

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 (scCO₂), at temperatures as low as 40 °C in the presence of palladium(II) acetate microencapsulated in polyurea [PdEnCat][®] 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 Poliakov 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 (scCO₂) 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

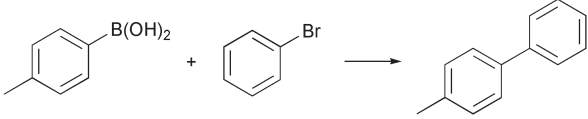
A polyurea-encapsulated Pd(OAc)₂ catalyst was discovered in our laboratories.⁴ Polyurea was deemed to be a suitable encapsulation matrix by virtue of the ability of the urea functionality to ligate and retain metal species, such as Pd(OAc)₂. The microcapsules were prepared by an *in situ* interfacial polymerisation approach. Subsequently, the versatility of the [PdEnCat][®] catalyst was demonstrated in a range of phosphine-free cross-coupling reactions (carbonylation, Heck, Suzuki and Stille) in organic solvents as well as scCO₂.⁵ 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 ⁿBu₄NOAc 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 (ⁿBu₄NX, 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 ⁿBu₄NOAc, ⁿBu₄NOH (1M in MeOH), ⁿBu₄NOME (20% w/v in MeOH) and ⁿBu₄NF (1M in THF). At 110 °C and in the presence of [PdEnCat][®] 40 [0.4 mmol g⁻¹ Pd(OAc)₂, 4.6% w/w Pd], all four ⁿBu₄NX 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 ⁿBu₄NOH (Table 1, entry 6). Good yields were observed with the use of ⁿBu₄NOME and ⁿBu₄NF at 40 °C (Table 1, entries 7 and 8). The higher yields of 4-methylbiphenyl observed with the use of ⁿBu₄NX (X = OH, OMe and F) relative to that seen with ⁿBu₄NOAc 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^d



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), ⁿBu₄NX (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.

† Electronic supplementary information (ESI) available: representative procedures for the batch and continuous flow Suzuki reactions. See <http://www.rsc.org/suppdata/cc/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 ${}^t\text{Bu}_4\text{NX}$ 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 hydrogenation⁷ 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 ${}^t\text{Bu}_4\text{NX}$ (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 ${}^t\text{Bu}_4\text{NOMe}$ (Table 2, entry 8). With ${}^t\text{Bu}_4\text{NOH}$ and ${}^t\text{Bu}_4\text{NOMe}$, 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 ${}^t\text{Bu}_4\text{NX}$ (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 ${}^t\text{Bu}_4\text{NOAc}$ and ${}^t\text{Bu}_4\text{NF}$ (Table 3, entries 1 and 4), the use of ${}^t\text{Bu}_4\text{NOH}$ and ${}^t\text{Bu}_4\text{NOMe}$ gave rise to 4-methylbiphenyl in high yields (70% and 85%

Table 2 Batch-mode Suzuki reaction of bromobenzene and *p*-tolylboronic acid catalysed by [PdEnCat][®] 40 in scCO_2 ^a

Entry	Method	${}^t\text{Bu}_4\text{NX}$	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), ${}^t\text{Bu}_4\text{NX}$ (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

Entry	${}^t\text{Bu}_4\text{NX}$	T (°C)	GC yield (%)					
			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 ${}^t\text{Bu}_4\text{NX}$ (1 mmol) in MePh–MeOH 20 cm³ (9:1, v:v); [PdEnCat] 40 column [5 cm (I) × 0.45 cm (ID)]; flow rate: 0.2 cm³ min⁻¹ [residence time ca. 4 min]. ^b Significant phase separation. ^c Fine emulsion. ^d Homogeneous solution. ^e Phase separation. See ESI.

respectively) after just three passes through the [PdEnCat] column (Table 3, entries 2 and 3). Most impressive is the performance of ${}^t\text{Bu}_4\text{NOMe}$ at 70 °C; a quantitative yield of 4-methylbiphenyl was obtained after a single pass through the [PdEnCat] stationary bed (Table 3, entry 5). ${}^t\text{Bu}_4\text{NOMe}$ 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 ${}^t\text{Bu}_4\text{NOMe}$ allow maximum interaction between the reagents and the catalyst. Methanol formed *in situ* from the neutralisation of ${}^t\text{Bu}_4\text{NOMe}$, may solubilise the various species in the reaction mixture as a co-solvent and maintain the reaction mixture as a homogeneous solution.

The combination of microencapsulated Pd(OAc)₂ [PdEnCat][®] 40 and ${}^t\text{Bu}_4\text{NX}$ (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†).

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