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Heck Reactions in the Presence of P(*t*-Bu)$_3$: Expanded Scope and Milder Reaction Conditions for the Coupling of Aryl Chlorides

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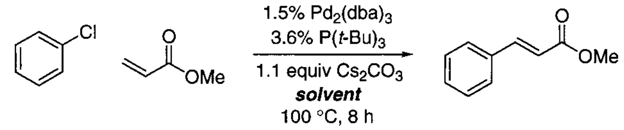
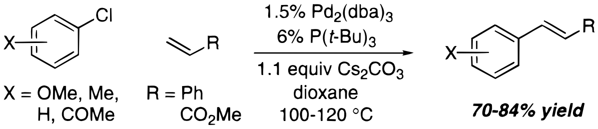
Aryl chlorides are both more readily available and less expensive than aryl bromides and aryl iodides. Unfortunately, for many years, reports of palladium-catalyzed coupling reactions of aryl chlorides were relatively rare.[1] This situation has changed rapidly in the past few years. For example, in the case of the Heck reaction,[2] noteworthy advances in the use of aryl chlorides have been described by Milstein,[3] Herrmann,[4] Reetz,[5] and Beller,[6] although, with the exception of an example by Milstein,[3b] highly electron-rich or hindered aryl chlorides have not proved to be synthetically useful substrates.[7,8]

Table 1. Effect of the Solvent on the Rate of the Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$-Catalyzed Heck Coupling of Chlorobenzene and Methyl Acrylate



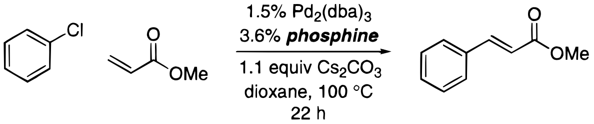
entry	solvent	% yield (GC)
1	CH$_3$CN	14
2	*N*-methylpyrrolidine	14
3	*N*,*N*-dimethylacetamide	16
4	DMF	19
5	toluene	27
6	THF	30
7	dioxane	39

Recent work by us and by others has established that certain palladium-catalyzed coupling reactions of aryl chlorides can be accomplished quite efficiently in the presence of sterically hindered, electron-rich phosphines (e.g., P(*t*-Bu)$_3$).[9,10] Perhaps the simplest explanation for this enhanced reactivity is that oxidative addition of an aryl chloride is more facile with a more electron-rich palladium complex; however, in at least some instances, the true explanation is probably not so straightforward.[11] To the best of our knowledge, the possibility that the Heck reaction might also be susceptible to this P(*t*-Bu)$_3$ effect has not been investigated. In this paper, we establish that in the presence of P(*t*-Bu)$_3$ the Heck reaction can indeed be achieved with good efficiency (eq 1).

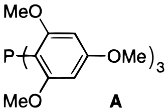


(1)

We have determined that P(*t*-Bu)$_3$ is an unusually effective ligand for the Pd$_2$(dba)$_3$-catalyzed coupling of chlorobenzene with methyl acrylate (eq 2; dba = dibenzylideneacetone). Not only triarylphosphines, but also other trialkylphosphines (even PCy$_3$), appear to be completely ineffective ligands for this process. Especially noteworthy is the fact that we observe essentially no coupling in the presence of phosphine **A** (eq 2), which has steric and electronic properties that are quite similar to P(*t*-Bu)$_3$ (cone angles: P(*t*-Bu)$_3$, 182°; **A**, 184°) (pK_a of conjugate acid: P(*t*-Bu)$_3$, 11.40; **A**, 11.02).[12]



(2)



A

	% yield (GC)
P(*t*-Bu)$_3$	***56%***
PPh$_3$, P(*o*-tol)$_3$, BINAP, dppf, **A**	*<2%*
P(*n*-Bu)$_3$, Cy$_2$P(CH$_2$)$_2$PCy$_2$, PCy$_3$	*<2%*
no phosphine	*<2%*

The rate of the coupling reaction is solvent-dependent, with dioxane being the solvent of choice, although THF and toluene are also suitable (Table 1). Cs$_2$CO$_3$ and K$_3$PO$_4$ are the bases of choice among those that we have surveyed

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(1) The low reactivity of aryl chlorides in cross-coupling reactions is generally ascribed to their reluctance to oxidatively add to Pd(0). For a discussion, see: Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062.

(2) For reviews of the Heck reaction, see: (a) Bräse, S.; de Meijere, A. In *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; Chapter 3. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7. (c) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411. (d) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, Chapter 4.3.

(3) (a) Chlorobenzene and electron-poor aryl chlorides (150 °C): Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995−1996. (b) Chloroanisole, chlorobenzene, and electron-poor aryl chlorides (140 °C): Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734−4735. (c) Portnoy, M.; Ben-David, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465−3479.

(4) (a) 4-Chlorobenzaldehyde (150 °C): Herrmann, W. A.; Brossmer, C.; Ofele, K.; Beller, M.; Fischer, H. *J. Mol. Catal. A* **1995**, *103*, 133−146. (b) Electron-poor aryl chlorides (130 °C): Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844−1848. Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Reirmeier, T. H.; Ofele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357−1364. (c) Electron-poor aryl chlorides (130 °C): Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371−2374.

(5) Chlorotoluene, chlorobenzene, and chlorobenzaldehyde (150 °C): Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 481−483.

(6) Electron-poor aryl chlorides (140−160 °C): Beller, M.; Zapf, A. *Synlett* **1998**, 792−793.

(7) For an overview of Heck couplings of aryl chlorides, see: Riermeier, T. H.; Zapf, A.; Beller, M. *Top. Catal.* **1997**, *4*, 301−309.

(8) Electron-poor aryl halides oxidatively add to Pd(0) more readily than do the corresponding electron-rich aryl halides. For a discussion, see refs 1 and 2.

(9) Suzuki cross-coupling: Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.*, in press.

(10) For example, see: (a) Carbonylation: Huser, M.; Youinou, M.-T.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1386−1388. Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742−8744. (b) Dechlorination: Ben-David, Y.; Gozin, M.; Portnoy, M.; Milstein, D. *J. Mol. Catal.* **1992**, *73*, 173−180. (c) Cross-coupling with vinylsilanes and arylsilanes: Gouda, K.-i.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232−7233. (d) Suzuki cross-coupling: Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575−5578. Firooznia, F.; Gude, C.; Chan, K.; Satoh, Y. *Tetrahedron Lett.* **1998**, *39*, 3985−3988. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (e) Amination: Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807−4810. Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620. Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723.

(11) For example, see: (a) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1655−1664. Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665−1673. Reference 3. (b) Reference 4a. (c) Beller has shown that Heck reactions of electron-poor aryl chlorides can be effected with electron-poor phosphites as ligands: Reference 6.

(12) Wada, M.; Higashizaki, S. *J. Chem. Soc., Chem. Commun.* **1984**, 482−483. For an extensive compilation of cone angles and pK_a data for phosphines, see: Rahman, M. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1−7.

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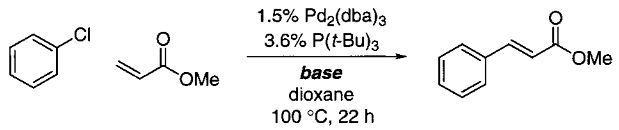
Table 2. Effect of the Base on the Rate of the $Pd_2(dba)_3$/$P(t\text{-}Bu)_3$-Catalyzed Heck Coupling of Chlorobenzene and Methyl Acrylate

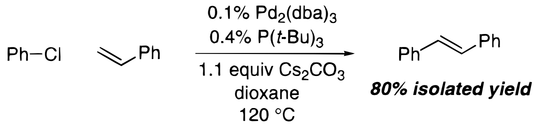


entry	base	% yield (GC)
1	none	5
2	K_2CO_3	9
3	NaOAc	21
4	NEt_3	37
5	K_3PO_4	50
6	Cs_2CO_3	56

(Table 2). Finally, we have found that use of 2.0 equiv, rather than 1.2, of $P(t\text{-}Bu)_3$ per palladium leads to a longer lifetime for the catalyst.

Under our optimized conditions (1.5% $Pd_2(dba)_3$, 6% $P(t\text{-}Bu)_3$, 1.1 equiv of Cs_2CO_3, dioxane, 100−120 °C), we can effect the Heck reaction of a wide array of aryl chlorides with methyl acrylate and styrene in good yield (Table 3).[13,14] Thus, chlorobenzene and *p*-chloroanisole couple efficiently with methyl acrylate to selectively generate the trans olefin product (entries 1 and 2; one isomer by ^1H NMR). We have also established that a range of electronically diverse aryl chlorides react with styrene to form stilbene derivatives with high stereoselection (entries 3−5; ≥25:1 trans/cis by ^1H NMR). Furthermore, even sterically hindered *o*-chlorotoluene couples in good yield (entry 6), although a longer reaction time is required.

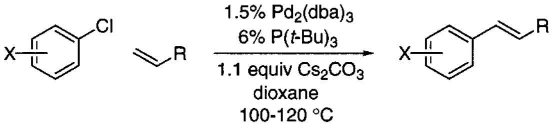
We have begun to investigate the maximum number of turnovers that is possible with this system. In preliminary experiments, we have found that with a catalyst loading of 0.1% $Pd_2(dba)_3$, we obtain an 80% yield for the coupling of chlorobenzene and styrene (120 h at 120 °C; turnover number ~400) (eq 3).

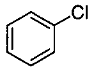
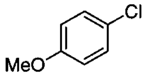
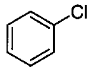
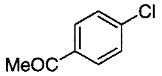
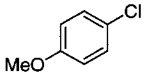
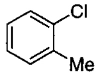


(3)

In summary, we have developed a useful new catalyst system for the Heck coupling of aryl chlorides (1.5% $Pd_2(dba)_3$, 6% $P(t\text{-}Bu)_3$, 1.1 equiv of Cs_2CO_3, dioxane, 100−120 °C). The choice of ligand appears to be critical for activity, and $P(t\text{-}Bu)_3$ is uniquely effective among the phosphines that we have examined. Under our reaction conditions, which employ only commercially available reagents, we can accomplish the Heck reaction of an array of substrates, including sterically hindered and electron-rich aryl chlorides. In terms of both scope and reaction temperature, this catalyst system compares quite favorably with those previously reported.

Table 3. Scope of the $Pd_2(dba)_3$/$P(t\text{-}Bu)_3$-Catalyzed Heck Coupling of Aryl Chlorides



Entry	Aryl Chloride	R	Temp/Time	Isolated Yield[a,b]
1		CO_2Me	100 °C/42 h	76%
2		CO_2Me	120 °C/24 h	82%
3		Ph	120 °C/21 h	83%
4		Ph	100 °C/37 h	74%
5		Ph	120 °C/30 h	84%
6		Ph	120 °C/114 h	70%

[a] Average of two runs. [b] Only the trans product was detected by ^1H NMR, except for entry 6, which was a ~15:1 trans:cis mixture.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H NMR spectra (9 pages).

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[13] Sample experimental data (Table 1, entry 1): Under an atmosphere of argon, a solution of chlorobenzene (104 mg, 0.924 mmol; in 0.5 mL of dioxane) and a solution of $P(t\text{-}Bu)_3$ (11.2 mg, 0.055 mmol; in 0.42 mL of dioxane) were added in turn to a Schlenk tube charged with $Pd_2(dba)_3$ (12.5 mg, 0.014 mmol), Cs_2CO_3 (330 mg, 1.01 mmol), and a magnetic stir bar. Methyl acrylate (158 mg, 1.83 mmol) was then added by syringe, and the Schlenk tube was sealed and placed in a 100 °C oil bath and stirred for 42 h. The reaction mixture was then cooled to room temperature, diluted with Et_2O, filtered through a pad of Celite, concentrated, and purified by flash chromatography (5% EtOAc/hexane), which yielded 118 mg (79%) of methyl cinnamate.

[14] (a) Use of $Pd(OAc)_2$ leads to a slower reaction. (b) With 2.0 equiv of $P(t\text{-}Bu)_3$ per palladium, Cs_2CO_3, K_3PO_4, and NEt_3 display comparable effectiveness as bases.