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Tetraphosphine/palladium-catalyzed Heck reactions of aryl halides with disubstituted alkenes

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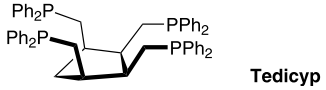
Abstract—*cis*,*cis*,*cis*-1,2,3,4-Tetrakis(diphenylphosphinomethyl)cyclopentane/$[PdCl(C_3H_5)]_2$ efficiently catalyses the Heck reaction of disubstituted alkenes such as methyl crotonate, ethyl cinnamate, methyl methacrylate or α-methylstyrene with a variety of aryl halides. In the presence of 1,2-disubstituted alkenes the stereoselectivities of the reactions strongly depend on the substituents of the alkenes. Selectivities up to 97% in favor of *E*-isomers can be obtained for the addition to methyl crotonate. With the 1,1-disubstituted alkenes methyl methacrylate or α-methylstyrene mixtures of products are obtained.

The palladium-catalyzed Heck vinylation reaction is one of the most powerful methods for the formation of C–C bonds.[1] The efficiency of several catalysts for the reaction of aryl halides with acrylates or styrene derivatives has been studied in detail. On the other hand, the reaction in the presence of disubstituted alkenes such as ethyl cinnamate or α-methylstyrene has attracted less attention.[2–4] A few ligands have been successfully employed for the reaction in the presence of disubstituted alkenes. The most popular one is triphenylphosphine, but the palladium complexes formed with this ligand are generally not very efficient in terms of substrate/catalyst ratio. In recent years, more efficient catalysts such as palladacycles have been tested with these substrates.[5] For example, Beller et al. reported that a phosphapalladacycle is very efficient for the reactions with 1,1-disubstituted olefins.[4b] In the monophosphine ligand series, good results have been reported recently by Fu et al. They reported that the ligand $P(t\text{-}Bu)_3$ is an efficient catalyst for the reaction of 4-dimethylaminobromobenzene with methyl methacrylate even at room temperature.[2h,4d] If monophosphine ligands or palladacycles have been successfully used for the reaction with these alkenes, to the best of our knowledge, the efficiency of tetraphosphine ligands has not been demonstrated.

In order to obtain stable and efficient palladium catalysts, we have prepared the new tetraphosphine ligand, *cis*,*cis*,*cis* - 1,2,3,4 - tetrakis(diphenylphosphinomethyl) cyclopentane or tedicyp[6] (Fig. 1) in which four diphenylphosphino groups are stereospecifically bound to the same face of a cyclopentane ring. We have already reported the results obtained in allylic substitutions,[6] for Suzuki cross-couplings,[7] for Heck reactions[8] and for Sonogashira alkynylations[9] using tedicyp as the ligand. In order to further establish the requirements for a successful Heck reaction with our catalyst, we herein report on the reaction of aryl halides with disubstituted alkenes.

For this study, based on previous results,[8] DMF was chosen as the solvent and K_2CO_3 as the base. The reactions were performed at 130°C under argon in the presence of a 1:2 ratio of $[Pd(C_3H_5)Cl]_2$/tedicyp as catalyst.

We first studied the reactivity of 1,2-disubstituted alkenes with several aryl halides in the presence of 1–0.01 mol% catalyst (Scheme 1, Table 1). In all cases, mixtures of isomers were obtained, however, the selectivity



Tedicyp

Figure 1.

Keywords: palladium; tetraphosphine; Heck reaction; disubstituted alkene.

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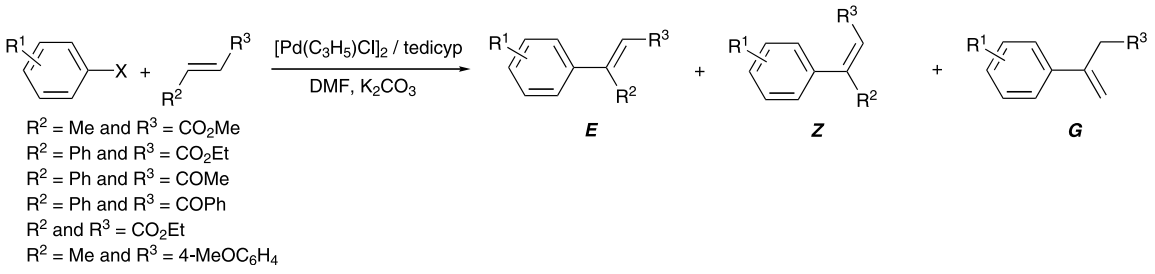


Scheme 1.

Table 1. Heck reactions with 1,2-disubstituted alkenes catalyzed by the tedicyp-palladium complex (Scheme 1)[10]

Entry	Aryl halide	Alkene	Ratio substrate/catalyst	Selectivity for isomers *E*/*Z*/*G* (%) (Scheme 1)[a]	Yield (%)[b]
1	Iodobenzene	Methyl crotonate	1000	88/6/6	91 (100)
2	Iodobenzene	Methyl crotonate	10,000	*E*>95	(60)
3	4-Bromoacetophenone	Methyl crotonate	1000	*E*>97	60
4	4-Bromobenzophenone	Methyl crotonate	250	86/8/6	89 (100)
5	4-Fluorobromobenzene	Methyl crotonate	1000	*E*>95	88 (100)
6	4-Dimethylaminobromobenzene	Methyl crotonate	1000	*E*>97	82
7	4-Bromoanisole	Methyl crotonate	1000	*E*>95	81
8	4-^{t}Butylbromobenzene	Methyl crotonate	1000	*E*>95	81
9	3-Bromopyridine	Methyl crotonate	250	*E*>97	87
10	Iodobenzene	*E*-Ethyl cinnamate	1000	–	(100)
11	Bromobenzene	*E*-Ethyl cinnamate	250	–	82
12	Bromobenzene	*E*-Ethyl cinnamate	1000	–	(25)
13	3-Trifluoromethylbromobenzene	*E*-Ethyl cinnamate	1000	67/33/–[c]	88
14	4-Bromotoluene	*E*-Ethyl cinnamate	1000	84/16/–	90
15	4-Dimethylaminobromobenzene	*E*-Ethyl cinnamate	1000	74/26/–	91
16	4-Bromoanisole	*E*-Ethyl cinnamate	250	79/21/–	93
17	4-Bromoanisole	*E*-Ethyl cinnamate	1000	82/18/–	(46)
18	2,4,6-Trimethylbromobenzene	*E*-Ethyl cinnamate	100	62/38/–	81
19	Iodobenzene	*E*-Benzalacetone	250	–	80
20	Bromobenzene	*E*-Benzalacetone	100	–	90
21	4-Methylbromobenzene	*E*-Benzalacetone	250	53/47/–[c]	72
22	4-Bromoanisole	*E*-Benzalacetone	100	54/46/–[c]	83 (100)
23	Iodobenzene	*E*-Benzalacetophenone	1000	–	85 (100)
24	4-Methylbromobenzene	*E*-Benzalacetophenone	250	50/50/–	89 (100)
25	4-Bromoanisole	*E*-Benzalacetophenone	100	50/50/–	81 (97)
26	Iodobenzene	Diethyl maleate	250	30/70[d]	92 (100)
27	Iodobenzene	Diethyl maleate	1000	39/61[d]	(100)
28	Iodobenzene	Diethyl fumarate	50	17/83[d]	81 (100)
29	4-Bromoanisole	*E*-Anethole	25	38/20/42[e]	75

Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/tedicyp 1:2 see Ref. 6, ArX (1 equiv.), alkene (2 equiv.), K_2CO_3 (2 equiv.), DMF, 20 h, 130°C, under argon, isolated yields (mixture of isomers), ratio substrate/catalyst based on the aryl halide.

[a] Selectivities determined by GC and NMR.

[b] Yields in parentheses correspond to GC or NMR yields.

[c] Stereochemistry of the isomers was not determined.

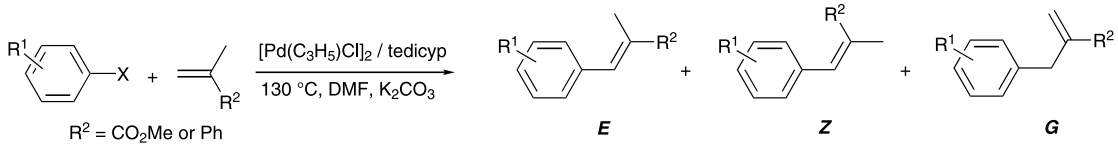
[d] Ratio diethyl phenylfumarate: diethyl phenylmaleate.

[e] Ratio *E*-1,2-bis(4-methoxyphenyl)prop-1-ene: 2,3-bis(4-methoxyphenyl)prop-1-ene:1,1-bis(4-methoxyphenyl)prop-1-ene.

strongly depended on the substituents of the alkenes. In the presence of methyl crotonate high selectivities in favor of the *E*-isomer were obtained (up to 97%) (Table 1, entries 1–9). A minor influence of the electronic factors of the aryl halide on the reaction rate was observed. Similar turn over numbers (TONs) were observed using activated 4-bromoacetophenone and deactivated 4-bromoanisole: 600 and 810 (Table 1, entries 3 and 7) indicating that, as expected, the rate-limiting step of the reaction with this sterically hindered alkene is not the oxidative addition of the aryl halide. Similar reaction rates were obtained for the addition of aryl halides to ethyl cinnamate but lower selectivities in favor of the *E*-isomer were observed (62–84%) (Table 1, entries 10–18). Almost equimolar mixtures of *E*- and *Z*-isomers were obtained for the addition to benzalacetone and benzalacetophenone (Table 1, entries 19–25). The observed lack of stereoselectivity of these reactions might be due to equilibration of the products subsequent to the Heck reaction by base-catalyzed isomerization.[2e]

The reaction of diethyl maleate with iodobenzene in the presence of 0.1 mol% catalyst led to mixtures of diethyl 2-phenylfumarate and diethyl 2-phenylmaleate (Table 1, entries 26 and 27). A similar selectivity but a much lower reactivity was observed with diethyl fumarate (Table 1, entry 28). The reactivity of *E*-anethol was also studied (Table 1, entry 29). With this substrate a mixture of three regio- and stereoisomers was obtained. In summary, many of these 1,2-disubstituted alkenes can be reacted in the presence of low catalyst loadings and the selectivity strongly depends on the substituents of the alkene.

We next studied the reactivity of two 1,1-disubstituted alkenes (Scheme 2, Table 2). In all cases, mixtures of three isomers were obtained. With methyl methacrylate, the *E*-isomer was obtained in 35–93% selectivity (Table 2, entries 1–17). The formation of large amounts of *G*-isomers and traces of *Z*-isomers were also observed in some cases. The highest selectivities were obtained in the presence of electron-poor aryl bromides. For example a selectivity of 93% in favor of the *E*-isomer was obtained for the reaction with 4-bromobenzonitrile (Table 2, entry 3). On the other hand, with the electron-rich aryl bromide, 4-bromoanisole, a lower selectivity of 57% in favor of the *E*-isomer was obtained (Table 2, entry 8). Even the di-*ortho*-substituted aryl bromide 2,4,6-trimethylbromobenzene was efficiently converted into the adducts. However, in this case a greater quantity of catalyst was required, and the formation of 65% of the *G*-isomer was observed (Table 2, entry 14). Presumably, the steric demand of the two *ortho* methyl



Scheme 2.

Table 2. Heck reactions with 1,1-disubstituted alkenes catalyzed by tedicyp-palladium complex (Scheme 2)[10]

Entry	Aryl halide	Alkene	Ratio substrate/catalyst	Selectivity for isomers *E*/*Z*/*G* (%) (Scheme 2)[a]	Yield (%)[b]
1	Iodobenzene	Methyl methacrylate	10,000	62/0/38	94
2	Iodobenzene	Methyl methacrylate	100,000	62/0/38	(15)
3	4-Bromobenzonitrile	Methyl methacrylate	1000	93/0/7	82 (100)
4	4-Trifluoromethylbromobenzene	Methyl methacrylate	1000	70/12/18	88 (100)
5	4-Bromobenzophenone	Methyl methacrylate	1000	75/10/15	81 (100)
6	4-Dimethylaminobromobenzene	Methyl methacrylate	100	68/6/26	55
7	4-Fluorobromobenzene	Methyl methacrylate	1000	56/0/44	91 (100)
8	4-Bromoanisole	Methyl methacrylate	1000	57/4/39	90
9	4-^{t}Butylbromobenzene	Methyl methacrylate	1000	57/5/38	87 (100)
10	2-Bromobenzonitrile	Methyl methacrylate	100	70/6/24	50 (57)
11	2-Fluorobromobenzene	Methyl methacrylate	100	50/2/48	84
12	2-Methylbromobenzene	Methyl methacrylate	250	66/6/28	78 (100)
13	2-Methoxybromobenzene	Methyl methacrylate	100	58/4/38	80 (100)
14	2,4,6-Trimethylbromobenzene	Methyl methacrylate	50	35/0/65	83 (100)
15	3-Bromopyridine	Methyl methacrylate	250	49/2/49	83 (100)
16	3-Bromoquinoline	Methyl methacrylate	250	77/6/17	87 (100)
17	2-Bromothiophene	Methyl methacrylate	1000	48/16/36	95
18	Iodobenzene	α-Methylstyrene	250	62/12/26	(100)
19	Iodobenzene	α-Methylstyrene	1000	54/11/35	62 (70)
20	Iodobenzene	α-Methylstyrene	10,000	38/7/55	(28)
21	Bromobenzene	α-Methylstyrene	250	46/6/48	(100)
22	Bromobenzene	α-Methylstyrene	1000	42/4/54	87 (97)
23	Bromobenzene	α-Methylstyrene	10,000	37/5/58	(30)
24	4-Dimethylaminobromobenzene	α-Methylstyrene	1000	52/6/42	76
25	4-Bromoanisole	α-Methylstyrene	250	46/7/47	80 (99)
26	4-Bromoanisole	α-Methylstyrene	1000	44/8/48	(51)
27	4-Bromoacetophenone	α-Methylstyrene	250	78/13/9	(100)
28	4-Bromoacetophenone	α-Methylstyrene	1000	72/14/14	82
29	2-Methylbromobenzene	α-Methylstyrene	250	50/5/45	95
30	2-Methylbromobenzene	α-Methylstyrene	1000	50/5/45	(86)
31	2,4,6-Trimethylbromobenzene	α-Methylstyrene	250	18/0/82	65

Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/tedicyp 1:2 see Ref. 6, ArX (1 equiv.), alkene (2 equiv.), K_2CO_3 (2 equiv.), DMF, 20 h, 130°C, under argon, isolated yields (mixture of isomers), ratio substrate/catalyst based on the aryl halide.

[a] Selectivities determined by GC and NMR.

[b] Yields in parentheses correspond to GC or NMR yields.

groups disfavors one of the two possible β-hydride eliminations to generate mainly the olefin *G*.[2h]

Heteroaromatic substrates such as 3-bromopyridine, 3-bromoquinoline or 2-bromothiophene in the presence of methyl methacrylate also led to the expected mixture of adducts (Table 2, entries 15–17).

Selectivities similar to those obtained with methyl methacrylate were observed for the addition of aryl halides to α-methylstyrene (Table 2, entries 18–31). The *E*-isomer was obtained in 18–78% selectivity. Higher selectivities in favor of the *E*-isomer were observed in the presence of electron-poor aryl bromides than with electron-rich aryl bromides. The sterically congested 2,4,6-trimethylbromobenzene also led mainly to the *G*-isomer (Table 2, entry 31). With this alkene the oxidative addition of the palladium(0) is apparently not the rate-limiting step of the reaction. For example, TONs of 2800 and 3000 were obtained for the addition of iodobenzene and bromobenzene to α-methylstyrene (Table 2, entries 18–23).

In summary, in the presence of the tedicyp/palladium complex, the Heck vinylation of several aryl halides with 1,1- and 1,2-disubstituted alkenes can be performed with as little as 0.01 mol% catalyst. In general, mixtures of isomers were obtained. The selectivity of the reactions depends on the substituents of the alkenes. Addition to methyl crotonate is highly selective in favor of the *E*-isomer. Addition to *E*-benzalacetophenone led to almost equimolar mixtures of *E*- and *Z*-isomers. For the addition to methyl methacrylate, in general the major isomer was the *E*-isomer. The behavior of all these reactions depends on the electronic and steric factors of the aryl halides and of the alkenes. These observations suggest that the product distribution in some cases not only comes from the conformation of the Pd-substrate intermediates but also from thermodynamic stability and base-catalyzed isomerization of the products. In general the rate-limiting step of these reactions does not seem to be the oxidative addition of the aryl halides. For this reason, this method is applicable to the coupling of both electron-deficient and electron-rich aryl bromides. Both in terms of substrate/catalyst ratio and reaction scope, this catalyst is effective for Heck reactions of disubstituted alkenes. Due to the high price of palladium, the advantage of such low catalyst loading reactions could become increasingly important for industrial processes.

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