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Stille couplings in supercritical CO_2 catalyzed with perfluoro-tagged and un-tagged Pd complexes

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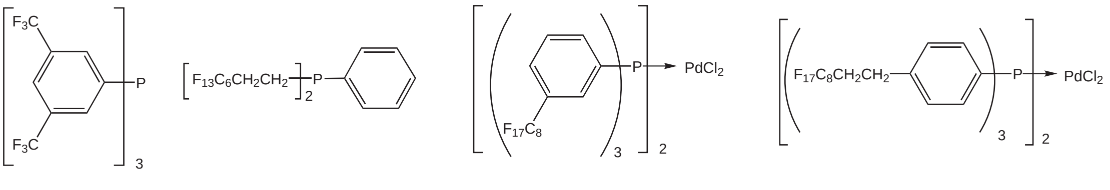
Abstract—Stille CC-couplings in supercritical CO_2 (*sc*CO_2) were performed with perfluoro-tagged and un-tagged Pd complexes in high yields. With fluoro-tagged complexes yields were generally slightly higher. A recycling of the perfluoro-tagged catalyst was also achieved. © 2001 Elsevier Science Ltd. All rights reserved.

Supercritical CO_2 (*sc*CO_2) is an environmentally benign medium for chemical reactions. It shows a high solvating power for certain gases, there is no gas–liquid boundary, its low viscosity leads to high diffusivity, it is non-flammable, and can be easily removed from the products of a reaction.[1] Due to these favorable properties it is becoming increasingly important as a reaction medium and especially so in metal catalyzed reactions.[2,3] However, its application is limited due to low polarity which creates solvation problems for polar and ionic catalysts.

The solubility of such catalysts in *sc*CO_2 can be enhanced by incorporating 'CO_2-philic' ligands.[4,5] This can be achieved by inserting perfluoro tags into parent ligands thereby enhancing their lipophilicity. This was demonstrated impressively for Rh-catalyzed hydroformylations in *sc*CO_2.[4] In these experiments the activity of the Rh catalyst was highly dependent on the basicity of the phosphine ligands. The activity increased with decreasing basicity of the phosphine ligands caused by the electron-withdrawing perfluoro entities.[5]

Pd complex-mediated CC-couplings are currently a topic of high interest. In a recent report, Holmes et al.[6] have applied the phosphine ligand **1** for solubilization of Pd complexes and employed them for Heck, Suzuki and Sonogashira couplings in *sc*CO_2. Tumas et al.[7] have demonstrated that ligand **2** was suitable for Heck and Stille couplings in *sc*CO_2. Fluorinated Pd sources such as $Pd(OCOCF_3)_2$ in combination with phosphines are another alternative as to allow for CC-couplings in *sc*CO_2.[8]

Recently, we have synthesized a set of new perfluoro-tagged Pd complexes and demonstrated their application in Stille couplings in a fluorous biphasic system (FBS).[9] Out of this set, we have selected the Pd complexes **3** and **4** to evaluate Stille reactions in *sc*CO_2 (Scheme 1). In complex **3** the perfluoro tag is attached



1 **2** **3** **4**

Scheme 1.

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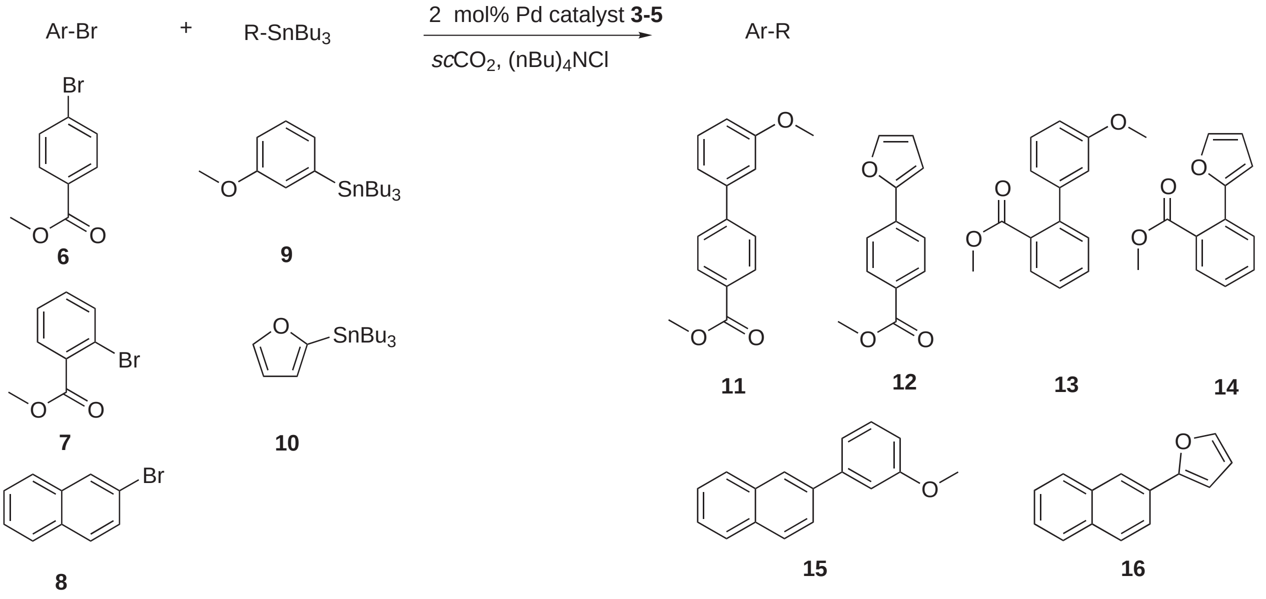

Scheme 2.

directly to the *meta* position in the phosphine ligand whereas in complex **4** the fluoro tag is attached to the para position and has an inserted CH_2CH_2 spacer to diminish the electron withdrawing properties of the perfluoro entity. The application of the catalysts **3** and **4** opens up the possibility to recover and re-use them for further couplings. $Pd(PPh_3)_2Cl_2$ (**5**) was used for comparison since it was reported to be not soluble in *sc*CO_2.[6]

Three different aryl bromides **6**–**8** were selected and reacted with the stannanes **9** and **10** to yield the cross-coupling products **11**–**16** in *sc*CO_2 employing 2 mol% of the catalysts **3**–**5** (Scheme 2).

Addition of LiCl can enhance the yield of Stille couplings and is essential when working in fluorous biphasic systems.[10] Due to the low solubility of LiCl in *sc*CO_2, it was substituted by one equivalent of the more lipophilic tetrabutylammonium chloride (TBACl).

Since significant decomposition of the Pd complexes was observed above 100°C, the reactions were carried out at lower temperature (90°C). The results are summarized in Table 1.[11] The yields are based on the ^1H NMR spectra of the crude reaction mixtures, by comparing the integrals of products with those of the starting materials. No trace of a possibly formed *cine* product was detected.

Generally the reaction times of the couplings in *sc*CO_2 were longer as compared to the same reaction carried out in the fluorous biphase system.[9] It was expected that the electron withdrawing effect of the perfluoro tag would have an influence on the coordination properties of the phosphine ligands and thus have an effect on the catalytic properties of the Pd complexes, but the yields obtained for the same Stille coupling applying the perfluoro-tagged catalysts **3** and **4** were virtually identical. These observations are identical with those obtained from Stille couplings in fluorous biphase systems mediated by perfluoro-tagged Pd complexes.[9]

The coupling yields are generally high, and moderate only for those couplings where steric hindrance is involved due to *ortho*-substitution of the starting materials, which is a common problem in Stille couplings, especially for the stannanes.[12]

To our surprise, catalyst **5** was also able to mediate Stille couplings in *sc*CO_2 efficiently. The yields obtained with this catalyst were only slightly lower as compared to the same reaction performed with the perfluoro-tagged catalysts **3** and **4**. The results indicate that at least some of the catalyst **5** must be soluble in *sc*CO_2 under the conditions applied to the coupling reactions. Such activity of seemingly insoluble catalysts has so far only been reported for Rh complex-mediated hydroformylations in *sc*CO_2.[13]

In order to recycle the perfluoro-tagged catalysts **3** and **4**, the residue after dissipation of the CO_2 was distributed between dimethyl formamide (DMF) and perfluorohexane (FC 72). After phase separation, the DMF was extracted two times with FC 72. The com-

Table 1. Stille couplings with catalysts **3**–**5**

Product	Aryl-bromide	Stannane	Yield (%)		
			3	**4**	**5**
11	**6**	**9**	93	88	87
12	**6**	**10**	95	95	91
13	**7**	**9**	55	54	43
14	**7**	**10**	48	40	34
15	**8**	**9**	94	91	87
16	**8**	**10**	91	91	84

Table 2. Repetitive Stille couplings with catalyst **3**

Compound	Yield (%) (1st run)	Yield (%) (2nd run)
11	93	95
12	95	93
13	52	61
15	92	95
16	90	93

bined FC 72 layers were evaporated and the catalyst recovered in such a way was re-used for a consecutive Stille coupling. The DMF layer was evaporated and the yield was estimated from the ^{1}H NMR spectra as described above. The results obtained with catalyst **3** are summarized in Table 2.

In summary, we have demonstrated that Stille CC-cross couplings in *sc*CO_2 can be catalyzed with perfluoro-tagged Pd catalysts **3** and **4** as well as with the un-tagged Pd complex **5**. The yields with complexes **3** and **4** were slightly higher. Furthermore we have demonstrated that a recycling of the catalyst can also be achieved.

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References

1. *Chemical Synthesis in Supercritical Fluids*; Jessop, P. G.; Leitner, W., Eds.; Wiley-VCH: New York, 1999 and references cited therein.
2. Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475–493.
3. Darr, J. A.; Poliakoff, M. *Chem. Rev.* **1999**, *99*, 495–541.
4. Koch, D.; Leitner, W. *J. Am. Chem. Soc.* **1998**, *120*, 13398–13404.
5. Palo, D. R.; Erkey, C. *Organometallics* **2000**, *19*, 81–86.
6. Carrol, M. A.; Holmes, A. B. *Chem. Commun.* **1998**, 1395–1396.
7. Morita, D. K.; Pesiri, D. R.; David, S. A.; Glaze, W. H.; Tumas, W. *Chem. Commun.* **1998**, 1397–1398.
8. Shezad, N.; Oakes, R. S.; Clifford, A. A.; Rayner, C. M. *Tetrahedron Lett.* **1999**, *40*, 2221–2224.
9. Schneider, S.; Bannwarth, W. *Angew. Chem.* **2000**, *112*, 4293–4296; *Angew. Chem., Int Ed.* **2000**, *39*, 4142–4145.
10. Hoshino, M.; Degenkolb, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 8341–8349.
11. General procedure: In a glove box (O_2 <1 ppm), an autoclave (volume 36.5 ml) was charged with 0.2 mmol of aryl bromide, 0.24 mmol of stannane, 1 equiv. of tetrabutylammonium chloride and 2 mol% of Pd catalyst. The autoclave was sealed and argon pressure (6 bar) was applied. After cooling (dry ice/acetone), 15–16 g CO_2 was condensed into the vessel. After heating for 24 h at 90°C, the autoclave was cooled down to rt and the CO_2 was carefully vented. To the residue were added 3 ml of DMF and 3 ml of FC 72. After phase separation, the DMF layer was extracted twice with FC 72 (1–2 ml each). Evaporation of the fluorous phase yielded the catalyst. To the DMF layer was added 5 ml of diethyl ether and then it was extracted twice with water (5 ml each). The organic layer was concentrated to a volume of 3–5 ml and then 5 ml of a KF solution were added. After stirring overnight the organic layer was extracted again with water, dried over Na_2SO_4, filtered over a small plug of SiO_2 and evaporated to yield the crude product. Yields were determined by ^{1}H NMR spectroscopy (see Ref. 9).
12. Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.
13. Sellin, M. F.; Cole-Hamilton, D. J. *J. Chem. Soc., Dalton Trans.* **2000**, 1681–1683.