

Diphosphinoazine palladium(II) complexes as catalysts for the Heck reaction of bromides and an activated chloride

J. Včelák, J. Storch, M. Czakoová, J. Čermák*

Institute of Chemical Process Fundamentals, AS CR, Rozvojová 135, CZ-16502 Prague 6, Czech Republic

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Abstract

Five diphosphinoazine palladium(II) amido complexes together with two phosphine-free and two triphenylphosphine-modified palladium(II) complexes were investigated as catalysts for the Heck reaction of styrene with 4-chlorobenzonitrile, bromobenzene and 4-bromobenzonitrile in dimethylacetamide with tributylamine as a base. The diphosphinoazine complexes competed well with the traditional catalysts; best conversions and turnover numbers were achieved with a vinyl-amide complex $[(\text{CH}_3\text{OCOCH}=\text{CCOOCH}_3)\text{Pd}\{\text{PPh}_2\text{CH}=\text{C}(\text{Bu}^t)\text{NN}=\text{C}(\text{Bu}^t)\text{CH}_2\text{PPh}_2\}]$ giving TON of about 680 000 and TOF of 7710 h^{-1} in the reaction of 4-bromobenzonitrile. The TON of the chloroarene with the same complex was 729. Selectivities of the product formation were independent on the catalyst and little dependent on the substrate, the selectivity of the main product, (Z)-1,2-diarylethylene, being always over 90%.

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1. Introduction

The palladium catalyzed coupling of haloarenes and haloalkenes with alkenes discovered in the late sixties [1,2] and later named after Heck is now one of the most valuable palladium-catalyzed reactions in use in organic synthesis. Numerous reviews [3–10] on both inter- and intramolecular variants of the reaction have appeared and the interest does not cease [11]. It is now clear [11,12] that iodides which are the most reactive halides cannot be used for benchmarking of the catalytic activity since palladium in almost any form and at very low concentrations (and thus very high TONs) can catalyze the Heck reaction of iodides. Therefore, a recent review was devoted solely to reactions of bromides and chlorides [12]. Remarkable progress was achieved in reactions of bromobenzene with styrene catalyzed by phosphine-free Pd(II) catalysts with the addition of *N,N*-dimethylglycine as an activator [13]. Addition of tetraphenylphosphonium chlo-

ride to Pd salts resulted in better reactivity and regioselectivity even in the Heck reaction of chlorobenzene [14]. Recently, attention was drawn also to the detailed role of various forms of Pd in the intimate mechanism of Heck reaction carried out with classic phosphine-free and triphenylphosphine-modified Pd(II) catalysts [15].

While diphosphines were initially considered (even by Heck himself) to be very poor ligands for the reaction, later it was shown [16,17] that their activity is comparable to monodentate phosphines if the activation goes via a cationic pathway. Palladium(II) PCP pincer complexes that combine the features of both diphosphines and orthometallated palladacycles were used by Milstein and coworkers [18] for reactions of methyl methacrylate with bromobenzene and 4-bromobenzaldehyde with TONs over 10^5 .

Recently, we have synthesized palladium(II) *trans*-chloro-amido complexes **1–3** with azine diphosphines in an unsymmetrical PNP' pincer-type coordination mode [19]. In this paper we demonstrate that these complexes as well as similar amido complexes **4** and **5** already reported [20,21] are active catalysts of the Heck reaction of styrene with bromo-

* Corresponding author. Tel.: +420 220390356; fax: +420 220920661.
E-mail address: cermak@icpf.cas.cz (J. Čermák).

and activated-chloroarenes. For comparison, standard palladium(II) catalytic systems found in the literature were also employed.

2. Experimental

2.1. General

All the manipulations were carried out in an inert atmosphere of nitrogen or argon using standard Schlenk techniques unless stated otherwise. Starting 4-bromobenzonitrile, 4-chlorobenzonitrile as well as stilbene and 1,1-diphenylethylene used as standards for GC analysis (all Aldrich), palladium(II) acetylacetonate (Fluka), and bromobenzene (Riedel de Haen) were commercial products used without further purification. Styrene (Aldrich), *N,N*-dimethylacetamide (BDH Chemicals), and tributylamine (Fluka) were distilled in a vacuum and kept under argon. $[\text{PdCl}_2(\text{PPh}_3)_2]$ [22], $[\text{PdCl}_2(\text{C}_6\text{H}_5\text{CN})_2]$ [23], and diphosphinoazine complexes **1–5** [19–21] were prepared according to literature methods.

2.2. Heck reaction

- (i) In ampoules: haloarene (2.0 mmol), styrene (2.5 mmol), and tributylamine (3 mmol) were dissolved in DMA (1 ml) in an ampoule and 5 μl of DMA solution of a catalyst added via syringe. The ampoule was closed by a septum stopper allowing periodical sample withdrawal and placed in a bath at 145–150 °C.
- (ii) In a stirred reactor: haloarene (2.0 mmol), styrene (3.5 mmol), and tributylamine (3 mmol) were dissolved in DMA (10 ml) in a thermostated glass reactor with a magnetic stirrer. Solutions of a catalyst in 20 μl DMA were injected into the reactor at the desired temperature.

2.3. Analyses of the reaction mixtures

Samples of the reaction mixtures (100 or 200 μl) were decomposed in a mixture of 3 ml of diluted hydrochloric acid (1:3, v/v) and 2 ml of toluene. Organic layer was separated and samples for GC–MS analysis prepared by mixing 20 μl of the organic layer with the toluene solution of 1,2,4,6-tetrachlorobenzene as internal standard (100 μl).

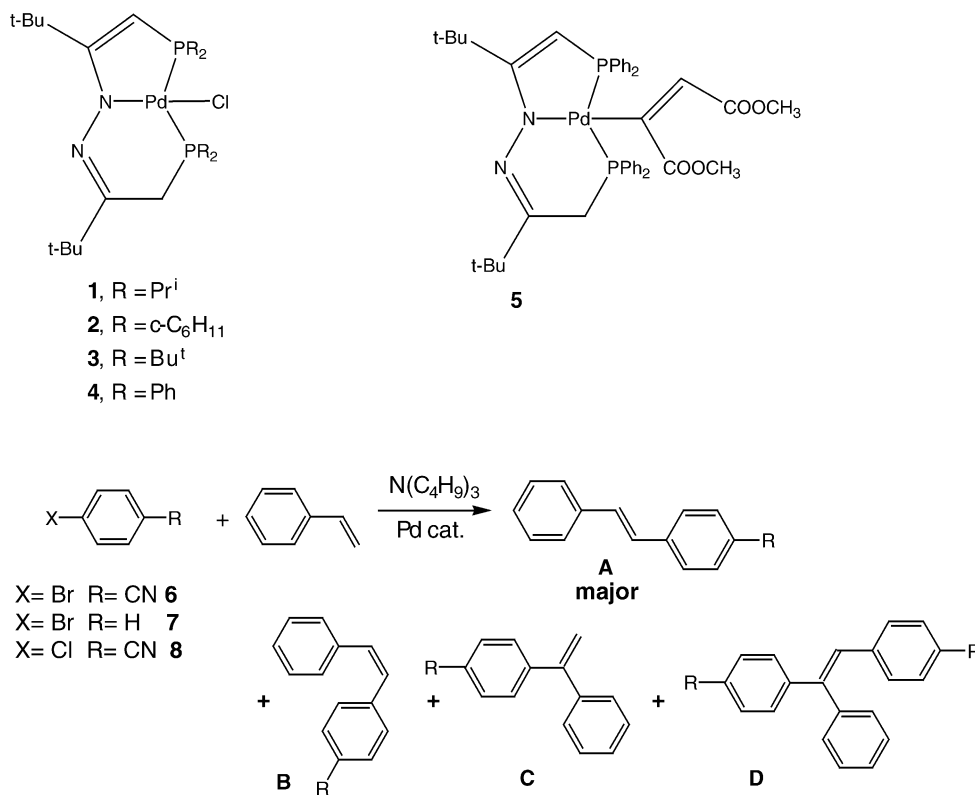
GC–MS analysis was run on a Varian 3500 gas chromatograph equipped with a capillary column coated with poly(dimethylsiloxane-co-5% methylphenylsiloxane) phase (temperature program 90–250 °C) connected to a Finnigan Mat mass ITD detector working at 70 eV. The acquisition range was 45–350 amu. Concentrations of unreacted styrene, haloarene as well as concentrations of products ((*E*)- and (*Z*)-stilbenes and 1,1-diphenylethylene) resulted from the analysis.

3. Results and discussion

Reaction runs (Scheme 1) were carried out either in septum-capped ampoules in dimethylacetamide with tributylamine as a base at the fixed temperature of 150 °C or in a stirred reactor in the same solvent at temperatures between 120 and 140 °C with 10-fold dilution of the reaction mixtures allowing better monitoring of changes in composition. Three substrates were used: 4-bromobenzonitrile, **6**, as an example of activated bromoarenes, bromobenzene, **7**, and 4-chlorobenzonitrile, **8**, as a representative of activated chloroarenes; the results are summarized in Tables 1–3. Reactions were generally run in an argon atmosphere but for comparison several experiments were run in air. Although conversions (with respect to haloarene) in air were in some cases only slightly lower than those under an inert atmosphere, product mixtures from the former experiments are strongly depleted of styrene, originally used in excess, indicating that oligomerization and polymerization of styrene is competing successfully with the Heck reaction when the reactions are carried out in air. Higher dilution, together with the possibility of adventitious oxygen introduction into an open stirred reactor, may explain generally lower conversions and turnover numbers in that experimental setup.

Two examples of phosphine-free catalysts, $\text{Pd}(\text{acac})_2$, **9**, and $\text{PdCl}_2(\text{PhCN})_2$ [24,25], **10**, and two examples of triphenylphosphine-modified systems, viz. $\text{Pd}(\text{acac})_2/\text{PPh}_3$ [26] and $\text{PdCl}_2(\text{PPh}_3)_2$ [27], **11**, were used as catalysts together with the amide complexes **1–5** in experiments in sealed ampoules. As expected, the conversions and turnovers with the same catalyst decreased along the series: 4-bromobenzonitrile > bromobenzene > 4-chlorobenzonitrile. The only catalyst capable of activating the chloroarene was the vinyl-amide complex **5**, affording almost quantitative conversion of the chloroarene with a moderate TON of 729 (entry 6). With bromobenzene, phosphine-free catalysts gave better results than triphenylphosphine-modified ones but on the whole TONs did not exceed 10^4 . With the vinyl-amide complex **5**, the highest TON was almost 20 000 at 42% conversion (entry 20); total conversion was achieved by a slight decrease in substrate/catalyst ratio at much lower reaction time with TON = 14 800 (entry 19). Among chloro-amido complexes **1–4**, the consistently good activity was exhibited by the cyclohexyl complex **2**, phenyl and isopropyl analogs were less active and the worst results were achieved with the *tert*-butyl complex **3**.

With the activated bromoarene, phosphine-free catalysts did not show the activity of triphenylphosphine-modified ones; the best one in the latter group was $\text{PdCl}_2(\text{PPh}_3)_2$ with TON = 141 050 (entry 26). Diphosphinoazine amido complexes were again better: with the vinyl-amide complex **5** the highest TON of 682 280 (entry 32) achieved in this study was found. Surprisingly, the second best with this substrate was the phenyl complex **4**, cyclohexyl and isopropyl complexes **2** and **1** were comparable in activity.



Scheme 1.

As already mentioned above, in a stirred reactor the conversions were generally lower, therefore the chloroarene was not tested. While **5** was a good catalyst for bromobenzene, with 4-bromobenzonitrile it showed only a medium activity and the best catalyst was the complex **2**. In this experimental setup, however, changes in the composition of the product mixtures were better to follow and are summarized in Table 3. Time course of the reaction of 4-bromobenzonitrile with styrene (entry 43) is shown in Fig. 1 as an example. Decrease of 4-bromobenzonitrile concentration apparently follows approximately zero order kinetics with a prolonged start period ((*Z*)-stilbene-4-nitrile being a major product, minor products are not shown). It should be mentioned that the kinetics is that of a complex reaction and no attempt was done to propose a kinetic scheme.

The selectivities of the formation of disubstituted ethylenes were independent on the catalyst and only slightly depended on the substrate. The main product was always (*Z*)-stilbene (**A**) (with >89% selectivity over (*E*)-stilbene (**B**), the relative amount of 1,1-diphenylethylene (**C**) was negligible with the chloroarene and the highest with bromobenzene. The product of multiple Heck coupling reaction (**D**) was observed in trace amounts only in the experiments with the highest catalyst loading (1 mol% and more, not shown in the tables). In the presence of a Pd catalyst the composition of the product mixture remained unchanged for a long time in accord with the literature data [28]. After stopping the reaction by diluted aq. HCl, (*Z*)-disubstituted ethylenes slowly

isomerized to their (*E*)-analogs in the organic (toluene) layer (being exposed to diffuse day light), therefore the composition of the product mixtures had to be determined very soon after the acid workup. The isomerization of (*Z*)-disubstituted ethylenes was complete after 2 days standing under day

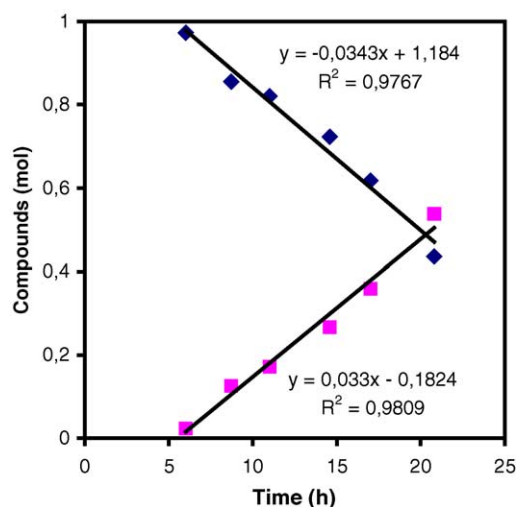


Fig. 1. Time course of the reaction of 4-bromobenzonitrile with styrene (entry 43 from Table 3) in a stirred reactor. Time decrease of 4-bromobenzonitrile (diamonds) and increase of (*Z*)-stilbene-4-nitrile (squares; minor amounts of 1,1-diphenylethylene and (*E*)-stilbene-4-nitrile are not depicted).

Table 1
Heck reactions in sealed ampoules^a

Entry	Substrate	Catalyst	Substrate/catalyst ratio	Time (h)	Conversion (%)	TON	TOF (h ⁻¹)
1	8	9	1925	206	0	0	0
2	8	11	11000	116	2	190	1.6
3	8	1	7350	160	0	0	0
4	8	2	1030	137	8	85	0,6
5	8	3	1930	103	0	0	0
6	8	5	736	61	99	729	12
7	7	9	15100	90	60	9060	101
8	7	9^b	14100	63	32	4512	71
9	7	9^b	8980	66.5	64	5750	86
10	7	11	13700	43.5	40	5500	126
11	7	10	24320	48	26	6330	131
12	7	1	9125	115	80	7300	63
13	7	2	36150	89	42	15200	171
14	7	2	18000	45	57	10300	229
15	7	2^c	35800	68.5	42	15050	220
16	7	2^d	15750	24.5	35	5430	222
17	7	3	6410	45	37	2390	53
18	7	4	24750	43.5	35	8663	199
19	7	5	14800	18	100	14800	822
20	7	5	46050	107.5	42	19340	180
21	7	5^d	21600	40	25	5390	135
22	6	9	17900	93.5	99	17800	190
23	6	9^b	13330	17.5	100	13330	762
24	6	9^b	64200	93	100	64200	690
25	6	11	141050	89	100	141050	1580
26	6	10	27200	22.5	74	20130	895
27	6	1	25100	17	100	25100	1480
28	6	2	25600	18	100	25600	1420
29	6	2	89000	138.5	27	24050	174
30	6	3	1980	19.3	100	1980	103
31	6	4	277500	67.5	81	224800	3330
32	6	5	886075	88.5	77	682280	7710
33	6	5	62650	17	100	62650	3690
34	6	5^d	167500	67	25	41200	615

^a Styrene (2.5–3.5 mmol), substrate (2 mmol), Bu₃N (3 mmol), DMA (10 ml), 150 °C.

^b One equivalent of PPh₃ added.

^c 10 ml of dimethylacetamide.

^d Reaction in air.

light exposure. An independent experiment based on literature [29] showed the isomerization being promoted by UV light.

The general mechanism of the Heck reaction (if exists) remains unknown, so called Pd⁰/Pd^{II} catalytic cycle broadly accepted in older literature has been doubted for pallada-

cycles and pincer-type complexes and several mechanisms [11,12,30,31] based on Pd^{II}/Pd^{IV} cycle were published. However, the Pd⁰/Pd^{II} catalytic cycle has been evoked recently [32,33] with Pd⁰ either formed by reductive elimination from a hydridocarbopalladate complex or being present as an anionic very electron rich species.

Table 2
Heck reactions in a stirred reactor^a

Entry	Substrate	Catalyst	Substrate/catalyst ratio	Temperature (°C)	Time (h)	Conversion (%)	TON	TOF (h ⁻¹)
35	7	9^b	35000	140	5	7	2450	490
36	7	11	14200	140	7.3	53	7530	1030
37	7	10	8400	140	6	18	1510	252
38	7	4	10650	140	10	66	7050	705
39	7	5	8050	140	9.3	91	7300	790
40	6	9	910	120	4	45	410	103
41	6	2	87000	130	6.5	18	15700	2430
42	6	3	2030	140	9.2	8	162	18
43	6	5	5410	140	20.8	56	3030	145

^a Styrene (2.5–3.5 mmol), substrate (2 mmol), Bu₃N (3 mmol), DMA (10 ml).

^b One equivalent of PPh₃ added.

Table 3
Composition of product mixtures^a

Substrate	PhR'C=CH ₂	(E)-PhCH=CHR'	(Z)-PhCH=CHR'
8	0.5	5	94.5
7	8	3	89
7^b	7	0	93
7^c	6.5	4.5	89
7^d	5.7	59.4	34.9
6	4.5	4.5	91
6^c	3.5	1.5	95
6^e	3.0	19.5	77.5
6^b	4	1	95

^a Average percent values from all experiments.

^b Reaction in air.

^c Individual values analyzed immediately after the treatment of reaction mixture.

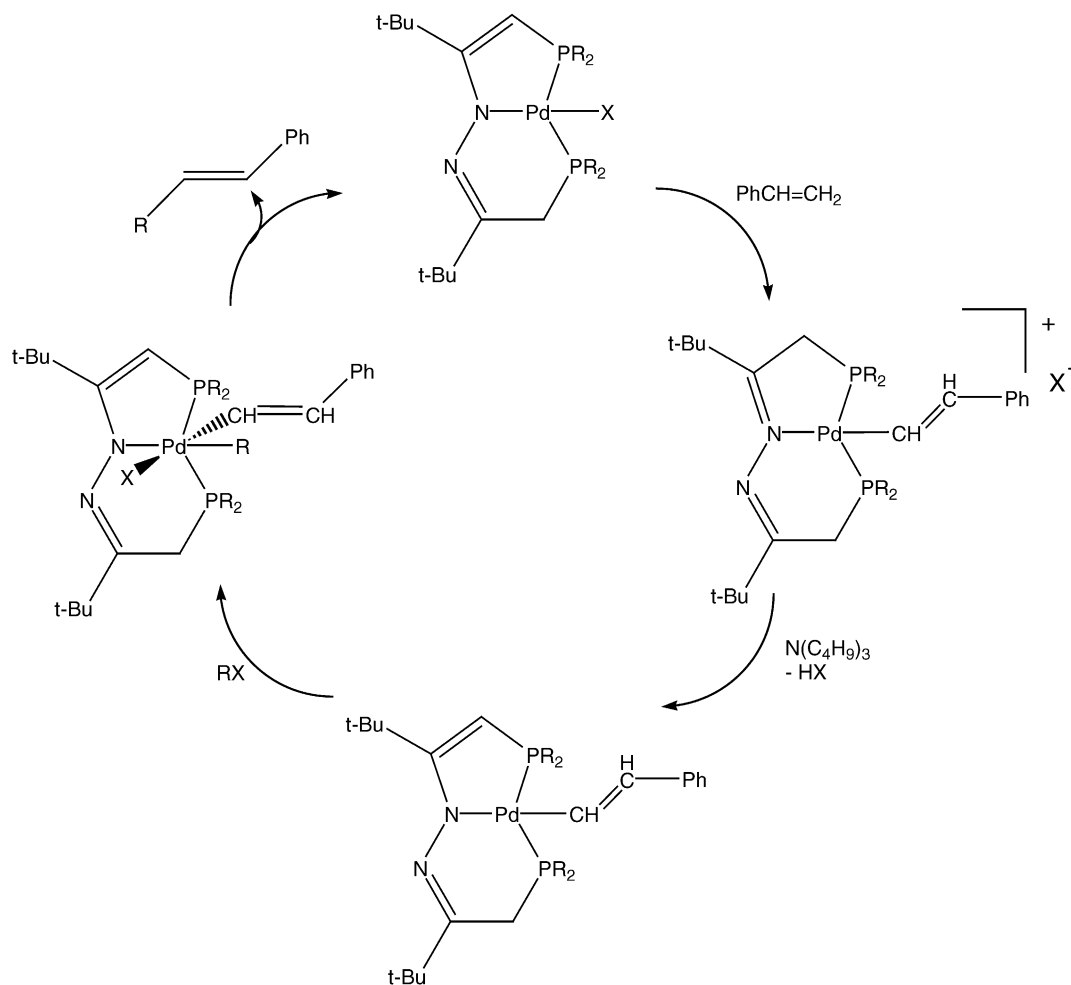
^d Individual values analyzed after 1 h exposition of UV light (254 nm).

^e Individual values analyzed 18 h after the treatment of reaction mixture (partly on a diffuse day light).

Formation of a Pd⁰ species in our system is improbable, therefore our suggestion of the reaction sequence (Scheme 2) is based on Jensen's mechanism [31] for Pd pincer complex catalysis taking into account the specific feature of diphosphi-

noazines in ene-hydrazone form, i.e. the ability to reversibly accommodate hydrogen on the backbone.

As in the Jensen's mechanism, it starts with the reaction of an olefin with the ene-hydrazone Pd–X complex, hydrogen is, however, moved onto the ligand backbone and the X becomes an anion, therefore the net result is the formation of a Pd^{II} instead of Pd^{IV} intermediate. The cationic complex with the ligand backbone terdentate but neutral is favored in the polar solvent [34]. The latter complex is then deprotonated by a base in a step that is well documented in the diphosphinoazine chemistry forming a vinyl-amide complex. Oxidative addition of the haloarene followed by the reductive elimination of the product completes the cycle reforming the starting halo-amide complex. There is only one proposed Pd^{IV} intermediate in this cycle and the oxidative addition leading to this intermediate should be facilitated by the electron-donating amide nitrogen. Halo-amide and vinyl-amide complexes are already known [19–21] as is the deprotonation of a cationic terdentate complexes to ene-hydrazone [19,20], therefore the mechanism sounds plausible. Nevertheless, based only on the data from this work, it needs further verification.



Scheme 2.

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