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On the use of phosphine-free $PdCl_2(SEt_2)_2$ complex as catalyst precursor for the Heck reaction

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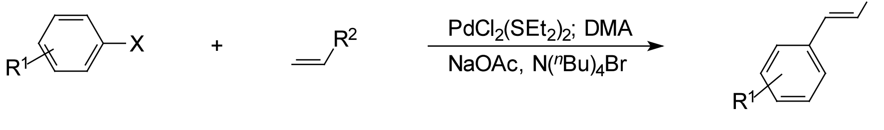
Abstract—A simple and efficient experimental protocol has been developed for the catalytic arylation of alkenes by the air and water stable, and phosphine-free compound $PdCl_2(SEt_2)_2$ associated with tetrabutyl ammonium bromide. Using this catalytic protocol, aryl iodides and bromides, and electron-poor aryl chlorides are coupled with *n*-butylacrylate and styrene under relatively mild reaction conditions with high catalytic activity. Reaction vessel ultra-trace amounts (ppt) of this Pd precursor promotes the coupling of iodo benzene with *n*-butylacrylate with turnover numbers (mol product/mol Pd) up to 10^9. © 2001 Elsevier Science Ltd. All rights reserved.

The arylation and vinylation of alkenes (the 'Heck reaction') is one of the most investigated C–C coupling reactions mediated by Pd complexes. The coupling of aryl iodides and electron-poor aryl bromides with alkenes can be catalyzed by almost any Pd(0) or Pd(II) catalyst precursor under relatively mild reaction conditions and in high turnover numbers (TON). Even ligand-less $Pd(OAc)_2$ is an effective catalyst precursor to promote the coupling of aryl iodides with C=C double bonds.[1] However, in the case of less reactive aryl chlorides and electron-rich aryl bromides it is believed that Pd catalyst precursor should be associated with stabilizing ligands to effective promote these couplings.[2] Thus, Pd complexes associated with bulky and electron rich phosphines, imidazol carbenes and palladacycles are able to catalyze the Heck reaction involving these less activated aryl bromides and chlorides.[1–3] For example, the cyclopalladated complex $[PdCl\{C_6H_3(OP^iPr_2)_2\text{-}2,6]$ promotes the coupling of electron-rich aryl chlorides such as 4-chloroanisol with styrene in high yields[4] and the use of $Pd_2(dba)_3$ associated with $P(^tBu)_3$ that allows the reaction to be conducted at room temperature.[5] Moreover, the reaction conditions, such as the temperature, solvent, the addition of quaternary ammonium salt additives,[6] or running the reaction in ionic liquids also have a strong influence on the reactivity of the aryl halides.[7] However, the majority of these catalytic systems involves usually the use of 'sensitive' reagents such as phosphines and carbenes, or the synthesis of ligands and their Pd complexes. Therefore, the use of these methods in organic synthesis is not usually straightforward. We wish to report here that the air and water stable and easily prepared compound $PdCl_2(SEt_2)_2$, when associated with tetra butyl ammonium bromide, effectively promotes the Heck reaction involving great part of the substrates (aryl halides and alkenes) generally used in organic synthesis. Moreover, we note that even Pd ultra-trace amounts in the reaction vessel catalyze the coupling of aryl iodides and bromides substituted with electron-withdrawing groups with alkenes.

The air and water stable $PdCl_2(SEt_2)_2$ complex was prepared in almost quantitative yield from the reaction of lithium tetrachloropalladate with diethylsulfide as described earlier.[8]



Scheme 1.

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Based on our recent success with sulfur-containing palladacycles as catalyst precursors in Heck coupling reactions of aryl halides, we employed the same experimental protocol.[9] As in early experiments, dimethylacetamide (DMA) was chosen as the solvent and sodium acetate as the base for the reaction of aryl halides with styrene and *n*-butylacrylate (Scheme 1) at 120°C using $PdCl_2(SEt_2)_2$ as catalyst precursors (Table 1).

From the experimental point of view, this method is extremely simple: an oven-dried resealable Schlenk flask was evacuated and back-filled with argon and charged with NaOAc (1.4 mmol), alkene (1.2 mmol), and additive $N(^tBu)_4Br$ (0.2 mmol). The flask was evacuated and back-filled with argon and then the aryl halide (1.0 mmol) and a solution of $PdCl_2(SEt_2)_2$ in 5 mL of DMA were added. The reaction mixture was stirred at 120°C for the desired time (Table 1). The solution was then taken up in ether (20 mL) and washed with aqueous NaOH (1 M, 5 mL) and brine (2×5 mL), and then dried over $MgSO_4$. After filtration, solvent was evaporated to give the respective product, which was characterized by GC–MS, ^1H and ^{13}C NMR.

As shown in Table 1, $PdCl_2(SEt)_2$ generates catalytic active species for the arylation of styrene and *n*-butyl acrylate with aryl iodides, bromides and chlorides activated with electron withdrawing groups. However, higher palladium concentrations (0.1 mol%) need to be used in the case of electron neutral and rich aryl bromides and electron-poor aryl chlorides in order to obtain good yields in reasonable reaction times. This catalytic system fails to promote the Heck reaction involving electron-neutral or rich aryl chlorides such as chlorobenzene or chloro anisol. Notwithstanding the limitations, this is one of the simplest phosphine-free palladium catalyst precursor to promote the coupling of aryl iodides, bromides and electron-poor aryl chlorides with alkenes.

The use of the salt additive $[N(^nBu)_4Br]$ is essential to obtain almost complete arylation of the alkenes. For example, the reaction of iodobenzene and *n*-butylacrylate, under the same reaction conditions described in Table 1, entry 1, only 44% iodo benzene conversion was observed in the absence of the ammonium salt.

Electron-withdrawing groups on the aryl ring increase the reaction rate. For example, in a competitive experiment mediated by $PdCl_2(SEt_2)_2$ (2×10^{-4}M) the reaction of 4-fluoroiodoobenzene, iodobenzene, 4-iodotoluene, and 4-iodoanisol (0.5 mmol each) with styrene (20 mmol) in DMA (5 mL) at 120°C gave after 30 min the *trans*-substituted stilbenes (4-fluorophenyl, phenyl, 4-methylphenyl, 4-methoxyphenyl) in a proportion of 15:10:8.5:7.7, respectively. This trend is similar to those observed for the majority of the palladium catalyst precursors associated or not with phosphine ligands, suggesting that the aryl halide oxidative addition is the rate-determining step.[1,2] Moreover, these results also suggest that $PdCl_2(SEt_2)_2$ acts as reservoir of Pd(0) catalytic active species.[10]

This catalyst system is not sensitive to oxygen and water, and the reaction can be carried out in air, with no change in efficiency. For example, the reaction of 4-chloroacetophenone with and *styrene*, under the same

Table 1. Heck reaction between alkenes and aryl halides catalyzed by $PdCl_2(SEt_2)_2$[a] (Scheme 1)

Entry	ArX	Alkene[d]	[Pd] (mmol)	T (°C)	Time (h)	Yield (%)[b]	TON[c]
1	PhI	Acrylate	2×10^{-5}	120	20	100	50,000
2	PhI	Acrylate	2×10^{-6}	120	50	100	500,000
3	PhI	Styrene	2×10^{-5}	120	23	71	45,000
4	PhI	Styrene	2×10^{-6}	120	240	70	350,000
5	4-MeC_6H_4I	Acrylate	2×10^{-5}	120	20	100	50,000
6	4-MeC_6H_4I	Styrene	2×10^{-5}	120	23	98	49,000
7	4-MeOC_6H_4I	Acrylate	2×10^{-5}	120	20	100	50,000
8	4-MeOC_6H_4I	Styrene	2×10^{-5}	120	23	90	45,000
9	PhBr	Acrylate	1×10^{-3}	120	24	45	450
10	PhBr	Styrene	1×10^{-3}	150	24	76	760
11	4-MeOC_6H_4Br	Acrylate	1×10^{-3}	150	24	65	650
12	4-MeOC_6H_4Br	Styrene	1×10^{-3}	150	24	38	380
13	4-ClC_6H_4Br	Acrylate	2×10^{-5}	120	69	72	36,000
14	4-ClC_6H_4Br	Styrene	2×10^{-5}	120	27	80	40,000
15	4-MeCOC_6H_4Br	Acrylate	2×10^{-5}	120	39	98	49,000
16	4-MeCOC_6H_4Br	Styrene	2×10^{-5}	120	16	100	50,000
17	4-CNC_6H_4Cl	Acrylate	1×10^{-3}	120	48	88	880
18	4-CNC_6H_4Cl	Styrene	1×10^{-3}	120	92	95	950
19	4-MeCOC_6H_4Cl	Styrene	1×10^{-3}	120	92	87	870
20	$4\text{-NO}_2C_6H_4Cl$	Acrylate	1×10^{-3}	150	22	91	910

[a] Reaction conditions: DMA (5 mL), NaOAc (1.4 mmol), alkene (1.2 mmol) ArX (1 mmol) and $N(^nBu)_4Br$ (0.2 mmol).

[b] GC yield (using undecane as internal standard). Isolated yields after extraction and purification were usually 5–10% lower. *trans*-Stilbenes were obtained almost exclusively in the reactions involving styrene.

[c] TON (mol product/mol of Pd).

[d] Acrylate = *n*-butylacrylate.

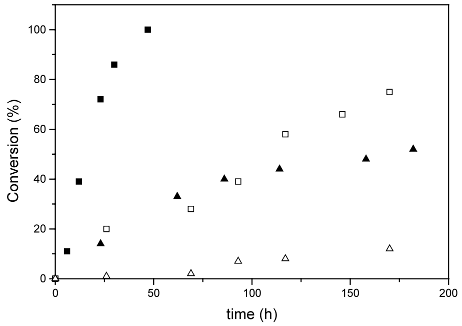

Figure 1. PhI conversion (determined GC using undecane as internal standard) in the arylation of *n*-butylacrylate and styrene promoted by $PdCl_2(SEt_2)_2$ (2×10^{-6} mmol) and by the 'reaction vessel' Pd catalyst. Reaction conditions: PhI (1.0 mmol) olefin (1.2 mmol); NaOAc (1.4 mmol); DMA (5 mL); 120°C; ■ = $PdCl_2(SEt_2)_2$, *n*-butylacrylate; □ = washed reaction vessel from reaction ■; ▲ = $PdCl_2(SEt_2)_2$, styrene; △ = washed reaction vessel from reaction ▲.

reaction conditions described in Table 1, entry 19, a 84% arylhalide conversion was observed in the presence air. Only in cases where catalyst concentrations are lower than 2×10^{-5} M should the purified aryl halides and the olefins be used and the reaction conducted in an inert atmosphere (N_2 or Ar). While investigating the Pd loading we have observed that after the first run (using new resealable Schlenk tube and a new Teflon coated stirring bar) the 'washed' reaction vessel is still active for the Heck reaction. Thus, after the quantitative arylation of methylacrylate by iodobenzene catalyzed by $PdCl_2(SEt_2)_2$ ([Pd]/PhI = 1/500000) the reaction vessel and the magnetic stirring bar were washed with water (3×5 mL) and acetone (3×5 mL) and oven-dried (1 h). A new loading of reagents: PhI (1 mmol), triethylamine (1.4 mmol) and *n*-butylacrylate (1.2 mmol) in DMA (5 mL) were introduced in this 'washed' reaction vessel. After 1 h at 130°C, 20% PhI conversion was observed. A similar behavior was observed using styrene instead *n*-butylacrylate (Fig. 1).

The 'reaction vessel catalytic activity' was only suppressed (for Heck-type reactions involving iodo-arenes or bromo-arenes substituted with electron-withdrawing groups) when the glass-reaction tube was washed with aqua regia (3×15 mL), sodium hydroxide (3×15 mL (1 M)), water (3×15 mL) and acetone (3×15 mL) before being oven-dried (1 h).[11] The residual Pd levels have been measured by ICP-MS analysis of the reaction vessel and the magnetic stirring bar to be of the order of 0.05 ppb of Pd (2.3×10^{-9} mmol of Pd) from an initial Pd loading of 43 ppb (2×10^{-6} mmol of Pd) after the first run and water/acetone washes. These results clearly show that ultra-trace[12] amounts of Pd can promote these coupling reactions giving an estimated TON of 1×10^{9}.[13,14]

In summary $PdCl_2(SEt_2)_2$ is an effective catalyst precursor for the Heck reaction involving most aryl halides (except for electron neutral and rich aryl chlorides) under relatively mild reaction conditions. Moreover, our results show that even palladium ultra-traces promote the Heck reaction involving aryl iodides and bromides substituted with electron withdrawing groups and therefore, these substrates should be not employed as benchmarks for testing the catalytic activity of new Pd catalyst precursors.

Acknowledgements

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References

1. For recent reviews see: (a) de Meijere, A.; Bräse, S.; *J. Organomet. Chem.* 1999, *576*, 88; (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.*, **2000**, *100*, 3009.
2. See for example: (a) Stambuli, J. P.; Stauffer, S. R.; Shausghnessy, K. H. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677; (b) Yang, C. L.; Lee, H. M.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1511; (c) Bohm, V. P. W.; Herrmann, W. A. *Chem. Eur. J.* **2000**, *6*, 1017; (d) Littke, A. F.; Fu, C. *J. Org. Chem.* **1999**, *64*, 10; (e) Gürtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107; (f) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481; (g) Beller, M.; Zapf, A.; *Synlett* **1998**, 792; (h) Jeffery, T. In *Advances In Metal-Organic Chemistry*; Liesbeskind, L. S., Ed.; JAI: London, 1996; Vol. 5, pp. 153–160; (i) Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734.
3. For a review on the use of palladacycles in homogeneous catalysis, see: Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, *4*, 1917.
4. Morales-Morales, D.; Redón, R.; Yung, C.; Jensen, C. M. *Chem. Commun.* **2000**, 1619.
5. Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719.
6. Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.
7. (a) Kaufman, D. E.; Nouroozian, M.; Henze, H. *Synlett* **1996**, 1091; (b) Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, *1*, 997; (c) Herrmann, W. A.; Böhm, V. P. W. *J. Organomet. Chem.* **1999**, *572*, 141; (d) Xu, L.; Chen, W.; Xiao, J. *Organometallics* **2000**, *19*, 1123; (e) Howarth, J.; Dallas, A. *Molecules* **2000**, *5*, 851; (f) Dupont, J.; Consorti, C. S.; Spencer, J. *J. Braz. Chem. Soc.* **2000**, *11*, 337.
8. For the synthesis and the use of $PdCl_2(SEt_2)_2$, see: Zim, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2000**, *41*, 8199.
9. Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287.
10. Dupont, J.; Gruber, A. S.; Fonseca, G. S.; Monteiro, A. L.; Ebeling, G.; Burrow, R. A. *Organometallics* **2001**, *20*, 171 and references cited therein.
11. Note that Pd on porous glass is an effective heterogeneous catalyst for the liquid-phase Heck coupling of iodobenzene or 4-bromoacetophenone with alkenes: Li, J.; Mau, A. W.-H.; Strauss, C. R. *Chem. Commun.* **1997**, 1275.

12. The relative component content of a sample is classified as: major (1–100%), minor (0.01–1%), or trace (less than 0.01%) to ultra-trace (ppb or less). Rubinson, J. F.; Rubinson, K. A. *Contemporary Chemical Analysis*, Prentice Hall, Upper Saddle River: NJ, 1998, Chapter 5, pp. 141–143.
13. TON's up to 10^{10} have been reported for the reaction of PhI with *n*-butyl acrylate and for the hydro-arylation of norbornene with PhI. (a) Miyazaki, F.; Yamaguchi, K.; Shibaski, M. *Tetrahedron Lett*. **1999**, *40*, 7379; (b) Brunel, J. M.; Heumann, A.; Buono, G. *Angew*. *Chem*., *Int*. *Ed*. **2000**, *39*, 1946.
14. Similar 'reaction vessel catalytic activities' were observed in the Heck reactions promoted by sulfur-containing palladacycles: Zim, D.; Monteiro, A. L.; Dupont, J., unpublished results.