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Palladium-mediated cross-coupling reactions with supported reagents in supercritical carbon dioxide†

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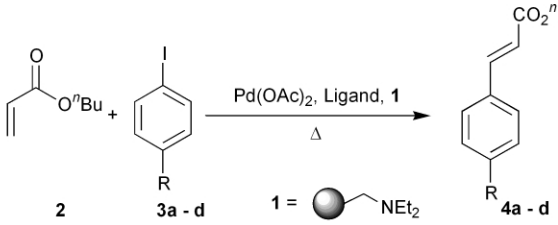
Commercially available polystyrene supported amine and phosphine resins facilitate palladium-mediated Heck and Suzuki reactions in supercritical carbon dioxide ($scCO_2$).

The unique physical and environmental properties of supercritical fluids have made them attractive solvents for chemical synthesis.[1–4] Palladium-mediated homogeneous cross-coupling reactions in $scCO_2$, using fluorinated phosphine ligands[5,6] or trifluoroacetate counterions,[7] have been reported. More recently attention has turned to the use of non-fluorinated phosphines.[7–9] In a further development we described examples of solid supported reactions in $scCO_2$, in which substrates were anchored to a solid support.[9]

The application of supported reagents[10] in $scCO_2$ has received little attention.[11] Cacchi has successfully used Pd/C as a heterogeneous catalyst to facilitate the Heck reaction in $scCO_2$, although these conditions required extended reaction times to realise reasonable yields.[12] Recently, dendrimer supported palladium has been reported to catalyse Heck reactions of aryl iodides with acrylates in $scCO_2$ to give 2-phenyl acrylate.[13] In this communication we report our investigations in $scCO_2$ where the reagent is immobilised on a commercially available solid support.

Initial experiments were carried out in which the previously favoured CO_2-soluble amine bases[5] were replaced by commercially available diethylaminomethyl-polystyrene **1**. The results of these investigations are summarised in Table 1 (Scheme 1).



Scheme 1

Entries 2–6 in Table 1 clearly demonstrate that polystyrene-supported amine base **1** is as effective as the previously preferred CO_2-soluble amine bases (*e.g.* di-isopropylethylamine, DIPEA, entry 1). The novelty in this approach is based on the ease of work-up, in which both amine and the bulk of the palladium trapped in the polymer matrix can be removed by filtration of the solvent into which the CO_2 reaction mixture is vented. Ligand-free Heck reactions in the presence of amine bases have been reported in conventional solvents.[14,15] Surprisingly, aryl iodides also couple with butyl acrylate under Heck conditions in $scCO_2$ in the presence of the polymer-supported amine base **1** in good yield (Table 1, entry 7–10).

Attention was then turned to the use of a polymer-supported phosphine catalyst **5** (resin–PPh_2-$Pd(OAc)_2$).[16–18] The CO_2 compatibility with a selection of bases was then screened in the presence of the catalyst **5** (Scheme 2, Table 2).

Several trends were observed from the results in Table 2. The use of inorganic bases (Entries 9 and 10) was not as effective as the 'soluble' alkyl organic bases (Entries 1–8). Diamine bases such as tetramethylethylenediamine (TMEDA) (entry 6) and *N*,*N*,*N*,*N*-tetramethylhexanediamine (entry 7) were evidently more soluble and effective in facilitating the coupling reaction. Although 3 mol% palladium (in relation to aryl iodide) was employed for the majority of screening experiments, the result from entry 2 indicates these ratios are by no means optimised,

$$\mathbf{2} + \mathbf{3a} \xrightarrow{\mathbf{5},\ \text{base},\ 80\ ^{\circ}\text{C},\ 16\ \text{h}} \mathbf{4a}$$

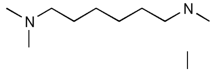
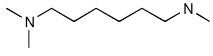
Scheme 2

Table 1 Heck reactions of butyl acrylate **2** with aryl iodides **3a–d** in the presence of polymer supported amine **1** in $scCO_2$ (Scheme 1)[a]

Entry	R	Pd	Ligand	Product	Temp °C	Yield[c]
1	H	$Pd(OAc)_2$[b]	$P(Bu^t)_3$	**4a**	100	92
2	H	$Pd(OAc)_2$	$P(Bu^t)_3$	**4a**	80	97
3	H	$Pd(OCOCF_3)_2$	$P(Bu^t)_3$	**4a**	80	100
4	COMe	$Pd(OCOCF_3)_2$	$P(Bu^t)_3$	**4b**	80	87
5	NO_2	$Pd(OCOCF_3)_2$	$P(Bu^t)_3$	**4c**	80	93
6	NO_2	$Pd(OAc)_2$	$P(Bu^t)_3$	**4c**	80	80
7	H	$Pd(OAc)_2$	—	**4a**	100	92[d]
8	COMe	$Pd(OAc)_2$	—	**4b**	100	87
9	NO_2	$Pd(OAc)_2$	—	**4c**	100	92
10	OMe	$Pd(OAc)_2$	—	**4d**	100	78[e]

[a] All reactions were carried out using 5 mol% Pd salt and (where applicable) 10 mol% phosphine and are heated for 16 h at *ca*. 3000 psi. [b] Control reaction carried out with DIPEA (see ref. 5). [c] Isolated yield. [d] 1.6 mol% catalyst used. [e] Result from reaction left for 72 h.

Table 2 Heck reactions of butyl acrylate **2** with iodobenzene **3a** in the presence of palladium-supported catalyst **5** in $scCO_2$ (Scheme 2)[a]

Entry	Pd (mol%)	Base (2 eq.)	Product	Yield[b]
1	3	DIPEA	**4a**	100
2	1	DIPEA	**4a**	90
3	1	NEt_3	**4a**	30
4	3	$N(Bu^n)_3$	**4a**	>85 (100[c])
5	3	$N(C_6F_{13})_3$	**4a**	10
6	3	TMEDA	**4a**	71
7	3		**4a**	100 (84[c])
8	3		**4a**	69
9	3	Cs_2CO_3	**4a**	15
10	3	NaOAc	**4a**	50
11	3	$(C_4H_9)_4NOAc$	**4a**	100 (98[c])

[a] All reactions were carried out using iodobenzene **3a** (1 mmol), butyl acrylate **2** (*ca*. 1.5 *eq*.), Pd-phosphine resin **5** (3 mol% where applicable), base (2–3 eq.) and are heated for 16 h at *ca*. 3000 psi. [b] Yield based on HPLC using 1,4-dimethoxybenzene as internal standard. [c] Isolated yield.

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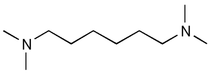
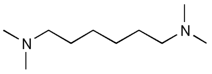
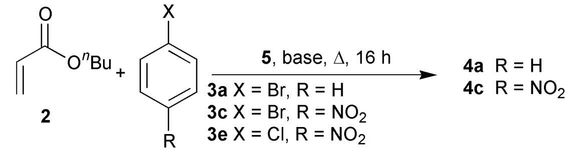
† Electronic supplementary information (ESI) available: experimental procedures for the preparation of compounds **4a-c**. See http://www.rsc.org/suppdata/cc/b1/b111430a/

Table 3 Heck reactions of butyl acrylate **2** with aryl halides in the presence of palladium-supported catalyst **5** in scCO$_2$ (Scheme 3)^a

Entry	X	R	Base (2 eq.)	Product	Temp/ °C	Yield^b
1	Br	H		**4a**	100	14
2	Br	H		**4a**	120	41
3	Br	H	Na(OTFA)$_2$	**4a**	100	15
4	Br	H	$(C_4H_9)_4NOAc$	**4a**	100	> 80
5	Br	H	$(C_4H_9)_4NOAc$	**4a**	120	100^c
6	Br	H	$(C_2H_5)_4NOAc{\cdot}4H_2O$	**4a**	100	30
7	Br	H	$(C_2H_5)_4NOAc{\cdot}4H_2O$	**4a**	120	> 80
8	Br	H	$(C_4H_9)_4NCl$	**4a**	100	21^c
9	Br	NO$_2$	$(C_4H_9)_4NOAc$	**4c**	100	92^c
10	Cl	NO$_2$	$(C_4H_9)_4NOAc$	**4c**	100	67^c
11	Br	H	$(C_4H_9)_4NOAc$	**4a**	100	70^d
12	Br	H	$(C_4H_9)_4NOAc$	**4a**	100	57^e

^{a} All reactions were carried out using iodobenzene **3a** (1 mmol), butyl acrylate **2** (*ca.* 1.5 eq.), Pd-phosphine resin **5** (3 mol%), base (2 –3 eq.) and are heated for 16 h at *ca.* 3000 psi. ^{b} Yield based on HPLC analysis using 1,4-dimethoxybenzene as internal standard. ^{c} Isolated yield. ^{d} Isolated yield for reaction containing no phosphine. ^{e} Isolated yield for reaction containing no phosphine resin or CO$_2$.



Scheme 3

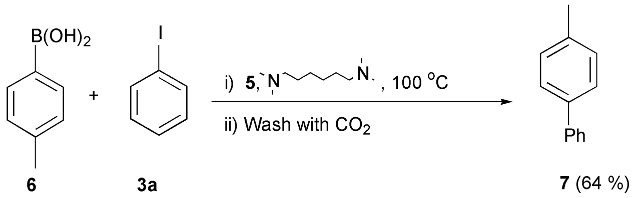
and it is expected that significantly lower palladium concentrations could be employed.

We have previously described the successful application of tetrabutylammonium acetate in conjunction with CO$_2$ as an effective medium to achieve palladium-mediated cross-coupling reactions.[9] It is now demonstrated that this combination of reagents is also effective when used with catalyst **5** (entry 11). Tetrabutylammonium salts are thought to act as ionic liquids,[19] and their efficacy in CO$_2$ under conditions where they melt and behave as phase transfer catalysts in conventional solvents[20] may be related to this property.

A more challenging test of the methodology in scCO$_2$ would be the successful application to the less reactive aryl bromides and chlorides.[21] These results are summarised in Table 3.

Several features are noteworthy. Firstly, the use of alkyl organic bases was less effective for Heck reactions involving aryl bromides than the corresponding iodides, and elevated temperatures were generally required to achieve any significant reaction (entries 1–2). Secondly, all reactions involving quaternary ammonium salts were encouraging, with tetrabutylammonium acetate being the most effective. Tetrabutylammonium chloride[8] was less promising (entry 8) as previously noted.[9] Finally, control experiments (entries 11–12) carried out with 3 mol% Pd(OAc)$_2$ in the absence of phosphine, although not as efficient, clearly demonstrate the importance of tetrabutylammonium acetate. The solvent-free reaction (entry 12) is of interest.[19,22]

Suzuki reactions have also been investigated (Scheme 4). Treatment of tolyl boronic acid **6** with iodobenzene **3a** and the base *N*,*N*,*N*,*N*-tetramethylhexanediamine in the presence of the polymer-supported phosphine-Pd catalyst **5** afforded the biaryl product **7** which was isolated by venting the liquid CO$_2$ isolution into a beaker containing EtOAc. Washing the remaining resin and amine salt with liquid CO$_2$ afforded the product in 64% yield. This technique is a most promising aspect of the present work.



Scheme 4

In conclusion, we have described the successful application of solid supported reagents in scCO$_2$ to the Heck reaction. The reaction is feasible if either the base or palladium-phosphine catalyst is supported on a resin. The application of molten tetraalkylammonium salts in scCO$_2$ appears a highly promising combination for cross-coupling reactions. We have demonstrated the successful application of solid supported palladium phosphine catalysts to facilitate a Suzuki reaction in scCO$_2$ in which the product is isolated by 'washing' with liquid CO$_2$.†

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