Palladium-catalysed carbon–carbon bond formation in supercritical carbon dioxide

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Novel fluorinated phosphine palladium complexes are prepared and employed in the first examples of palladium-catalysed carbon–carbon bond formation in supercritical carbon dioxide.

Supercritical carbon dioxide ($scCO_2$) has recently emerged as an environmentally benign substitute for volatile organic solvents.[1] Above the critical temperature (31.1 °C) and pressure (73.8 bar) carbon dioxide possesses hybrid properties of both a liquid and a gas. Control of the solvent density by variation of the temperature and pressure enables the solvent properties to be ‘tuned’ to substrates and reactants. These aspects have been used to advantage in polymer synthesis[2–4] and more recently in the preparation of ‘small molecules’.[4,5] The particular attraction of $scCO_2$ must reside in the ‘added value’ as has been recognised in its application to heterogeneous catalytic processes and in asymmetric catalytic hydrogenation/hydroformylation.[6,7] In this respect synthetic transformations on small molecules could be coupled with the advantages of processing (separation/purification) technologies[8] to provide significant benefits over the use of conventional solvents.

We have chosen to study metal-catalysed bond forming reactions, but the majority of the commercially available metal-based catalysts, typically those bearing phosphine or amine ligands, are unsuitable for use in CO_2 owing to their low solubility.[9] Here we describe the synthesis of a range of fluorinated phosphines which enable various palladium-mediated reactions to be conducted in $scCO_2$.

Highly fluorinated compounds have been shown to have unusually high solubility in $scCO_2$, and their incorporation into phosphine-based ligands was expected to improve the solubility of the corresponding metal complexes. Such compounds can be prepared by adding the Grignard reagent $C_6F_{13}CH_2CH_2MgI$ to chlorophosphines to give a range of potential ligands for the solubilisation of palladium complexes in carbon dioxide (Scheme 1). Similar work has recently been reported regarding the preparation of these and other, similar ligands for applications in the ‘fluorous’ phase.[10] A simple but indirect means of purification of the required phosphines was achieved by temporary conversion to the corresponding oxide. Regeneration of the phosphine was achieved in excellent yield by treatment with Cl_3SiH and Et_3N.

The effect of the fluorinated phosphines **1** and **2** on the solubility of palladium complexes in $scCO_2$ was then examined, and the results are summarised in Table 1. It is evident that the solubility of the palladium complexes was dramatically improved. However, the degree of ‘fluorination’ required to confer solubility is dependent on the particular complex, those species having a higher degree of ionic character requiring an increased level of fluorination (Table 1, entries 4 and 7).‡

$$C_6F_{13}CH_2CH_2I \xrightarrow{\text{i–iv}} (C_6F_{13}CH_2CH_2)_nPPh_{(3-n)}$$

1 $n = 1$, 67%
2 $n = 2$, 68%

Scheme 1 *Reagents and conditions*: i, Mg, Et_2O, room temp., 12 h; ii, $Cl_nPPh_{(3-n)}$, Et_2O, room temp., 3 h; iii, $NaIO_4$, acetone, room temp., 12 h; iv, Et_3N, Cl_3SiH, toluene, 100 °C, 12 h

The soluble palladium complexes§ (Table 1, entries 5 and 8) were then used to catalyse three important carbon–carbon bond forming reactions, namely the Heck, Suzuki and Sonogashira couplings. The Heck reaction has emerged as one of the most versatile members of this group.[11] Table 2 (entry 1) illustrates that the reaction in $scCO_2$ with electron deficient alkenes occurs in a superior yield to that reported for conventional solvents; intramolecular processes are also possible (entry 2). The palladium-catalysed coupling of boronic acids with aryl or vinyl halides, the Suzuki reaction, has certain advantages for the coupling of two sp^2 centres.[12] This too can be conducted in $scCO_2$ (entries 3 and 4) in yields that are comparable to those achieved in conventional solvents. Finally, the Sonogashira coupling reaction[13] affords functionalised acetylenic compounds also in satisfactory yield.¶ The use of a more basic (secondary rather than tertiary) amine in palladium-mediated transformations typically leads to an improvement in yield. However, in $scCO_2$ very little difference is observed between the two. It is not yet clear whether this is due to carbamic acid formation.[14] Electron deficient amines, such as perfluorotrihexylamine, despite having improved solubility, exhibit a detrimental effect.

It is of note that the work-up procedures are significantly easier than those associated with standard reaction conditions. Typically the use of a polar solvent such as DMF and a water soluble base (carbonate or alkoxide) requires extraction of the product with an organic solvent according to conventional isolation techniques. By contrast, a simple pressure change in the $scCO_2$ reactor allows the gaseous/liquid reaction medium to be vented (possibly through a conventional solvent) thus eliminating liquid/liquid partition.

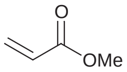
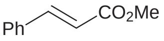
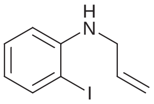
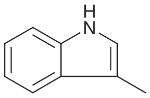
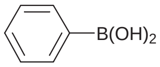
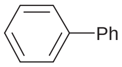
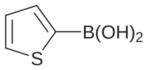
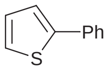
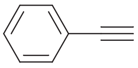
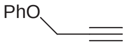
In summary, new fluorinated phosphine palladium complexes have been prepared and used as homogeneous catalysts in supercritical carbon dioxide. Important palladium-mediated carbon–carbon bond forming processes are now accessible and are expected to lead to considerable advances in synthetic methodology in due course.[15]

Table 1 Solubility of phosphine palladium complexes in $scCO_2$

Entry	Complex	L	Solubility
1	PdL_2Cl_2	PPh_3	Insoluble
2	PdL_2Cl_2	PCy_3	Insoluble
3	PdL_2Cl_2	dppf[a]	Insoluble
4	PdL_2Cl_2	**1**[b]	Partial[c]
5	PdL_2Cl_2	**2**[b]	Soluble
6	$PdL_2(OAc)_2$	PPh_3	Insoluble
7	$PdL_2(OAc)_2$	**1**[d]	Soluble[e]
8	$PdL_2(OAc)_2$	**2**[d]	Soluble

[a] 1,1′-Bis(diphenylphosphino)ferrocene. [b] Prepared in CH_2Cl_2 by the reaction (25 °C) of the phosphine (2 equiv.) and $(MeCN)_2PdCl_2$ (1 equiv.). [c] Incomplete disappearance of solid coupled with an increase in colour intensity on warming. [d] Prepared *in situ* from the phosphine (2 equiv.) and $Pd(OAc)_2$ (1 equiv.). [e] Decomposes at $T > 45$ °C.

Table 2 Palladium-catalysed carbon–carbon bond formation in $scCO_2$

Entry	Substrate 1	Substrate 2	Product	Catalyst[a]	T/°C	Yield (%)[b]
1	PhI			$PdL_2(OAc)_2$[c]	100	91
2				$PdL_2(OAc)_2$[c]	100	37
3	PhI			PdL_2Cl_2	100	52
4	PhI			PdL_2Cl_2	100	49
5	PhI		Ph—≡—Ph	PdL_2Cl_2[d]	60	62
6	PhI		$PhOCH_2$—≡—Ph	PdL_2Cl_2[d]	60	18

[a] L = **2** (5 mol%) for 64 h with Et_3N (1.1 equiv.) added. [b] Isolated yield, not optimised. [c] Prepared *in situ* from the phosphine **2** (2 equiv.) and $Pd(OAc)_2$ (1 equiv.). [d] 5 mol% CuI added.

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Notes and References

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‡ *Typical procedure* for determining solubility in supercritical carbon dioxide: $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol) was placed in a 10 ml stainless steel cell. The cell was sealed and completely filled with liquid carbon dioxide (*ca.* 1000 psi). The cell was then heated to 70 °C and the state of the solid was monitored by viewing through a sapphire observation window. After 10 min at the final temperature the cell was allowed to cool. When the pressure had dropped below 2000 psi the cell was vented into CH_2Cl_2 (100 ml), the cell was opened once atmospheric pressure was reached and was washed out with a further quantity of CH_2Cl_2 (20 ml).

§The determination of the crystal structure of PdL_2Cl_2 (L = **2**) is currently under investigation.

¶ *Typical procedure* for the Sonogashira reaction using the catalyst PdL_2Cl_2 (L = **2**) in $scCO_2$: Bis[bis(1*H*, 1*H*, 2*H*, 2*H*-perfluorooctyl)-phenylphosphino]palladium dichloride‖ (89 mg, 0.05 mmol), copper(I) iodide (9 mg, 0.05 mmol), iodobenzene (0.11 ml, 1 mmol), phenylacetylene (0.11 ml, 1 mmol) and triethylamine (0.15 ml, 1.1 mmol) were placed in a 10 ml stainless steel cell. The cell was sealed and pressurised to approximately 1000 psi (full of carbon dioxide). The suspended reagents were magnetically stirred and afforded a dark red-coloured medium as the cell was heated to 60 °C. The reagents were stirred at this temperature for 64 h when a crystalline deposit formed on the sapphire window. The cell was then cooled, and when the pressure had dropped below 2000 psi the cell was vented into Et_2O (100 ml). The cell was opened once atmospheric pressure was reached and washed out with a quantity of CH_2Cl_2 (10 ml). The organic fractions were combined and concentrated *in vacuo* to give the crude product. The product was purified by flash column chromatography on silica gel, eluting with hexane to give diphenylacetylene as a white crystalline solid (110 mg, 0.62 mmol, 62%), mp 58–60 °C; δ_H(250 MHz; $CDCl_3$) 7.56–7.61 (4 H, m, *o*-Ph), 7.33–7.43 (6 H, m, *m/p*-Ph); δ_C 131.7 (*o*-C), 128.5 (*m*-Ph), 128.4 (*p*-Ph), 123.4 (quaternary Ph), 89.5 (alkyne). A similar procedure (excluding CuI) was used for the Suzuki reaction. The Heck procedure employed the *in situ* generated palladium acetate complex. All reactions showed similar colour and physical behaviour.

‖ All new compounds gave spectroscopic (NMR, IR, HRMS) data in accordance with their proposed structure.

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