



A new efficient tetraphosphine/palladium catalyst for the Heck reaction of aryl halides with styrene or vinyl ether derivatives

Marie Feuerstein, Henri Doucet* and Maurice Santelli*

Laboratoire de Synthèse Organique associé au CNRS, Faculté des Sciences de Saint Jérôme,
Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

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Abstract—*cis,cis,cis*-1,2,3,4-Tetrakis(diphenylphosphinomethyl)cyclopentane/[PdCl(C₃H₅)₂] system efficiently catalyses the Heck reaction of aryl halides with styrene and vinyl ether derivatives. High turnover numbers can be obtained for the reaction of several aryl halides with styrene and styrene derivatives. Lower turnover numbers have been observed in the presence of vinyl ethers. © 2002 Elsevier Science Ltd. All rights reserved.

The Heck reaction is one of the most widely used palladium-catalysed methodologies in organic synthesis.¹ The efficiency of several catalysts for the reaction of aryl halides with acrylates has been studied in detail.² On the other hand, the reaction in the presence of styrene and especially vinyl ether derivatives has attracted less attention.^{3–5} A few ligands have been successfully employed for the reaction in the presence of these substrates. The most popular ones are triphenylphosphine, tri-*ortho*-tolylphosphine or 1,3-bis(diphenylphosphino)propane. Even if the catalysts formed by association of these ligands with palladium complexes are quite efficient in terms of yield of adduct, the efficiency in terms of ratio substrate/catalyst is quite low. In general, fast decomposition of the catalysts occurs, and 1–10% of these catalysts must be used. In recent years, some more robust catalysts have been tested with these substrates.² For example, Herrmann, Beller et al. have reported that the palladacycle [Pd(*o*-tol)(OAc)]₂ is very efficient for the reaction of 4-bromoacetophenone with styrene.³ A cyclopalladated imine complex and an *ortho*-palladated phosphite complex also led to high turnover numbers.^{4d,4e} Recently, Fu et al. described that the ligand P(*t*-Bu)₃ is also an efficient catalyst for the reaction of aryl chlorides with styrene even at room temperature.^{4h} The phosphine-free complex PdCl₂(SEt₂)₂ also led to high TONs even when the reaction was performed in air.⁴ⁱ A few other ligands also led to efficient catalysts.⁴ If mono- or diphosphine

ligands have been successfully used for this reaction, to the best of our knowledge, the efficiency of tetraphosphine ligands has not been demonstrated.

The nature of phosphine ligands on complexes has an important influence on the rate of catalysed reactions. In order to obtain highly stable palladium catalysts, we have prepared the new tetraphosphine ligand,⁶ *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane or tedicyp^{7a} (Fig. 1) in which four diphenylphosphino groups are stereospecifically bound to the same face of a cyclopentane ring. The presence of these four phosphines close to the metal centre seems to increase the coordination of the ligand to the metal and therefore increase the stability of the catalyst. We have reported recently the first results obtained in allylic substitution,⁷ for Suzuki cross-coupling⁸ and for Heck reaction using tedicyp as the ligand.⁹ Herein, we wish to report on the Heck reaction in the presence of aryl halides and styrene or vinyl ether derivatives using tedicyp as the ligand.

For this study, based on our previous results,⁹ DMF was chosen as the solvent and potassium carbonate as the base. The reactions were performed at 140°C in the presence of a 1/2 ratio of [Pd(C₃H₅)Cl]₂/tedicyp as catalyst. First, we tried to evaluate the reactivity of

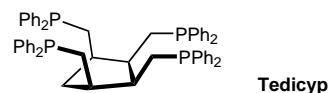


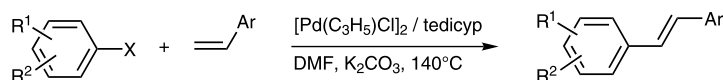
Figure 1.

* Corresponding authors. Tel.: 00-33-4-91-28-84-16; fax: 00-33-4-91-98-38-65 (H.D.); tel.: 00-33-4-91-28-88-25 (M.S.); e-mail: henri.doucet@univ-u-3mrs.fr; m.santelli@univ-u-3mrs.fr

styrene and styrene derivatives (Scheme 1, Table 1). Surprisingly, we observed no significant electronic effect of the *para*-substituents on the aryl bromide on the rate of the reaction. For example when a ratio substrate/catalyst of 1000 000 was used in the presence of the deactivated bromoanisole or in the presence of the activated 4-bromobenzophenone, conversions of 21 and 58% were obtained, respectively (entries 4 and 15). We also obtained similar reaction rates with 4-fluorobromobenzene, 4-nitrobromobenzene or 3,5-bistrifluoromethylbromobenzene (entries 8, 11 and 18). Moreover, the reaction performed with iodobenzene or bromobenzene also led to similar reaction rates (entries 1 and 5). On the other hand, in the presence of sterically hindered aryl bromides, lower TONs were obtained (entries 21 and 22). Next we studied the influence of the

substituents on styrene on the rate of the reaction. Activated or deactivated styrene derivatives led to similar reaction rates (entries 23–27). In the presence of *ortho*-substituted styrene derivatives, a significant steric effect was observed. For example, the reaction using 9-vinylanthracene with 4-trifluoromethylbromobenzene led to a TON of 325 (entry 28).

Several reactions were also performed in air^{9a} and we observed that in all cases the catalyst retains activity (Table 1, entries 3, 7–9, 14–16 and 18). In air, TONs of 95 000 and 400 000 can be obtained with substrates such as 4-bromo-*N,N*-dimethylaniline or 4-bromobenzophenone. In order to confirm the respective reaction rates of styrene derivatives, we also performed competitive reactions using an equimolar mixture of styrene



Scheme 1.

Table 1. Heck reaction with styrene derivatives catalysed by tedicyp–palladium complex (Scheme 1)¹⁰

Entry	Aryl halide	Styrene derivative	Ratio substrate/catalyst	Yield (%) ^{a,c}
1	Iodobenzene	Styrene	100 000	52 ^b
2	Iodobenzene	Styrene	1 000 000	11
3	4-Bromoanisole	Styrene	100 000	82 ^b (80)
4	4-Bromoanisole	Styrene	1 000 000	21
5	Bromobenzene	Styrene	100 000	87 ^b
6	Bromobenzene	Styrene	1 000 000	7
7	4-Fluorobromobenzene	Styrene	100 000	75 ^b (99)
8	4-Fluorobromobenzene	Styrene	1 000 000	(54)
9	4-Bromo- <i>N,N</i> -dimethylaniline	Styrene	100 000	(95) ^b
10	4-Bromo- <i>N,N</i> -dimethylaniline	Styrene	1 000 000	28
11	4-Nitrobromobenzene	Styrene	100 000	75 ^b
13	4-Bromobenzophenone	Styrene	10 000	100 ^d
14	4-Bromobenzophenone	Styrene	100 000	92 ^b (95)
15	4-Bromobenzophenone	Styrene	1 000 000	58 (40)
16	4-Trifluoromethylbromobenzene	Styrene	100 000	95 ^b (99)
17	4-Trifluoromethylbromobenzene	Styrene	1 000 000	14
18	3,5-Bistrifluoromethylbromobenzene	Styrene	100 000	66 (47) ^b
19	2-Bromoanisole	Styrene	10 000	70 ^b
20	2-Bromofluorobenzene	Styrene	10 000	89 ^b
21	9-Bromoanthracene	Styrene	1000	65 ^b
22	2,4,6-Triisopropylbromobenzene	Styrene	1000	20 ^b
23	4-Trifluoromethylbromobenzene	3,5-Bistrifluoromethylstyrene	100 000	88 ^b
24	4-Trifluoromethylbromobenzene	3,5-Bistrifluoromethylstyrene	1 000 000	56
25	4-Bromoanisole	4-Methoxystyrene	100 000	51 ^b
26	4-Trifluoromethylbromobenzene	4-Methoxystyrene	100 000	100
27	4-Trifluoromethylbromobenzene	4-Methoxystyrene	1 000 000	56
28	4-Trifluoromethylbromobenzene	9-Vinylanthracene	500	65 ^b
30	4-Trifluoromethylbromobenzene	2,4,6-Trimethylstyrene	1000	82
31	4-Bromobenzophenone	2,4,6-Trimethylstyrene	1000	75 ^{b,c}
32	4-Bromobenzophenone	4-Vinylpyridine	1000	100
33	4-Bromobenzophenone	4-Vinylpyridine	10 000	68

Conditions: catalyst [Pd(C₃H₅)Cl]₂/tedicyp 1/2 see: Ref. 7a, ArX (1 equiv.), styrene derivative (2 equiv.), K₂CO₃ (2 equiv.), DMF, 140°C, 24 h, under argon, *E* isomer was obtained selectively in all cases (>95%).

^a GC or NMR yields.

^b Isolated yields.

^c Yields in parentheses correspond to reactions performed in air.

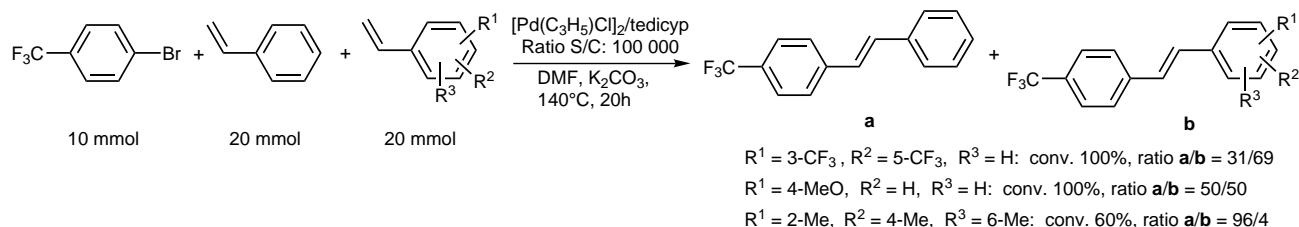
^d Reaction time: 1 h.

^e Ratio of regioisomers *E*-1,2-diarylethene/1,1-diarylethene was 55/45.

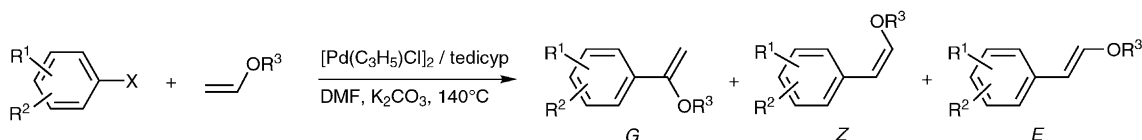
and styrene derivatives (Scheme 2). A minor electronic effect and an important steric effect on the rate on the reaction were confirmed.

Next, we tried to determine the efficiency of the Pd/tedicyc catalyst in the presence of vinyl ether derivatives. First, we studied the reaction in the presence of *n*-butylvinylether. With this vinyl derivative, we observed a very important electronic effect of the aryl bromide on the rate of the reaction. With deactivated

bromoanisole a very low TON of 25 was obtained (Table 2, entry 3; Scheme 3). On the other hand, with activated aryl bromides such as 4-bromobenzaldehyde, 4-bromobenzophenone or 3,5-bistrifluoromethyl bromobenzene TONs of 8500–42 000 were obtained (entries 4–10). In the presence of iodobenzene a high TON was also observed (entries 1 and 2). With *ortho*-substituted aryl bromides lower reaction rates were observed (entries 11–15). In all cases mixtures of linear and branched products were obtained. The regioselect-



Scheme 2.



Scheme 3.

Table 2. Heck reaction with vinyl ether derivatives catalysed by tedicyc–palladium complex (Scheme 3).¹⁰

Entry	Aryl bromide	Vinylether	Ratio substrate/catalyst	Selectivity G/Z/E	Yield (%)
1	Iodobenzene	<i>n</i> -Butylvinylether	10 000	53/19/28	89
2	Iodobenzene	<i>n</i> -Butylvinylether	100 000	49/23/28	66 ^a
3	4-Bromoanisole	<i>n</i> -Butylvinylether	100	66/10/24	25
4	4-Bromobenzaldehyde	<i>n</i> -Butylvinylether	10 000	14/32/54	90
5	4-Bromobenzophenone	<i>n</i> -Butylvinylether	10 000	23/28/49	100 ^a
6	4-Bromobenzophenone	<i>n</i> -Butylvinylether	100 000	22/29/49	42
7	4-Bromobenzonitrile	<i>n</i> -Butylvinylether	10 000	20/33/47	88
8	4-Trifluoromethylbromobenzene	<i>n</i> -Butylvinylether	1000	25/25/50	99 ^a
9	4-Trifluoromethylbromobenzene	<i>n</i> -Butylvinylether	10 000	29/29/42	45
10	3,5-Bistrifluoromethylbromobenzene	<i>n</i> -Butylvinylether	10 000	29/41/30	85
11	2-Bromotoluene	<i>n</i> -Butylvinylether	1000	46/17/37	83
12	2-Bromobenzaldehyde	<i>n</i> -Butylvinylether	1000	23/27/50	73
13	2-Bromobenzonitrile	<i>n</i> -Butylvinylether	1000	28/30/42	61
14	2-Trifluoromethylbromobenzene	<i>n</i> -Butylvinylether	1000	28/21/51	26
15	9-Bromoanthracene	<i>n</i> -Butylvinylether	1000	60/18/22	45
16	Iodobenzene	Cyclohexylvinylether	10 000	25/52/23	100 ^a
17	Iodobenzene	Cyclohexylvinylether	100 000	42/41/17	58
18	4-Bromoanisole	Cyclohexylvinylether	200	48/15/37	68
19	4-Bromobenzophenone	Cyclohexylvinylether	100 000	6/36/58	60
20	4-Bromobenzaldehyde	Cyclohexylvinylether	10 000	9/32/59	100 ^a
21	4-Bromobenzaldehyde	Cyclohexylvinylether	100 000	8/30/62	61
22	Iodobenzene	<i>t</i> -Butylvinylether	1000	33/54/13	78
23	4-Trifluoromethylbromobenzene	<i>t</i> -Butylvinylether	1000	14/34/52	90
24	4-Bromobenzophenone	<i>t</i> -Butylvinylether	10 000	4/49/47	52
25	4-Bromobenzaldehyde	<i>t</i> -Butylvinylether	1000	8/34/58	100 ^a
26	4-Bromobenzaldehyde	<i>t</i> -Butylvinylether	10 000	7/34/59	22
27	4-Bromoacetophenone	<i>t</i> -Butylvinylether	1000	1/49/50	100 ^a
28	3,5-Bistrifluoromethylbromobenzene	<i>t</i> -Butylvinylether	1000	14/52/34	88

Conditions: catalyst [Pd(C₃H₅)Cl]₂/tedicyc 1/2, see: Ref. 7a, ArX (1 equiv.), vinyl ether (2 equiv.), K₂CO₃ (2 equiv.), DMF, 140°C, 24 h, under argon, isolated yields.

^a GC or NMR yields.

tivity in favour of the linear isomer was higher in the presence of activated aryl bromides. Finally, we performed the reaction with the sterically demanding ethers cyclohexylvinylether and *t*-butylvinylether. In all cases we observed higher regioselectivities in favour of the linear isomer. For example, for the reaction of 4-bromobenzophenone in the presence of cyclohexylvinylether a ratio linear/branched isomers of 94/6 was observed (entry 19). In the presence of *n*-butylvinylether the ratio was 78/22 (entry 6). With cyclohexylvinylether quite high reaction rates were observed. On the other hand, with *t*-butylvinylether much lower TONs were obtained.

In conclusion, the use of the tetradentate ligand Tedicyp associated with a palladium complex provides a convenient catalyst for the Heck reaction with styrene and vinylether derivatives. This catalyst seems to be much more efficient than the complexes formed with triphenylphosphine ligand. This efficiency probably comes from the presence of the four diphenylphosphinoalkyl groups stereospecifically bound to the same face of the cyclopentane ring which probably increases the coordination of the ligand to the metal and prevent precipitation of the catalyst. In the presence of this catalyst the Heck vinylation of aryl bromides with styrene derivatives can be performed with as little as 0.001 mol% catalyst. These results represent an environmentally friendly procedure. Moreover, due to the high price of palladium, the practical advantage of such low catalyst loading reactions can become increasingly important for industrial processes.

Acknowledgements

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 10. As a typical experiment, the reaction of 4-bromobenzophenone (2.61 g, 10 mmol), styrene (2.08 g, 20 mmol) and K₂CO₃ (2.76 g, 20 mmol) at 140°C during 20 h in dry DMF (10 mL) in the presence of *cis,cis,cis*-1,2,3,4-tetrakis (diphenylphosphinomethyl)cyclopentane/[PdCl-(C₃H₅)₂]₂ complex (0.0001 mmol) under argon affords the corresponding product after evaporation and filtration on silica gel in 92% (2.61 g) isolated yield.