnCat] stationary bed (Table 3, entry 5). ^{n}Bu$_4$NOMe is superior to the other bases examined as it does not lead to phase separation of the reaction mixtures. The homogeneous mixtures observed with the use of ^{n}Bu$_4$NOMe allow maximum interaction between the reagents and the catalyst. Methanol formed *in situ* from the neutralisation of ^{n}Bu$_4$NOMe, may solubilise the various species in the reaction mixture as a co-solvent and maintain the reaction mixture as a homogeneous solution.

Table 2 Batch-mode Suzuki reaction of bromobenzene and *p*-tolylboronic acid catalysed by [PdEnCat]$^{\text{TM}}$ 40 in scCO$_2$[a]

Entry	Method	^{n}Bu$_4$NX	GC yield (%)
1	(i)	X = OAc	96[b]
2	(i)	X = OH	97
3	(i)	X = OMe	97
4	(i)	X = F	74
5	(i)	X = OAc	51
6	(ii)	X = OAc	38[b]
7	(ii)	X = OH	16
8	(ii)	X = OMe	66
9	(ii)	X = F	<1[c]

[a] *Reagents and conditions*: [PdEnCat] (4.6% w/w Pd), ^{n}Bu$_4$NX (1.0 mmol), PhBr (1.0 mmol), MePhB(OH)$_2$ (1 mmol), scCO$_2$; method (i) 100 °C, 3000 psi, 21 h; (ii) 40 °C, 1400 psi, 2.5 d. [b] A small quantity of MeOH (0.5 mL) was used as an additive. [c] Reproducible result. See ESI.

Table 3 Continuous flow Suzuki reaction of iodobenzene and *p*-tolylboronic acid with [PdEnCat] column in toluene–methanol[a]



			GC yield (%)					
Entry	^{n}Bu$_4$NX	T (°C)	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
1[b]	X = OAc	55	4.7	7.5	11	12	14	15
2[c]	X = OH	55	3.1	13	70	—	—	—
3[d]	X = OMe	55	12	48	85	—	—	—
4[e]	X = F	55	36	40	55	—	—	—
5[d]	X = OMe	70	100	—	—	—	—	—

[a] *Reagents and conditions*: 0.05 M solution of MePhB(OH)$_2$ (1 mmol), PhI (1 mmol) and ^{n}Bu$_4$NX (1 mmol) in MePh–MeOH 20 cm^3 (9:1, v:v); [PdEnCat] 40 column [5 cm (*l*) × 0.45 cm (ID)]; flow rate: 0.2 cm^3 min^{-1} [residence time *ca.* 4 min]. [b] Significant phase separation. [c] Fine emulsion. [d] Homogeneous solution. [e] Phase separation. See ESI.

The combination of microencapsulated Pd(OAc)$_2$ [PdEnCat]$^{\text{TM}}$ 40 and ^{n}Bu$_4$NX (X = OMe and OH) is demonstrated to be an efficient and economical catalytic system for batch Suzuki cross-couplings at low temperatures in both organic solvents and scCO$_2$. Continuous flow results are promising.

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Notes and references

‡ ICP-MS analysis indicated Pd levels between 1–13 ppm (see ESI†).

1 P. Licence, J. Ke, M. Sokolova, S. K. Ross and M. Poliakoff, *Green Chem.*, 2003, **5**, 99.

2 J. R. Hyde, P. Licence, D. Carter and M. Poliakoff, *Appl. Catal., A*, 2001, **222**, 119.

3 (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*b*) N. Miyaura, T. Yanagi and A. Suzuki, *Synth. Commun.*, 1981, **11**, 513; (*c*) A. Suzuki, *Pure Appl. Chem.*, 1985, **57**, 1749; (*d*) M. Sato, N. Miyaura and A. Suzuki, *Chem. Lett.*, 1989, 1405; (*e*) A. Suzuki, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. F. Diederich and P. J. Stang, Wiley-VCH, New York, 1998, pp. 49–97; (*f*) A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147.

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

5 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.

6 (*a*) *Chemical Synthesis Using Supercritical Fluids*, ed. P. G. Jessop and W. Leitner, Wiley-VCH, Weinheim, 1999; (*b*) R. S. Oakes, A. A. Clifford and C. M. Rayner, *J. Chem. Soc., Perkin Trans. 1*, 2001, 917.

7 M. Poliakoff, N. J. Meehan and S. K. Ross, *Chem. Ind.*, 1999, 750.

8 (*a*) R. S. Gordon and A. B. Holmes, *Chem. Commun.*, 2001, 640; (*b*) T. R. Early, R. S. Gordon, M. A. Carroll, A. B. Holmes, R. E. Shute and I. F. McConvey, *Chem. Commun.*, 2001, 1966.