Palladium-catalyzed cross-coupling reactions in supercritical carbon dioxide

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Palladium-catalyzed carbon–carbon bond coupling reactions, the Heck and Stille reactions, proceed in supercritical carbon dioxide with a number of phosphine ligands including tris[3,5-bis(trifluoromethyl)phenyl]phosphine, which affords high conversions and selectivities.

Elevated pressures[1] have been reported to offer benefits for homogeneous catalyst lifetime[2] and selectivity.[3] Such pressure-related advantages, in combination with the properties of supercritical carbon dioxide (scCO$_2$), led us to explore homogeneous catalytic reactions in this medium. A number of recent reports describe examples of homogeneous catalytic reactions in scCO$_2$ including hydrogenations,[4] hydroformylations,[5] epoxidations[6] and polymerizations.[7] We report the first demonstration that palladium-catalyzed carbon–carbon coupling reactions can be carried out in supercritical CO$_2$. We have examined catalyst activity, selectivity and ligand effects in scCO$_2$ in a first step toward capitalizing on the benefits of high pressures for homogeneous palladium-catalyzed reactions. The reactivity and selectivity of Heck[8] and Stille[9] reactions using several different phosphine ligands in scCO$_2$[10] were compared to those in organic solvents (THF and toluene).

All reactions in scCO$_2$ were carried out batchwise in magnetically stirred, custom built 316 stainless steel reactors with sapphire windows to allow viewing of the contents at high pressure.[11] Stille cross-coupling reactions of PhI and vinyl-(tributyl)tin in CO$_2$ (345 bar) were run at 90 °C for 5 h using a number of different ligands (Table 1). The highest conversion in scCO$_2$ was achieved with the tris[3,5-bis(trifluoromethyl)phenyl]phosphine ligand **4** (>99%) which was comparable to the results using tri-2-furylphosphine **3** (86%), a ligand noted for high palladium-coupling activity.[9c] PPh$_3$ **2** and tri-

o-tolylphosphine **1** were characterized by significantly lower turnover numbers, with PPh$_3$ **2** resulting in conversions only slightly higher than the reaction in the absence of added ligand. We also ran the Stille coupling reaction of PhI with vinyl-(tributyl)tin with the same ligands in CO$_2$ and THF at 50 °C and found that the conversions were considerably higher in THF. For example, in THF at 50 °C the tri-2-furylphosphine and tris[3,5-bis(trifluoromethyl)phenyl]phosphine ligands both resulted in conversions above 95% while slightly lower conversions (81%) were measured with PPh$_3$. The conversion in scCO$_2$ at 50 °C for the Stille reaction was only 28% after 5 h using the tri-2-furylphosphine ligand.

The much higher conversions in scCO$_2$ for tris[3,5-bis(trifluoromethyl)phenyl] phosphine appear to arise from the enhanced solubilization of the catalytically active palladium–phosphine complexes. A number of reports have demonstrated the ability of fluorine substitution on organic polymers and ligands to enhance solubility in scCO$_2$.[7a,7b,12,13] In particular, Leitner has recently reported catalytic activity in scCO$_2$ for rhodium catalysts containing perfluoroalkyl-substituted arylphosphines.[12] Although we have not carried out any quantitative solubility studies, we observed no visible precipitation for the Stille coupling reactions in CO$_2$ using the tris[3,5-bis(trifluoromethyl)phenyl]phosphine ligand. We did, however, observe significant precipitation in CO$_2$ (presumably palladium–phosphine complexes) under identical conditions with PPh$_3$. The perfluorinated ligand, tris(pentafluorophenyl)-phosphine, also conferred solubility indicated by no observed precipitation, although lower conversions (≤ 75%) were obtained.

In order to further probe these ligand effects, and to benchmark the chemical reactivity in CO$_2$ with organic solvents, we carried out preliminary kinetic studies of the Stille coupling of PhI and vinyl(tributyl)tin at 75 °C in scCO$_2$ and toluene. Reaction rates were determined as initial rates[14] using a high pressure reactor with a six-port sampling valve for CO$_2$, which has been described previously,[11] and standard Schlenk-ware for toluene. As shown in Table 2, the initial rate of reaction using tris[3,5-bis(trifluoromethyl)phenyl]phosphine **4** was twice that of PPh$_3$ **2** in both CO$_2$ and toluene. Moreover, the

Table 1 Stille cross-coupling of PhI with vinyl(tributyl)tin using Pd$_2$(dba)$_3$ in supercritical CO$_2$[a]
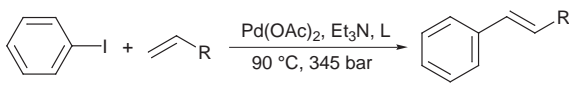

Ligand	Conversion (%)	Selectivity[c] (%)	TON[d]/h^{-1}
Tri-o-tolylphosphine **1**	9	99	0.5
No ligand	38	96	1.9
PPh$_3$ **2**	49	96	2.5
Tri-2-furylphosphine **3**	86	97	4.3
P[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_3$ **4**	>99	99	>5

[a] 90 °C, 5 h, 345 bar CO$_2$, 2 equiv. of phosphine ligand for each equiv. of palladium(0) in all coupling reactions, [2.7 mmol (0.790 ml) vinyl-(tributyl)tin, 2.7 mmol (0.3 ml) PhI, 0.054 mmol (0.048 g) Pd$_2$(dba)$_3$, 0.216 mmol phosphine ligand], reactions were quenched in acetone and analyzed by GC using known standards and confirmed by GC–MS and/or ^{1}H NMR spectroscopy. [b] Conversion = iodobenzene reacted (%). [c] Selectivity = styrene (%) with respect to all products formed. [d] TON/h^{-1} = [(moles of iodobenzene) × (% conversion)]/[(moles of catalyst added) × (hours of reaction)].

Table 2 Rates of Stille coupling reactions in supercritical CO$_2$ and toluene[a]

Ligand	k/min^{-1}	
	CO$_2$	Toluene
PPh$_3$ **2**	0.016	0.034
P[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_3$ **4**	0.036	0.057

[a] 75 °C, 0.024 mmol (0.022 g) Pd$_2$(dba)$_3$, 2.4 mmol vinyl(tributyl)tin, 2.4 mmol PhI, 33 ml toluene or 33 ml CO$_2$ at 310 bar used. Initial rates measured by GC with internal standard (octafluoronaphthalene). Initial rates (30 min) were obtained from a ln [c/c_o] vs. time plot and are accurate to within 10%.

Table 3 Heck cross-coupling reaction in supercritical CO_2^a

L	R = CO_2Me			R = Ph		
	Conversion (%)	Selectivity (%)	TON/h^{-1}	Conversion (%)	Selectivity (%)	TON/h^{-1}
Tri-o-tolylphosphine **1**	35	80	1	—	—	—
No ligand	17	82	0.5	37	99	1
PPh$_3$ **2**	—	—	—	20	99	0.6
Tri-2-furylphosphine **3**	96	78	2.7	—	—	—
P[3,5-$(CF_3)_2C_6H_3]_3$ **4**	94	91	2.6	99	99	2.8
P(C_6F_5)$_3$ **5**	—	—	—	99	99	2.8

^{a} 90 °C, 24 h (R = CO_2Me), 12 h, 0.3 mmol ligand, 0.15 mmol (0.034 g) Pd(OAc)$_2$, 15 mmol (2.25 ml) Et$_3$N, 5 mmol (0.560 ml) PhI, 25 mmol (2.25 ml) methyl acrylate, octafluoronaphthalene internal standard. Reactions were analyzed as in Table 1.

observed rates in scCO$_2$ were within a factor of two of those observed in toluene for both phosphine ligands (Table 2). The initial rates of the PPh$_3$ **2** and tris[3,5-bis(trifluoromethyl)phenyl]phosphine **4** ligands are similar but the conversions are so different, suggesting that the enhanced solubility of the trifluoromethyl substituted system is probably more important than any increased activity through electronic effects. We found that the much less basic fluorinated ligand, tris(pentafluorophenyl)phosphine **5**, also enhanced solubility relative to PPh$_3$ **2** but the initial rate was two orders of magnitude less than the other ligands, presumably due to electronic effects.

We have also examined the palladium-catalyzed Heck coupling of PhI with simple olefins using several phosphines in scCO$_2$ at 90 °C. As Table 3 illustrates, we observe that the fluorinated phosphines result in high conversions for both styrene and methyl acrylate (>94%), similar to the proven tri-2-furylphosphine ligand. The non-fluorinated triarylphosphines led to lower conversions (20–35%), which were comparable to reactions run in the absence of added ligand. Unlike the Stille couplings, the reaction solution for all the Heck couplings was dark and opaque and prevented even qualitative observation of precipitation; however, we believe the higher turnovers for the fluorinated phosphines probably arise from enhanced solubilization of the palladium complexes.

In summary, we have observed that both Heck and Stille couplings can proceed in supercritical CO$_2$ with rates and selectivites comparable to those in toluene. Of particular note, we find that fluorinated phosphines, particularly tris[3,5-bis(trifluoromethyl)phenyl]phosphine, result in high conversions due to the ability of these ligands to enhance the solubility of the metal complexes in scCO$_2$. 'CO$_2$-philic' ligands such as fluorinated phosphines should expand the utility of scCO$_2$ for homogeneous catalysis. Another logical extension of our work would be to explore supercritical fluids at pressures reported[2] to be high enough (>1 kbar) to enhance some catalytic reactions.

Notes and References

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