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LETTERS

Use of Fluorinated Palladium Sources for Efficient Pd-catalysed Coupling Reactions in Supercritical Carbon Dioxide

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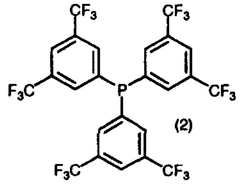
Abstract: Commercially available palladium sources [$Pd(OCOCF_3)_2$ and $Pd(F_6\text{-acac})_2$] containing fluorinated ligands are superior to non-fluorinated sources [$Pd(OCOCH_3)_2$ and $Pd_2(dba)_3$] for carrying out a variety of palladium catalysed coupling reactions in supercritical carbon dioxide. Significantly reduced temperatures and catalyst loadings are possible, and also the range of phosphine ligands which can be used is increased, including those that are often considered to be poor ligands for coupling reactions under conventional conditions (PCy_3, PBu_3).

Introduction.

The use of supercritical carbon dioxide ($scCO_2$) as an environmentally benign solvent for carrying out synthetic organic transformations is currently receiving much attention. In our own laboratories we have shown that using $scCO_2$ as a reaction medium also offers other very significant advantages, such as dramatic enhancements in diastereoselectivity simply by switching from conventional solvents to $scCO_2$.[1] New methods of carbon-carbon bond formation such as those catalysed by transition metals, are of great importance to synthetic chemists owing to their versatility and power in assembling complex and often synthetically challenging carbon frameworks. Recent reports by Holmes[2] and Tumas[3] have described the design and synthesis of fluorinated phosphine ligands (1) and (2) respectively, which when used in conjunction with $Pd(OCOCH_3)_2$ and $Pd_2(dba)_3$, allow a variety of coupling reactions to be carried out in $scCO_2$. It has been known for some time that organometallic reactions are facilitated in $scCO_2$ by the use of fluorinated ligands, which act by solubilising the intermediate metal complexes due to the known affinity of $scCO_2$ for fluorinated substrates.[4] However, such ligands are generally not commercially available, which limits their application, particularly if simple alternatives are possible.

$(C_6F_{13}CH_2CH_2)_2PPh$

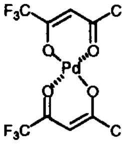
(1)



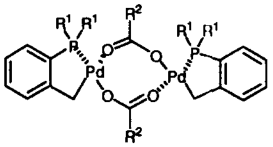
(2)

$Pd(OCOCF_3)_2$

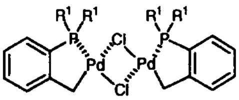
(3)



(4)



(5) R_1 = *o*-tolyl, $R_2 = CH_3$
(6) R_1 = *o*-tolyl, $R_2 = CF_3$



(7) R_1 = *o*-tolyl

We wish to report the results of our own studies in this area, which show that whilst the nature of the phosphine ligand is important, for the reactions we have investigated, the nature of the initial palladium source is

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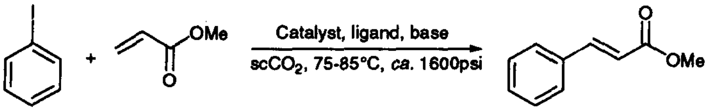
also of crucial, if not greater importance, and allows the use of a variety of commercially available phosphine ligands for efficient coupling reactions under generally milder conditions, with lower catalyst loadings and in shorter reaction times than those using more conventional palladium sources.

Development of catalyst systems for palladium mediated coupling reactions in $scCO_2$.

Whilst the solubility of intermediate metal complexes is no doubt important for palladium mediated coupling reactions, we were also aware that for many of these reactions, efficient ligand exchange processes are also vital. It is thus essential that if a ligand dissociation process plays an important role in a reaction, then the solubility of that ligand in the reaction medium is also an important consideration. Thus for carrying out palladium mediated coupling reactions in $scCO_2$, not only is it desirable to have soluble active species (whatever they may be[5]), but also the solubilities of any dissociated species needs to be considered, and of course, the solubility of the initial palladium source. We chose not to prepare any new fluorinated phosphine ligands and instead decided to concentrate on commercially available ligands as we believed this to be important if these procedures were to be adopted widely. We initially chose to investigate the classic Heck coupling reaction of iodobenzene and methyl acrylate in $scCO_2$ (Scheme 1). The results of this are given in table 1.



Scheme 1.

	Palladium source	mol% Pd	Ligand[a]	Base[b]	Temp (°C)	Time (h)	Conversion	Yield[c] (%)
1	$Pd(OCOCH_3)_2$	7	PPh_3	NEt_3	75	18	25	-
2	$Pd(OCOCH_3)_2$	7	P(2-furyl)$_3$	NEt_3	75	18	26	-
3	$Pd(OCOCH_3)_2$	14	PPh_3	NEt_3	75	40	>95	84
4	$Pd(OCOCH_3)_2$	14	P(2-furyl)$_3$	NEt_3	75	40	>95	-
5	$Pd(OCOCH_3)_2$	14	PCy_3	NEt_3	75	90	66	-
6	$Pd(OCOCH_3)_2$	7	P(2-furyl)$_3$	DIPEA	75	18	35	-
7	$Pd_2(dba)_3$	7	P(2-furyl)$_3$	DIPEA	75	18	55	-
8	$Pd(OCOCF_3)_2$	2	P(2-furyl)$_3$	DIPEA	75	15	>95	92
9	$Pd(OCOCF_3)_2$	2	PPh_3	DIPEA	80	15	71	-
10	$Pd(OCOCF_3)_2$	2	P(o-tolyl)$_3$	DIPEA	80	15	91	-
11	$Pd(OCOCF_3)_2$	2	PCy_3	DIPEA	80	15	81	-
12	$Pd(OCOCF_3)_2$	2	PBu_3	DIPEA	80	15	>95	-
13	$Pd(OCOCF_3)_2$	6	None	DIPEA	85	18	81	80
14	Pd(F_6-acac)$_2$	6	None	DIPEA	85	18	88	88
15	Pd(F_6-acac)$_2$	2	P(2-furyl)$_3$	DIPEA	80	17	>95	96
16	(5)	4	-	DIPEA	80	15	43	-
17	(6)	2	-	DIPEA	85	24	>95	94
18	(7)	2	-	DIPEA	80	15	20	-

[a]2 equiv. relative to palladium; [b]NEt_3 (2.5 eq.) or DIPEA (1.5 eq.); [c]isolated, after chromatography.

Table 1: Results of Heck Couplings

Both triphenylphosphine and tris(2-furyl)phosphine (also reported by Tumas[3] although we were unaware of this work at the time) gave promising results with $Pd(OCOCH_3)_2$ and $Pd_2(dba)_3$, although at the temperatures we were using, high catalysts loadings and prolonged reaction times were required for complete conversion (entries 3 and 4). Tricyclohexylphosphine (PCy_3) was a poor ligand requiring even longer reaction times, with incomplete reaction (entry 5). Changing base from triethylamine to diisopropylethylamine (DIPEA) gave a modest improvement in conversion (*cf.* entries 2 and 6), which could be further increased using $Pd_2(dba)_3$ as the palladium source (entry 7). However, the catalyst loadings and reaction times were still somewhat unsatisfactory.

Many Heck reactions are carried out at temperatures significantly higher than those we were using, however we were reluctant to increase our working temperature due to practical considerations. We therefore looked for other means of increasing reaction efficiency which led us to consider alternative sources of palladium as a possible way of improving this reaction.

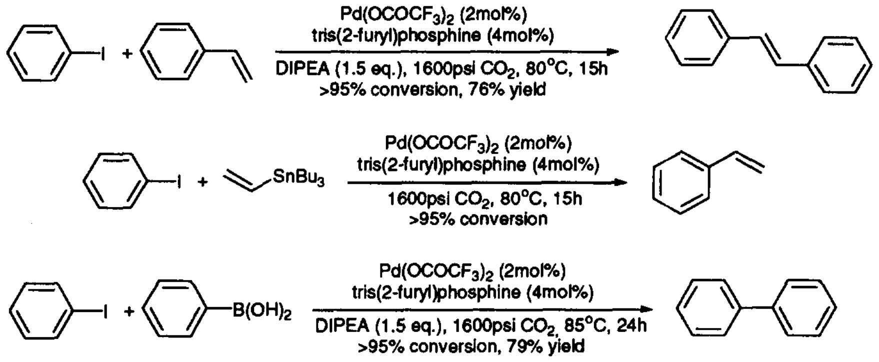
Use of fluorinated palladium complexes in $scCO_2$.

We reasoned that $Pd(OCOCH_3)_2$ and $Pd_2(dba)_3$ were not ideal sources of palladium for reactions in $scCO_2$ because of their own insolubility and that of their ligands. Alternative commercially available sources of palladium, which already contain fluorinated ligands are $Pd(OCOCF_3)_2$ (3) and $Pd(F_6\text{-}acac)_2$ (4). We believed these would show enhanced initial solubility in $scCO_2$ due to their fluorinated nature, as would be any free ligands dissociated from the metal centre. Upon investigating these reactions it rapidly became clear that they had very significant advantages over those reported previously (Table 1). In particular, reduced catalyst loadings were required for complete conversion (2%), and whilst tris(2-furyl)phosphine was still the best ligand, others which had previously been of little use and are usually regarded as poor ligands for Heck reactions,[6] notably tricyclohexylphosphine and tributylphosphine, now gave acceptable conversions at low temperatures (80°C) with 2% catalyst (entries 11 and 12), and both were superior to triphenylphosphine (entry 9), presumably due to their greater solubility in $scCO_2$. Interestingly, tri(o-tolyl)phosphine was also significantly better than triphenylphosphine (entries 9 and 10). In the absence of any phosphine, a 6% catalyst loading was required for complete conversion using either $Pd(OCOCF_3)_2$ or $Pd(F_6\text{-}acac)_2$ indicating that whilst not absolutely essential, the phosphines do play an important role in the efficiency of the reaction. $Pd(F_6\text{-}acac)_2$ in the presence of tris(2-furyl)phosphine also gave impressive results (entry 15).

There is much current interest in catalysts for the Heck reaction based on palladium (II) metallocycles, which have been reported to give very high turnover numbers and have high thermal stability.[5] We believed these may also show significant activity in $scCO_2$ and chose to investigate the metallocycles (5) and (7) reported by Herrmann,[5a] and the trifluoroacetate (6) prepared by us from $Pd(OCOCF_3)_2$ using an analogous procedure. These were also active in $scCO_2$ at a similar catalyst loading to those required above, although the trifluoracetate (6) (entry 17) was significantly better than the acetate (5) (entry 16) and the chloride bridged complex (7) (entry 18). Importantly these reactions showed no sign of catalyst decomposition, unlike those using (3), (4),

$Pd(OCOCH_3)_2$[3] or $Pd_2(dba)_3$ as palladium sources, which gave dark precipitates in the crude product, presumably due to metallic palladium residues. Attempted generation of (6) *in situ* using $Pd(OCOCF_3)_2$ and tri(o-tolyl)phosphine gave an efficient reaction, but the dark precipitation characteristic of catalyst decomposition was also observed (entry 10). Interestingly, using PBu_3 as ligand (entry 12), no significant catalyst decomposition was observed which may have important implications for future work.

Importantly, these catalyst systems could also be used in other palladium-mediated coupling reactions such as other Heck reactions, Stille[3] and Suzuki[2,3] couplings, again with good efficiency (Scheme 2).



Scheme 2.

In summary, we have shown that the use of fluorinated palladium sources for coupling reactions in $scCO_2$ can give superior results to those previously reported, including low catalyst loading at moderate temperatures, and allows the use of ligands usually considered to be poor in conventional Heck reactions. We are currently investigating such reactions in more detail, the results of which will be published in due course.

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