Efficient Heck Vinylation of Aryl Halides Catalyzed by a New Air-Stable Palladium-Tetraphosphine Complex

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The Heck reaction is one of the most widely used palladium-catalyzed methodologies in organic synthesis. Several ligands such as phosphines, phosphites, carbenes, or thioethers have been successfully employed for this reaction.¹⁻³ In the phosphine ligand series, some interesting results have been described with very simple phosphine ligands such as PPh₃ or dppe which largely compete with palladacycles.^{4,5} For example, Herrmann et al. have reported recently that the system Pd(OAc)₂/ PPh₃ is extremely efficient for the reaction of activated aryl bromides with *n*-butyl acrylate (turnover number (TON): 1 000 000).^{6,7} However, to the best of our knowledge, the efficiency of tetraphosphines for Heck reaction has not yet been demonstrated. In this paper we wish to report on the efficiency of a new tetraphosphine ligand for the Heck reaction.

The nature of the phosphine ligand on complexes has a tremendous influence on the stability of the catalysts and on the rate of catalyzed reactions. To find more stable and more efficient palladium catalysts, we have prepared

(2) For a review on palladacycles in Heck reactions, see: Herrmann,
W. A.; Böhm, V.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23.
(3) For recent examples of Heck reactions catalyzed by palladacycles,

see: (a) Albisson, D.; Bedford, R.; Scully, P. N. *Tetrahedron Lett.* **1998**, *39*, 9793. (b) Littke, A.; Fu, G. *J. Org. Chem.* **1999**, *64*, 10. (c) Miyazaki, F.; Yamaguchi, K.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 7379. (d) Okf A. Okf A. Difference and Complexity of the second seco (d) Ohff, M.; Ohff, A.; Milstein, D. Chem. Commun. 1999, 357. (e) Brunel, J.-M.; Hirlemann, M.-H.; Heumann, A.; Buono, G. *Chem. Commun.* **2000**, 1869. (f) Gai, X.; Grigg, R.; Ramzan, I.; Sridharan, V.; Collard, S.; Muir, J. *Chem. Commun.* **2000**, 2053. (g) Brunel, J.-M.; Heumann, A.; Buono, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1946. (h) Gruber, A.; Zim, D.; Ebeling, G.; Monteiro, A.; Dupont, J. *Org. Lett.* 2000, 2, 1287

(4) (a) Cabri, W.; Candiani, I.; Bedeschi, A. J. Org. Chem. 1992, 57, 3558.
(b) Heck, R. F. Acc. Chem. Res. 1979, 12, 146.
(5) Qadir, M.; Möchel, T.; Hii (Mimi), K. K. Tetrahedron 2000, 56,

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Figure 1. Tedicyp (1).

Scheme 1



the new tetrapodal⁸ phosphine ligand, *cis,cis,cis*-1,2,3,4tetrakis(diphenylphosphinomethyl)cyclopentane or Tedicyp (1) (Figure 1)⁹ in which the four diphenylphosphinoalkyl groups are stereospecifically bound to the same face of the cyclopentane ring, in several catalyzed reactions. We have reported recently the first results obtained in allylic substitution^{9,10} and in Suzuki crosscoupling¹¹ using **1** as ligand. For example, a TON of 9 800 000 for the addition of dimethyl sodiummalonate to allyl acetate had been observed.9

In this paper, we wish to describe the results obtained for the catalyzed Heck vinylation of aryl halides using our tetraphosphine 1 as ligand. First, to compare 1 with other classical ligands, several experiments have been performed using identical conditions in the presence of PPh₃, P(o-tolyl)₃, and dppe. This comparison has been carried out with one of the less reactive aryl bromides: 4-bromoanisole (2) (Scheme 1, Table 1). Herrmann et al. had obtained low TON's with this substrate (<100) in the presence of palladacycles or with the system Pd(OAc)₂/P(o-tolyl)₃.⁶ We observed a similar tendency when $[PdCl(C_3H_5)]_2$ was used as catalyst precursor (Scheme 1, Table 1). In the presence of 0.1 mol % of this complex and without added ligand, only 2% conversion was observed. When PPh₃ or P(o-tolyl)₃ was used as the ligand, slightly higher conversions and TON's of 270 and 150 were observed, respectively. In the presence of the diphosphine dppe much better results were obtained (TON 3800). Finally in the presence of **1** a TON of 82 000 has been obtained in the presence of 0.001 mol % of catalyst. The complex formed by association of Tedicyp (1) and $[PdCl(C_2H_5)]_2$ seems to be more stable and less sensitive to temperature and poisoning than the com-

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⁽¹⁾ For reviews on the palladium-catalyzed Heck reaction, see: (a) Heck, R. F. *Palladium Reagents in Organic Syntheses*, Katritzky, A. R., Meth-Cohn O., Rees, C. W., Eds.; Academic Press: London, 1985; p 2. (b) Heck, R. F. Vinyl Substitution with Organopalladium Intermediates. In *Comprehensive Organic Synthesis*, Vol. 4; Trost B. M., Fleming I., Eds.; Pergamon: Oxford, 1991. (c) Malleron, J.-L.; Fiaud, J.-C.; Legros, J.-Y. Handbook of Palladium-Catalyzed Organic Reactions; Academic Press: London, 1997. (d) Reetz, M. T. Transition Metal Catalyzed Reactions; Davies, S. G., Murahashi, S.-I., Eds.; Blackwell Sci.: Oxford, 1999. (e) Beletskaya, I.; Cheprakov, A. Chem. Rev. 2000, 100. 3009.

^{(6) (}a) Herrmann, W. A.; Brossmer, C.; Reisinger, C.; Riermeier, T.; Öfele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357. (b) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.; Riermeier, T.; Beller, M.; Fisher, H. Angew. Chem., Int. Ed. Engl. 1995, 34, 1844.

⁽⁷⁾ For examples on the influence of ammonium salts, see: (a) Jeffery, T. Tetrahedron 1996, 52, 10113. (b) Jeffery, T. Tetrahedron Lett. 1985, 26, 2667. (c) Jeffery, T. Chem. Commun. 1984, 1287.

⁽⁸⁾ For a review on the preparation of polypodal diphenylphosphine ligands, see: Laurenti, D.; Santelli, M. *Org. Prep. Proc. Int.* **1999**, *31*, 245

⁽⁹⁾ Laurenti, D.; Feuerstein, M.; Pèpe, G.; Doucet, H.; Santelli, M. J. Org. Chem. 2001, 66, 1633.

⁽¹⁰⁾ Feuerstein, M.; Laurenti, D.; Doucet, H.; Santelli, M. Chem. Commun. 2001. 43.

⁽¹¹⁾ Feuerstein, M.; Laurenti, D.; Bougeant C.; Doucet, H.; Santelli, M. Chem. Commun. 2001, 325.

Table 1.Palladium-Catalyzed Heck Reaction of4-Bromoanisole 2 with Butyl Acrylate 19^a

ligand	substrate–catalyst ratio	turnover frequencies $(h^{-1})^b$	turnover numbers	yield of 20 (%) ^c
no ligand	1 000	1	20	2
PPh_3	1 000	13	270	27
$P(o-tolyl)_3$	1 000	7	150	15
dppe	1 000	49	980	98
dppe	10 000	125	3 800	38^d
1	10 000	390	9 700	97^d
1	100 000	2 100	82 000	82^{e}
1	1 000 000	2 900	240 000	$24^{f,g}$

^{*a*}Conditions: catalyst: $[Pd(C_3H_5)Cl]_2$ /ligand 1/2, 4-bromoanisole (2) (10 mmol), butyl acrylate (19) (20 mmol), K₂CO₃ (20 mmol), DMF, 130 °C, 20 h, under argon. ^{*b*} TOF calculated between initial time and 20 h. ^{*c*} GC yields. ^{*d*} 40 h. ^{*e*} 72 h. ^{*f*} 96 h. ^{*g*} Addition of cetyltrimethylammonium bromide (1 mmol).

 Table 2. Heck Olefination of Aryl Halides with 19 Using

 1 as Ligand^a

				turnover	
aryl		substrate-catalyst		frequencies	yield
halide	<i>T</i> (h)	ratio	product	$(h^{-1})^{b}$	(%) ^c
3	20	100 000	21		99
3	72	1 000 000	21	19 000	46
4	20	1 000 000	22	48 500	97
4	20	1 000 000	22	49 000	98 ^e
4	72	10 000 000	22	42 000	25
5	16	100 000	23	6 250	100
5	20	1 000 000	23	22 000	44
6	48	100 000	24	3 100	59
7	20	100 000	25	5 000	100
7	20	100 000	25	5 000	100 ^e
7	20	1 000 000	25	6 000	12
8	72	100 000	26	1 900	81
9	72	10 000	27	155	95
9	96	100 000	27	1 100	87^d
10	20	100 000 000	28	5 000 000	100
10	40	100 000 000	28	1 625 000	78 ^e
10	72	1 000 000 000	28	3 800 000	21
11	20	1 000	29	26	52
12	20	1 000	30	37	75
13	20	1 000	31	22	44
14	72	10 000	32		91
14	20	100 000	32	2 1 5 0	43
15	48	100 000	33	4 400	96
16	20	1 000 000	34	19 000	38^{e}
16	48	1 000 000	34	27 500	96
17	20	10 000	35	170	34
18	20	1 000 000	27	50 000	100 ^e
18	20	100 000 000	27	4 950 000	99

^{*a*} Conditions: catalyst: $[Pd(C_3H_5)Cl]_2/ligand 1/2$, aryl bromide (10 mmol), butyl acrylate (**19**) (20 mmol), K₂CO₃ (20 mmol), DMF, 130 °C, under argon. ^{*b*} TOF calculated between initial time and 20 h. ^{*c*} GC or NMR yields. ^{*d*} Addition of cetyltrimethylammonium bromide (1 mmol). ^{*e*} Reactions performed in air.

plexes formed with classical mono- or diphosphines. In general, no deposition of palladium is observed during the reaction. Moreover, these reactions have been performed without addition of tetraalkylammonium salts which are generally used to avoid precipitation of the palladium. In the presence of 10 mol % of cetyltrimethylammonium bromide, an even higher activity has been observed (TON: 240 000).

These results prompted us to investigate the vinylation of other aryl bromides (Scheme 1, Table 2). A high activity has been observed for activated aryl bromides such as **3** to **7**. TON's as high as 59 000–2 500 000 have been achieved with these substrates. With 3,5-bistrifluoromethylbromobenzene (**10**), a very high reactivity has been observed. With this substrate, a TOF of 5 000 000 h^{-1} and a TON of 210 000 000 have been obtained. With nonactivated bromobenzene **9**, a reasonable TON (87 000) was observed. When we used *ortho*-substituted aryl bromides such as 2-fluorobromobenzene (**11**) or 2-methylbromobenzene (**12**), lower TON's were obtained. We noticed a similar decelerating effect with 2,4-dimethoxybromobenzene (**13**). Finally, heteroaromatic substrates such as 3-bromopyridine (**15**) or 3-bromoquinoline (**16**) led to TON's of 96 000 and 960 000, respectively. A lower TON was obtained in the course of the vinylation of 3-bromothiophene (**17**).

These results indicate that, as expected, both the electronic factors and the steric hindrance of the aryl bromides are important factors for the rate of this reaction. An electron-withdrawing substituent generally increases the TOF of the reaction, and lower reaction rates are observed in the presence of bulky substrates. Nevertheless, reasonable TOF's are observed even with electron-donating substituents on the aryl bromide in the presence of this catalyst. The catalytically active species with the ligand **1** appears to be much less sensitive to electronic factors than most of the catalysts which have been used so far for this reaction. These results suggests that, in the presence of this catalyst, the rate-determining step of the reaction is the insertion of the olefin into the aryl-palladium intermediate rather than the oxidative addition of the aryl bromide.

Since $Pd(OAc)_2$ alone is an active catalyst for Heck reactions when aryl iodides are used, we did not focus our attention on these substrates. Nevertheless, we checked that **1** is also active for the coupling of **19** to iodobenzene **18**. In the presence of 0.000001 mol % of catalyst, 99% conversion was observed after 20 h. On the other hand, reactions using aryl chlorides as substrates led to very slow reactions rates. For example, with 4-nitrochlorobenzene conversion was only 32% in the presence of 0.2% catalyst.

Next we performed some reactions in air¹² and surprisingly we observed that the catalyst retains activity even under air. Substrates **4**, **7**, and **18** led to TON's of 980 000, 100 000 and 1 000 000, respectively. Moreover, aryl bromide **10** led to a TON of 78 000 000. However, the catalyst solution is not totally air-stable, and after several hours some decomposition is observed.

In conclusion, the Tedicyp-palladium complex obtained by addition of Tedicyp to [Pd(C₃H₅)Cl]₂ provides a convenient catalyst for the Heck vinylation of aryl halides. This catalyst seems to be more stable and less sensitive to poisoning than the complexes formed with mono- and diphosphine ligands and appears to be more efficient than most of the palladacyles. This stability probably comes from the presence of the four diphenylphosphinoalkyl groups stereospecifically bound to the same face of the cyclopentane ring. All four phosphines probably cannot bind at the same time to the same palladium center, but the presence of these four phosphines on the ligand close to the metal center along with steric factors seem to increase the coordination of the ligand to the palladium complex. In the presence of this catalyst, the Heck vinylation of aryl bromides can be performed with as little as 0.000001 mol % of catalyst.

⁽¹²⁾ For examples of Heck reactions performed in air, see: (a) Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. J. Am. Chem. Soc. **1997**, 119, 11687. (b) Bergbreiter, D.; Osburn, P.; Liu, Y.-S. J. Am. Chem. Soc. **1999**, 121, 9531. (c) Peris, E.; Loch, J.; Mata, J.; Crabtree, R. Chem. Commun. **2001**, 201.

So we believe that this catalyst is among the most active and stable ones reported so far.

Experimental Section

General. All reactions under argon were run using vacuum lines in Schlenk tubes in oven-dried glassware. To avoid contamination with palladium residues, the reactions were performed in brand new Pyrex tubes for chromatography inserted in Schlenk tubes with new stirring bars; dry DMF was added in the Schlenk tube for the transmission of the temperature of the oil bath to the Pyrex tubes. Reactions in air were performed in brand new Pyrex tubes for chromatography with new stirring bars. DMF analytical grade (99.8%) and butyl acrylate (99+) were not distilled before use. Some of the aryl halides were distilled before use. Potassium carbonate (99+) was used without drying. The reactions were followed by GC and NMR for high boiling point substrates and by GC for low boiling point substrates. ¹H (400 or 300 MHz) spectra were recorded in CDCl₃ solutions. Chemical shift (δ) are reported in ppm relative to CDCl₃. Flash chromatography was performed on silica gel (230-400 mesh).

Preparation of the Pd–Tedicyp Catalyst. An over-dried 40-mL Schlenk tube equipped with a magnetic stirring bar under an argon atmosphere was charged with $[Pd(\eta^3-C_3H_5)Cl]_2$ (30 mg, 81 μ mol) and Tedicyp (140 mg, 162 μ mol). Anhydrous THF (10 mL) was added, the solution was stirred at room temperature for 10 min, and the THF was evaporated. The appropriate

catalyst concentration was obtained by successive dilution with an hydrous DMF. ³¹P NMR (162 MHz, CDCl₃) δ 25 (w = 80 Hz), 19.4 (w = 110 Hz).

(*E*)-3-(4-methoxyphenyl)acrylic Acid Butyl Ester (20).¹³ The reaction of bromoanisole **2** (1.87 g, 10 mmol), K₂CO₃ (2.76 g, 20 mmol), and butyl acrylate **19** (2.56 g, 20 mmol) at 130 °C during 40 h in anhydrous DMF (10 mL) in the presence of the Tedicyp– palladium complex (0.001 mmol) under argon affords the corresponding coupling product 20 after extraction with dichloromethane, separation, drying (MgSO₄), evaporation, and filtration on silica gel (diethyl ether/pentane: 1/2) in 96% (2.25 g) isolated yield. ¹H NMR (300 MHz, CDCl₃): δ = 7.55 (d, *J* = 16.0 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.21 (d, *J* = 6.8, 6.8 Hz, 2H), 1.33 (qt, *J* = 7.3, 6.8 Hz, 2H), 0.87 (q, *J* = 7.3 Hz, 3H).

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Supporting Information Available: Experimental procedures, ¹H NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹³⁾ Stephan, M. S.; Teunissen, A. J. J. M.; Verzijl, G. K. M.; de Vries, J. G. Angew. Chem., Int. Ed. **1998**, *37*, 662–690.