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Coordination chemistry and mechanisms of metal-catalyzed CC-coupling reactions [1]. Part 7. Heck vinylation of aryl halides with *n*-butyl acrylate: relevance of PC bond cleavage to catalyst deactivation

Wolfgang A. Herrmann [a,*], Christoph Broßmer [2,a], Karl Öfele [a], Matthias Beller [b], Hartmut Fischer [b]

[a] *Anorganisch-chemisches Institut der Technischen Universität München, Lichtenbergstraße 4, D-85747 Garching, Germany*
[b] *Central Research Laboratories, Hoechst AG, D-65926 Frankfurt, Germany*

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Abstract

The Heck reaction between aryl halides ArX (X = Br, Cl) and *n*-butyl acrylate was studied in the presence of catalyst systems containing $Pd(OAc)_2$ and a tertiary phosphine ligand (PR_3, $R_2P-(CH_2)-PR_2$). It is shown that *all* tested arylphosphines except $P(o\text{-Tol})_3$ and $P(Mes)_3$ undergo an extensive PC bond cleavage at temperatures higher than 120°C. As a consequence, vinylic side products are formed with concomitant catalyst deactivation. In the case of triarylphosphines side products originate from reaction intermediates of the type $Pd^{II}(PAr_3)_2(Ar)X$. These species undergo an aryl–aryl exchange between the palladium center and coordinated phosphine ligands. Subsequent intermolecular phosphine scrambling leads to several isomerized arylpalladium species, all of which couple with *n*-butyl acrylate to give the corresponding cinnamic ester side products.

Keywords: Aryl halides; Butyl acrylate; CC coupling reaction; Deactivation; Heck vinylation; Palladium; PC bond cleavage

1. Introduction

The palladium-catalyzed arylation of olefins with aryl halides according to the general Scheme 1 is a well-established method of carbon–carbon bond formation. Because this versatile reaction, discovered by Heck [1] and Mizoroki [2], is tolerant of a wide variety of functional groups on either coupling partner, it has gained much interest for the preparation of elaborate arenes from relatively simple starting materials [3].

However a serious limitation of the Heck reaction is that aryl chlorides are generally unreactive. This inertness is primarily due to the high C–Cl bond energy ($D_{Ph-Cl} = 96$ kcal/mol at 298 K) in comparison to the more reactive bromo and iodo derivatives ($D_{Ph-X} = 81$ and 65 kcal/mol for X = Br and I, respectively) [4]. Previous vinylation studies with aryl chlorides have resulted in low yields and low catalyst stability [5]. Recent approaches to solve this problem were reported by Bozell [6] and Milstein [7]. Especially com-

* Corresponding author.

[1] For Part 6 of this series, see ref. [22](a).

[2] New address: Degussa AG, Postfach 1345, 63403 Hanau, Germany.

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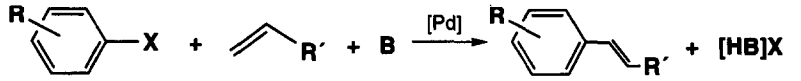


Scheme 1. X = Br, I; [Pd] = $Pd(OAc)_2$/n P(aryl)$_3$; B = base: $N(C_2H_5)_3$, K_2CO_3, NaOAc; R, R' = functional group: H, alkyl, aryl, CO_2R, CN.

plexes of the type $Pd(dippp)_2$ and $Pd(dippb)_2$ (dippp/dippb = bis(diisopropylphosphino)propane/-butane) catalyzed the CC coupling between chloroarenes and styrene [7]. Nevertheless, the activation of aryl chlorides remains a challenge in catalysis, because the multi-step synthesis and great air sensitivity of Milstein's ligands are unfavourable for an application beyond laboratory scale.

The present paper is to show that the choice and concentration of triarylphosphine ligands have a crucial influence on yield, selectivity and rate of the coupling reaction. Simple triarylphosphines prove to be responsible for undesired side reactions and early catalyst deactivation [8].

2. Results

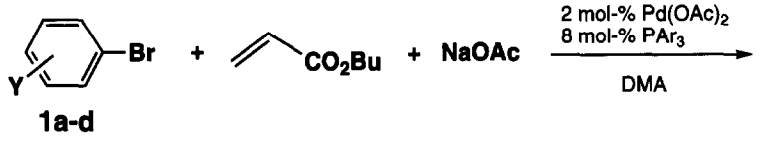
The presentation of the experimental results is organized according to the major substrates, namely aryl bromides and aryl chlorides.

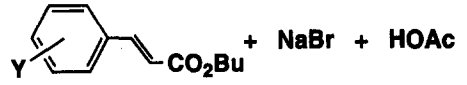
2.1. Aryl bromides

Early studies with aryl bromides have shown that Heck vinylation reactions strongly depend upon added ligands that keep the catalyst from precipitating as elemental palladium [3] (a,b). Especially PPh_3 and P(*o*-Tol)$_3$ have been found to form active catalysts with palladium acetate, the commonly used source of palladium [3,9].

We have investigated the Heck reaction of several aryl bromides with *n*-butyl acrylate using both conventional catalyst systems – $Pd(OAc)_2 + nP(aryl)_3$ – and isolated Pd complexes. Since inorganic bases proved to be superior to commonly used triethylamine [9](b), [10], reactions were performed with anhydrous NaOAc in *N,N*-dimethyl acetamide (DMA) (Scheme 2).

The results presented in Table 1 unfold a strong substituent effect on the reaction rate. Electron-withdrawing groups in the aryl bromide (−M/−I) support the Heck reaction ('activated arenes'), while electron-donating groups (+M/+I) are unfavourable ('deactivated arenes'). Therefore 4-bromobenzaldehyde reacts at significantly lower temperatures (80–120°C) than 4-bromoanisole which requires a minimum temperature of 135°C. However, *all* tested aryl bromides **1a–d** of Table 1 are converted regio- and stereoselectively into the corresponding *E*-cinnamic ester products **2a–d**. The *Z* isomers are found only in traces. The yields with P(*o*-Tol)$_3$ as the supporting ligand generally exceed 90%,





1, 2	a	b	c	d
Y	4-CHO	4-OCH_3	H	2-CH_3

Ar = *o*-tolyl; C_6H_5; mesityl

Scheme 2.

Table 1
Pd catalyzed CC coupling of aryl bromides with *n*-butyl acrylate (conversion > 99%) [a]

Aryl bromide	Pd component	Phosphine	Temperature/reaction time [°C]/[h]	Yield [b] [%]
4-bromobenzaldehyde	$Pd(OAc)_2$	PPh_3	140/4	86
		PPh_3	120/22	87
		$P(o\text{-Tol})_3$	140/1.5	95
		$P(Mes)_3$	140/0.2	88
		PPh_3O	100/0.3	89
	$Pd(PPh_3)_4$ [c]	–	140/5	85
	$Pd(PPh_3)_2(C_6H_4\text{-}p\text{-}CHO)Br$	PPh_3 [d]	120/22	88
	$Pd[P(o\text{-Tol})_3]_2$	$P(o\text{-Tol})_3$ [d]	140/0.3	92
bromobenzene	$Pd(OAc)_2$	PPh_3	140/8	94
		$P(o\text{-Tol})_3$	140/22	99
2-bromotoluene	$Pd(OAc)_2$	$P(o\text{-Tol})_3$	140/22	93
4-bromoanisole	$Pd(OAc)_2$	PPh_3	140/11	66
		$P(o\text{-Tol})_3$	140/22	94
		$P(o\text{-Tol})_3$	135/72	92

[a] Reaction conditions: 100 mmol aryl bromide, 140 mmol *n*-butyl acrylate, 110 mmol NaOAc (anhydrous), 100 ml *N,N*-dimethyl acetamide, 2 g diethylene glycol di-*n*-butyl ether (GC standard), 2 mmol Pd component, 8 mmol PR_3; Pd/P = 1/4.
[b] GC yield of corresponding Heck coupling product with reference to aryl bromide.
[c] 0.75 mmol.
[d] 4.0 mmol.

while the yields range between 66 and 89% for PPh_3 (except for bromobenzene, 94%). Surprisingly, only the catalyst system $Pd(OAc)_2 + 4P(o\text{-Tol})_3$ is able to convert deactivated substrates like 4-bromoanisole and 2-bromotoluene *quantitatively* into the desired Heck products. This remarkable difference in activities – compared with $Pd(OAc)_2 + 4PPh_3$ – inspired us to study the catalyst systems in greater detail.

Triphenylphosphine

Kinetic studies with the catalyst system $Pd(OAc)_2 + 4PPh_3$ revealed that Heck reactions with deactivated aryl bromides suffer from an *extensive PC bond cleavage* in the coordinated phosphine. As shown in Fig. 1, Heck coupling between 4-bromoanisole and *n*-butyl acrylate leads to *n*-butyl *E*-cinnamate as the major side product. This transfer of phenyl groups to the olefin is mainly thermal in origin and can be suppressed or fully avoided by lowering the reaction temperature to $T \leq 120°C$ (e.g. for 4-bromobenzaldehyde). The nature of the aryl bromide influences the extent of this side product formation, too. Activated substrates that are nearly insensitive to ligand degradation form *n*-butyl cinnamate even at higher temperatures (140°C) in only minor amounts. In contrast, deactivated aryl bromides (e.g. 4-bromoanisole) favour side product formation, so Heck products could be obtained in only 70% yield. In the case of bromobenzene yields exceed 90% because Heck coupling and side reaction result in the same product.

Until now phosphine degradation via PC bond cleavage was explained by oxidative addition to Pd^0 species or nucleophilic 1,2-aryl migration in Pd^{II} complexes [11]. However, in the present case these mechanisms seem to be of minor importance. We believe that side product formation is attributable to a differing stability of intermediates of the type *trans*-$Pd[P(C_6H_5)_3]_2(aryl)X$ (**3**, X = Cl, Br). ^1H- and ^{31}P-NMR studies revealed that especially donor-substituted derivatives undergo a facile aryl–aryl exchange between the Pd^{II} center and coordinated phosphine ligands [12]. Subsequent intermolecular phosphine scrambling promotes further isomerization to different phenylpalladium complexes (**4a–c**), which

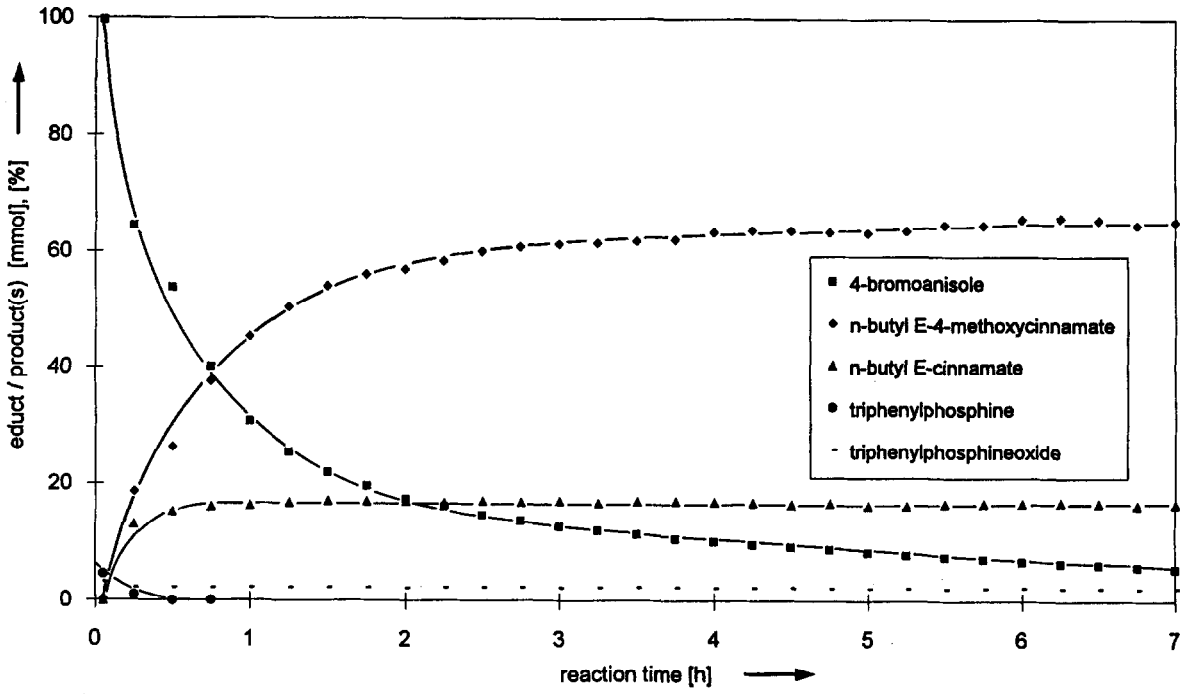


Fig. 1. Concentration vs. time diagram (GLC) for the Heck olefination of 4-bromoanisole (**1d**) with *n*-butyl acrylate. $T = 140°C$; catalyst: $Pd(OAc)_2 + 4P(C_6H_5)_3$ (Pd/P = 1/4), concentrations see Table 1.

all give the vinylic side product after coupling with added olefin in the presence of a base (Scheme 3). As shown in Fig. 1, Heck product and side product are formed in parallel reactions with similar initial rates and no induction periods.

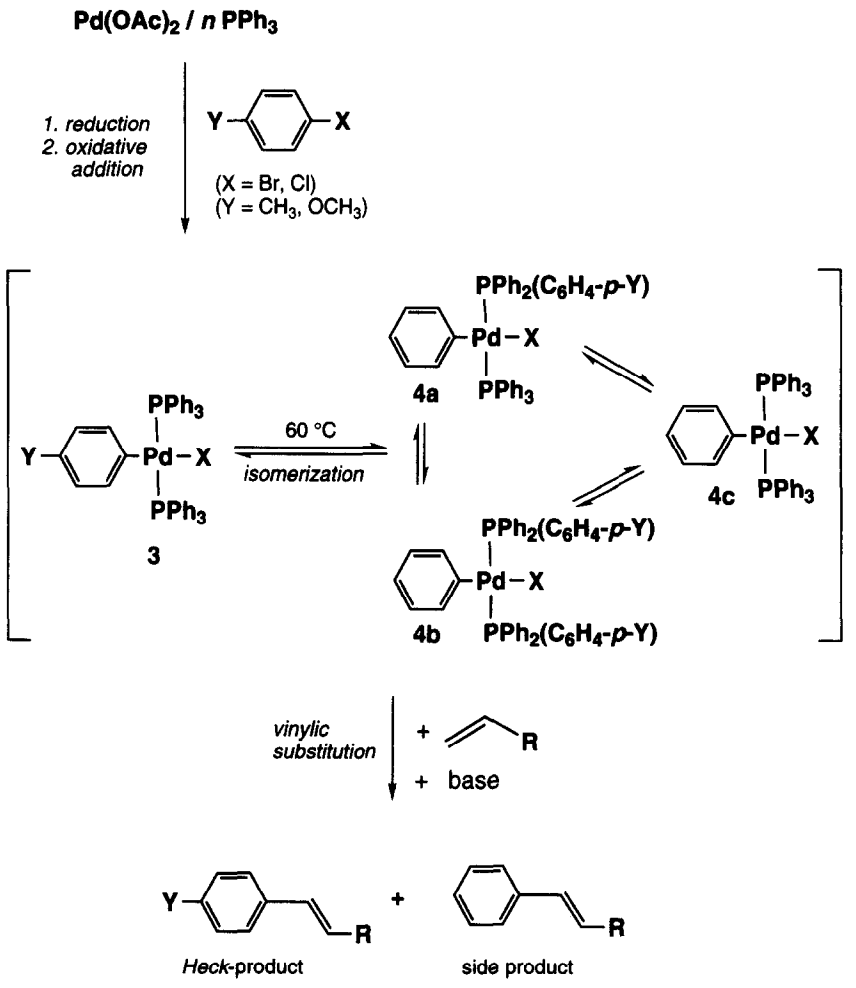
Because isomerization of donor substituted arylpalladium(II) halides **3** (Y = OCH_3, CH_3) is operative at temperatures far below the temperature of the Heck reaction, electron-rich aryl halides (4-bromo-, 4-chloroanisole) achieve considerably lower catalytic results. Although aryl halides are readily activated via insertion of Pd(0) into the C–X bond, subsequent rearrangements in the oxidative addition complex give more stable phenylpalladium species, which all lead to *n*-butyl *E*-cinnamate as side product (Scheme 3).

The labile constitution of Pd^{II} intermediates **3** is clearly seen in stoichiometric reactions: In the case of electron-donating substituents (Y = OCH_3, CH_3) **3** yields *predominantly* coupling products (i.e. cinnamate) derived from tri-*phenyl*phosphine (cf. Scheme 3) [13](b).

The amount of side product correlates with decrease in phosphine concentration (Fig. 1). Depending on substrate and reaction temperature, a maximum of *two* phenyl groups per phosphine is cleaved to account for the produced amount of side product. This continuous phosphine decomposition leads to a gradual subcoordination of the metal species, ultimately accelerating palladium precipitation with concomitant loss of activity.

Triphenylphosphine *oxide* is found right from the beginning in all catalytic runs with $Pd(OAc)_2 + 4PPh_3$ (^{31}P-NMR, GLC). The concentration remains approximately constant during the course of reaction (Fig. 1). It should now be generally accepted that PPh_3 not only is a ligand but also acts as a reducing agent for $Pd(OAc)_2$ [13]. However, triphenylphosphine oxide stabilizes the zerovalent Pd catalyst only insufficiently (early metal precipitation at 100°C in reaction with **1a**, Scheme 2).

The palladium complexes $Pd(PPh_3)_4$ and $Pd(PPh_3)_2(C_6H_4$–*p*-CHO)Br display very similar characteristics in catalysis (PC bond cleavage, kinetics, ^{31}P-NMR spectra). The concentration vs. time diagrams are almost identical to those obtained with $Pd(OAc)_2 + 4PPh_3$. Especially



Scheme 3. Formation of side products induced by isomerization of arylpalladium(II) intermediates (PC bond cleavage).

$Pd(PPh_3)_4$ and the mixture $Pd(OAc)_2/4PPh_3$ proved to be equivalent catalyst systems for the studied type of reaction [13](b).

Tri(o-tolyl)phosphine

Heck vinylations with the catalyst system $Pd(OAc)_2+4P(o\text{-}Tol)_3$ exhibited a different kinetic profile. High activity is noticed for electron-poor aryl bromides; they are quantitatively converted within minutes. Deactivated substrates require considerably longer reaction times; for 4-bromoanisole Fig. 2 shows a *sigmoidal* increase in product concentration. The most apparent characteristics is the high stability of this catalyst even at temperatures around 150–160°C and the absence of side reactions induced by PC bond cleavage. The phosphine concentration remains constant (Fig. 2). *No* formation of tri(*o*-tolyl)phosphine oxide is observed (^{31}P-NMR). A catalyst mixture consisting of $Pd(OAc)_2$ and $P(Mes)_3$ has similar characteristics including high phosphine stability (no PC bond cleavage) and product selectivity. The closely related complex $Pd[P(o\text{-}Tol)_3]_2$ also proved to be a catalyst of similar or even enhanced activity (Table 1) [13](b),[14].

Palladium/phosphine ratio

In further experiments the phosphine concentration was varied and optimized. The results presented in Fig. 3 for the Heck vinylation of 4-bromobenzaldehyde show that the P/Pd ratio has a major influence on catalyst stability and reaction rate. A P/Pd ratio of 1/1 results in instanta-

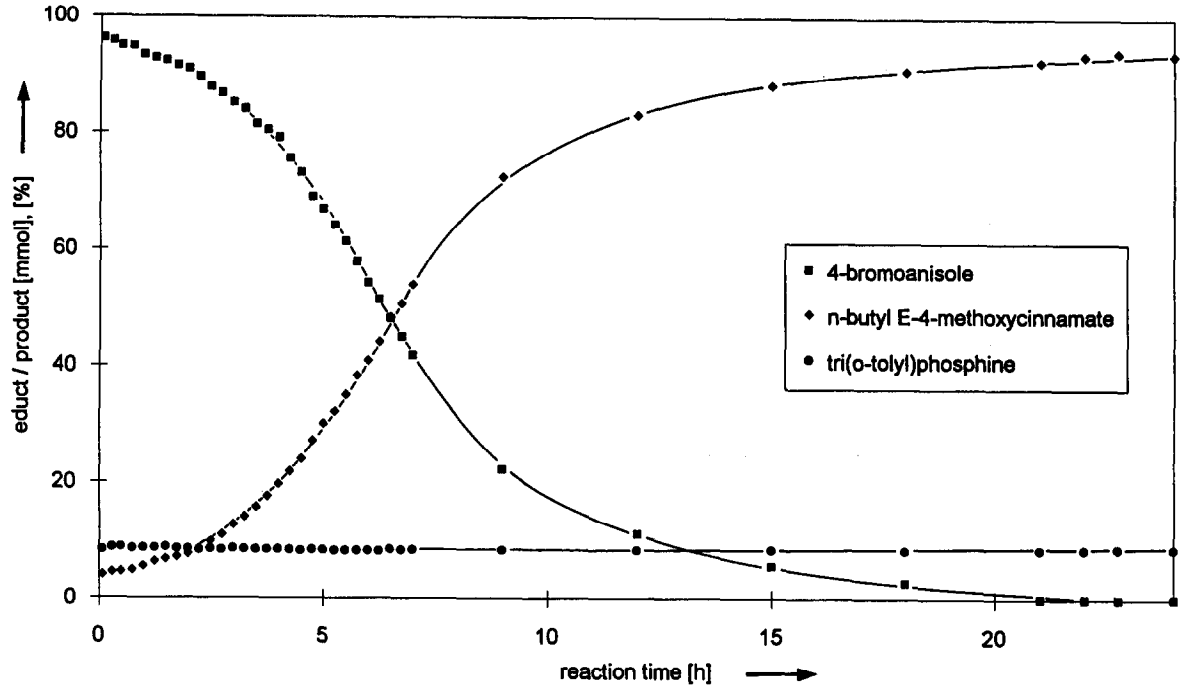


Fig. 2. Concentration vs. time diagram (GLC) for the Heck olefination of 4-bromoanisole (**1d**) with *n*-butyl acrylate. $T = 140°C$; catalyst: $Pd(OAc)_2 + 4P(o\text{-}Tol)_3$ (Pd/P = 1/4), concentrations see Table 1.

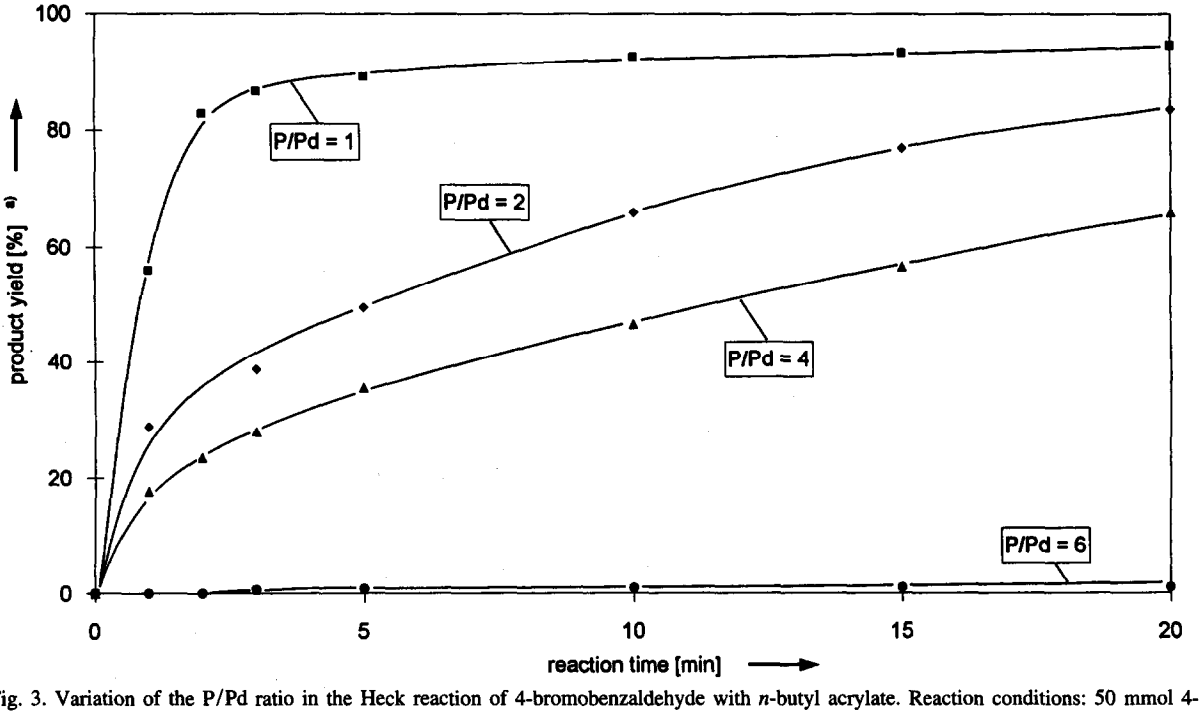
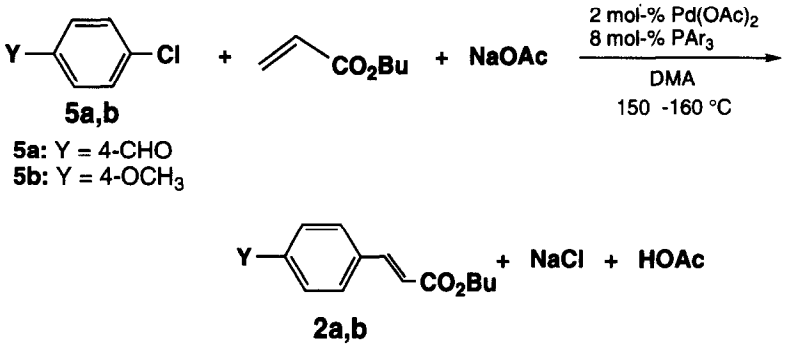


Fig. 3. Variation of the P/Pd ratio in the Heck reaction of 4-bromobenzaldehyde with *n*-butyl acrylate. Reaction conditions: 50 mmol 4-bromobenzaldehyde, 70 mmol *n*-butyl acrylate, 55 mmol NaOAc (anhydrous), 50 ml *N,N*-dimethyl acetamide, 1 g diethylene glycol di-*n*-butyl ether (GC standard), 1 mmol $Pd(OAc)_2$, $P(o\text{-}Tol)_3$: 1, 2, 4, 6 mmol. $T = 130°C$. [a] GC yield [%] of *n*-butyl *E*-4-formylcinnamate, refers to added amount of aryl bromide.



Scheme 4.

neous fast conversion; however Pd precipitation follows quickly. Higher P/Pd ratios (2/1–4/1) stabilize the catalyst while they reduce the rates. A large excess of phosphine ($P/Pd \geq 6/1$) strongly inhibits the Heck coupling. It is clear that unsaturated palladium phosphine species required for oxidative addition are not formed in this latter case to a sufficient extent.

2.2. *Aryl chlorides*

Based on our results with aryl bromides we assumed that coupling of aryl chlorides could similarly be controlled by the proper choice of a stabilizing phosphine. We thus carried out a phosphine screening using 4-chlorobenzaldehyde **5a** (electron-poor aryl chloride) and 4-chloroanisole **5b** (electron-rich) as model compounds for the Heck olefination of aryl chlorides (Scheme 4). Surprisingly, the best results with *n*-butyl acrylate as the olefin component are now found with simple triarylphosphines (PPh_3, $P(p\text{-Tol})_3$) and long-chain (diarylalkyl)diphosphines (dppb, dppen, bisbi): electron-poor 4-chlorobenzaldehyde is converted quantitatively, giving ca. 70% of the corresponding cinnamic ester (Table 2); deactivated 4-chloroanisole yields only ca. 40% of the desired coupling product (Table 3).

Triarylphosphines

Extensive PC bond cleavage, once again found in nearly all arylphosphines, is particularly detrimental to the catalytic reaction. Unwanted side products are formed via coupling of phosphine-bound aryl groups with *n*-butyl acrylate (Table 2 and Table 3). In Fig. 4a the parallel formation of *n*-butyl *E*-4-formylcinnamate (Heck product) and *n*-butyl *E*-4-methylcinnamate (side product) was recorded as a function of time for the catalyst system $Pd(OAc)_2 + 4P(p\text{-Tol})_3$. One can see that side product formation ceases directly after all $P(p\text{-Tol})_3$ has decomposed (≈ 2 h). After that, the concentration of Heck product continues to increase while that of the side product stays constant. The detected yield (≈ 12–15%) corresponds to a cleavage of more than *half* of all phosphine-bound aryl groups. At a conversion of approx. 70–80%, the catalyst seems no longer stabilized by the remaining phosphine oxide since palladium begins to precipitate from the solution.

Side products originate analogously from isomerization of oxidative addition products (aryl–aryl exchange and phosphine scrambling) and subsequent vinylic substitution with added *n*-butyl acrylate (Scheme 3). However, whereas only electron-rich aryl bromides lead to pronounced formation of side products, this is already true for electron-poor derivatives in the case of aryl *chlorides* (e.g. 4-chlorobenzaldehyde). This must be due to the higher reaction temperature (150°C) and lower reactivity of these substrates. The former is apparently high enough to allow for partial isomerization of even more stable acceptor-substituted arylpalladium(II) chlorides, e.g. $Pd(PPh_3)_2(C_6H_4\text{–}p\text{-CHO})Cl$.

Table 2
Pd catalyzed CC coupling of 4-chlorobenzaldehyde with *n*-butyl acrylate

Ligand/phosphine	θ [a] [deg]	ν [b] [cm^{-1}]	Conversion [c] [%]	Yield [c] of *n*-butyl *E*-4-formylcinnamate [%]	Yield [h] of side product (PC bond cleavage) [mmol]
PPh_3	145	2069	100, 100, 100	68; 71; 69	6.0; 6.0; 6.1 **1**
$Pd(PPh_3)_4$ [f]			100	69	6.4 **1**
$P(p\text{-Tol})_3$	145	2067	100, 100	63; 72	5.0; 6.1 **2a**
$PPh(p\text{-Anisyl})_2$	145	2067	100	70	2.1 **1**/4.0 **3a**
$P(p\text{-Anisyl})_3$	145	2066	100, 100	68; 72	6.0 **3a**
$PPh(C_6H_4\text{-}p\text{-}NMe_2)_2$	145	2067	78	47	1.8 **1**/1.6 **4**
$PPh_2(o\text{-Tol})$			100 [d], 100 [e]	56 [d]; 40 [e]	1.5 **1**/1.0 **2c**
$PPh(o\text{-Tol})_2$			53 [d], 62 [e]	21 [d]; 16 [e]	< 1.0 **2c**
$P(o\text{-Tol})_3$	194	2067	83 [d], 42	33 [d]; 27	–
$P(2\text{-furyl})_3$			100	64	4.1 **5**
$PPh(2\text{-pyridyl})_2$			28	8	–
$P(Mes)_3$	212	2064	23	0	–
$P(C_6F_5)_3$	184	2091	55	0	–
$AsPh_3$	142		8	0	–
dppe	125		71	34	2.1 **1**
dppp	127		91	50	2.7 **1**
bisbi [g]			77	39	1.5 **1**
PCy_3	170	2056	100	8	7.2 **6**
$P(Cy)_2(o\text{-Tol})$			10	0	2.0 **6**
$P(i\text{-Pr})_3$	160	2059	100	23	1.7 **6**
$P(n\text{-Bu})_3$	132	2060	84	25	1.6 **6**

Reaction conditions: 50 mmol 4-chlorobenzaldehyde, 70 mmol *n*-butyl acrylate, 55 mmol NaOAc (anhydrous), 50 ml *N,N*-dimethyl acetamide, 1 g diethylene glycol di-*n*-butyl ether (GC standard), 1 mmol $Pd(OAc)_2$ (2 mol-% Pd), 4 mmol monophosphine, 2 mmol diphosphine resp. (8 mol-% P^{III}); P/Pd = 4, T = 150°C, t = 24 h.

[a] Cone angle, from ref. [13].

[b] Frequency of the A_1 carbonyl mode of $Ni(CO)_3L$ (L = phosphine) in CH_2Cl_2, from ref. [13].

[c] GC yield/conversion with reference to 4-chlorobenzaldehyde.

[d] 70 h.

[e] 48 h/160°C.

[f] 1 mmol.

[g] 2,2′-Bis(diphenylphosphinomethyl)-1,1′-biphenyl.

[h] Side products: **1**: *n*-butyl *E*-cinnamate; **2a**: *n*-butyl *E*-4-methylcinnamate; **2b**: *n*-butyl *E*-3-methylcinnamate; **2c**: *n*-butyl *E*-2-methylcinnamate; **3a**: *n*-butyl *E*-4-methoxycinnamate; **3b**: *n*-butyl *E*-2-methoxycinnamate; **4**: *n*-butyl *E*-4-dimethylaminocinnamate; **5**: *n*-butyl *E*-3-(2-furyl)acrylate; **6**: di-*n*-butyl 2-methylene glutarate (butyl acrylate dimer).

Tri(o-tolyl)phosphine

The *ortho*-methyl substituted triarylphosphines $P(o\text{-Tol})_3$ and $P(Mes)_3$ display very similar stability characteristics in the olefination of aryl chlorides. The formation of side products via PC bond cleavage is effectively inhibited, but these sterically demanding ligands (Tolman angle > 190°) proved to be incapable of stabilizing the palladium catalyst in solution. Right before the minimum reaction temperature is reached, a sudden precipitation of palladium occurs. Therefore the reaction rate remains at a low level (Fig. 4b). Some residual catalytic activity may be due to colloidal or sintered palladium species although their thermal range of stability must be considered rather low [5]a,[15].

Diphosphines

Diphosphines of the type $Ph_2P(CH_2)_nPPh_2$ (n = 1–6) result in more stable metal complexes but they do *not* promote catalytic activity. Heck reactions in the presence of these ligands are often hampered by long induction periods (0.5–6 h). Prior to conversion of the aryl chlorides, signifi-

Table 3
Pd catalyzed CC coupling of 4-chloroanisole with *n*-butyl acrylate

Ligand/phosphine	θ [a] [deg]	ν [b] [cm^{-1}]	Conversion [c] [%]	Yield [c] of *n*-butyl *E*-4-methoxycinnamate [%]	Yield [n] of side product (PC bond cleavage) [mmol]
PPh_3	145	2069	57, 59, 70	37, 38, 48	6.3, 6.7, 6.2 **1**
$Pd(PPh_3)_4$ [k]			71	33	6.5 **1**
P(*p*-Tol)$_3$	145	2067	59, 58	41, 35	6.9, 6.7 **2a**
P(*m*-Tol)$_3$			32, 64 [d]	11, 30 [d]	4.0, 6.6 **2b**
P(*p*-Anisyl)$_3$	145	2066	36, 44	30, 33	–
P(*o*-Anisyl)$_3$	170	2058	16, 13	8, 8	1.2, 1.2 **3b**
PPh_2(*o*-Tol)			50 [e], 51	26 [e], 24	2.5 [e] **1**/1.6 [e] **2c**
PPh(*o*-Tol)$_2$			50 [e], 79 [f]	29 [e], 45 [f]	< 1.0 **2c**
P(*o*-Tol)$_3$	194	2067	34, 32; 31 [g], 5 [h]	27, 23, 24 [g], 5 [h]	–
P(2-furyl)$_3$			0	0	–
dppm	121		17, 14	9, 5	1.5, 1.0 **1**
dppe	125		37, 29	26, 16	3.1, 2.1 **1**
dppp	127		38, 44	29, 26	3.8, 3.1 **1**
dppb			51, 50	38, 38	3.4, 2.7 **1**
dppent			52, 51	43, 33	3.7, 3.2 **1**
dpph			52, 58	38, 36	4.0, 3.1 **1**
1,4-bis[bis(2-methoxyphenyl)phosphino]butane			8 [d], 19 [i]	1 [d], 14 [i]	7.7 **6**
bisbi [l]			56, 61	44, 43	2.3, 2.4 **1**
naphos [m]			54	37	1.9 **1**
$Ph_2P(CH_2)_2OCH_3$			43, 52	29, 40	2.8, 3.1 **1**
$Ph_2P(CH_2)_2N(CH_3)_2$			45, 29 [j]	29, 21 [j]	3.0, 2.3 **1**
$Ph_2P(CH_2)_3N(CH_3)_2$			63, 44 [j]	36, 25 [j]	4.0, 3.5 **1**
phenyl-3,4-dimethylphosphole			13, 2 [j]	0, 0 [j]	–
phenyl-5H-dibenzophosphole			23, 21	22, 10	2.2, 1.4 **1**
PCy_3	170	2056	34, 38 [h]	23, 6 [h]	6.4, 4.4 **6**

Reaction conditions: 50 mmol 4-chloroanisole, 70 mmol *n*-butyl acrylate, 55 mmol NaOAc (anhydrous), 50 ml *N,N*-dimethyl acetamide, 1 g diethylene glycol di-*n*-butyl ether (GC standard), 1 mmol $Pd(OAc)_2$ (2 mol-% Pd), 4 mmol monophosphine, 2 mmol diphosphine resp. (8 mol-% P^{III}); P/Pd = 4, T = 160°C, t = 24 h.

[a] Cone angle, from ref. [13].

[b] Frequency of the A_1 carbonyl mode of $Ni(CO)_3L$ (L = phosphine) in CH_2Cl_2, from ref. [13].

[c] GC yield/conversion with reference to 4-chloroanisole.

[d] 48 h.

[e] 4d/150°C.

[f] 8d/160°C.

[g] 6 mmol PR_3.

[h] 130°C.

[i] 72 h.

[j] 150°C.

[k] 1 mmol.

[l] 2,2′-Bis(diphenylphosphinomethyl)-1,1′-biphenyl.

[m] 2,2′-Bis(diphenylphosphinomethyl)-1,1′-binaphthalene.

[n] Side products: for abbreviations see Table 2.

cant amounts of ligand must degrade (via PC bond cleavage) in order to break up the phosphine inhibition. Increased chain lengths seem to favour the coupling reaction (Table 3). Short-chain diphosphines form either dinuclear Pd^I complexes (n = 1, e.g. $Pd_2Cl_2(\mu\text{-dppm})_2$) [16] or coordinatively saturated Pd^0 complexes (n = 2, 3) [17]. The stable chelate complexes $Pd(dppe)_2$ and

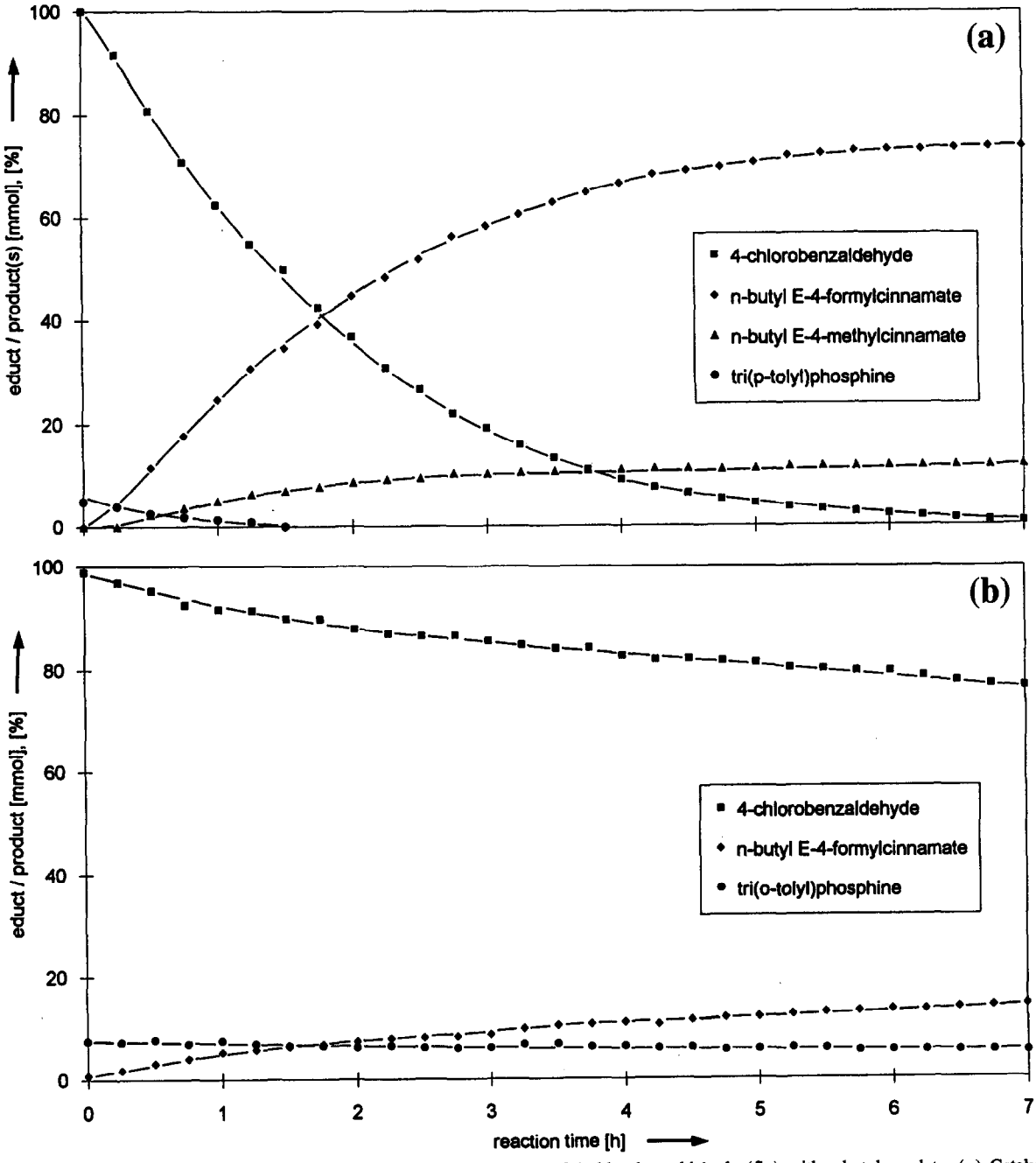


Fig. 4. Concentration vs. time diagrams (GLC) for the Heck olefination of 4-chlorobenzaldehyde (**5a**) with *n*-butyl acrylate. (a) Catalyst $Pd(OAc)_2+4P(p\text{-}Tol)_3$; (b) catalyst: $Pd(OAc)_2+4P(o\text{-}Tol)_3$. Reaction conditions: 100 mmol 4-chlorobenzaldehyde, 140 mmol *n*-butyl acrylate, 110 mmol NaOAc (anhydrous), 100 ml *N,N*-dimethyl acetamide, 2 g GC standard, 2 mmol $Pd(OAc)_2$, 8 mmol $P(aryl)_3$. $T=150°C$.

Scheme 5.

$Pd(dppp)_2$ showed only minor reactivity towards aryl chlorides [12,18]. Long-chain diphosphines ($n=4$–6, dppb, dpppen, dpph) have enhanced conformational flexibility in their backbones and allow for either monodentate or bidentate coordination. For this reason, Milstein proposed a reversible chelate opening for these ligands to rationalize the observed catalytic effects [7](a)[18]. We find better yields for long-chain derivatives, however significant improvements in comparison with ordinary triarylphosphines (PPh_3, P(*p*-Tol)$_3$) could not be established.

The chelating ligands bisbi and naphos [19] give comparable catalytic results ($\approx 40\%$ yield for **5b**) while producing less amounts of *n*-butyl cinnamate. The use of potentially chelating P–N and P–O donor ligands $Ph_2P(CH_2)_nN(CH_3)_2$ ($n=2$, 3) and $Ph_2P(CH_2)_2OCH_3$ [20] yielded no beneficial effects. Phospholes proved to be ineffective too, presumably because of their insufficient coordination potential.

Trialkylphosphines

The tri*alkyl*phosphines P(*i*-Pr)$_3$, P(Cy)$_3$ and P(*n*-Bu)$_3$ – in general supporting oxidative addition reactions at Pd^0 centers [21] – favour another unwanted side reaction: the oxidative coupling of olefinic substrates. This reaction type, which is characteristic of strongly nucleophilic phosphines and electron-poor olefins, is preferred under the reaction conditions and strongly dominates the Heck olefination. It is operative even in the absence of palladium acetate. For example PCy_3 was found to catalyze the dimerization of *n*-butyl acrylate to di-*n*-butyl 2-methylene glutarate and higher oligomers (Scheme 5).

3. Discussion

Our results in the Heck reaction show that application of the catalyst system $Pd(OAc)_2/PPh_3$ is confined to *activated* aryl bromides. The higher reactivity of these substrates as compared with deactivated bromides and aryl chlorides allows for quantitative conversion at temperatures well below 120°C, so that side product formation and palladium precipitation primarily caused by PC bond cleavage can be avoided effectively. Phosphines are even unnecessary for activated bromides, if the reaction is performed under the phase-transfer conditions reported by Jeffrey [10].

Both the mechanism for catalyst generation starting from palladium acetate ($Pd^{II} \rightarrow Pd^0$) and the kinetically verified analogy with the complex $Pd(PPh_3)_4$ confirm the participation of Pd^0 intermediates in the catalytic cycle. The oxidative addition products *trans*-$Pd(PPh_3)_2$(aryl)X are commonly believed to be intermediates, too. Stoichiometric reactions with olefins in the presence of base and similar kinetic behavior strongly support this view [13](b). Even if these species should not represent *direct* intermediates, their activity proves successful integration into the catalytic cycle. Hence all results obtained so far with the catalyst system $Pd(OAc)_2/PPh_3$ point to an interplay between Pd^0 and Pd^{II} in the catalytic cycle, according to the early mechanism proposed by Heck.

Tri(*o*-tolyl)phosphine is a much better ligand in Heck reactions of aryl bromides than triphenylphosphine. Both activated and deactivated aryl bromides are selectively and quantitatively converted into the corresponding cinnamic esters, without formation of side products. However, the high efficiency of the catalyst system $Pd(OAc)_2$/P(*o*-Tol)$_3$ is not based on steric grounds as has been proposed in the literature [9](a). The papers to follow [22](a,b) will show the true reason of this behavior; at the same time; a new structural catalyst principle for the Heck reaction will be presented [22,23].

The studies with aryl chlorides show only little influence of structurally different phosphines. Because of the necessarily high reaction temperature phosphines act primarily as *stabilizing* and not so much as steering ligands. The success of the Heck reaction is therefore highly dependent upon ligands that delay or prevent palladium precipitation. Simple triarylphosphines (PPh_3, P(*p*-Tol)$_3$) are found to stabilize the palladium

catalyst up to moderate or good conversions, whereas sterically demanding tri(*o*-tolyl)phosphine leads to immediate precipitation of palladium black. A complete prevention of metal precipitation seems impossible as long as arylphosphines are converted quantitatively into side products and phosphine oxide. Although side product formation is induced by PC bond cleavage in the oxidative addition complex (Scheme 3), its intrinsic mechanism is still a matter of speculation. A reaction sequence involving *orthometalation* of the phosphine can be excluded because *para*-substituted triarylphosphines yield exclusively *para*-substituted coupling products (Fig. 4a), otherwise PC bond cleavage would have resulted in *meta*-substituted cinnamic esters.

The poor performance of aryl chlorides in the Heck reaction has previously been attributed to the low reactivity of zerovalent palladium triphenylphosphine complexes with regard to oxidative addition of the aromatic carbon–chlorine bond. As a result, palladium species were thought to accumulate as Pd^0 with the ultimate consequence of ready metal precipitation [4],[5](b). Our results call these conclusions into question. We proved, for example, that all aryl chlorides, i.e. acceptor-*and* donor-substituted derivatives, *do* add oxidatively to the phosphine complexes $Pd(PPh_3)_4$ and $Pd(PPh_3)_2$(dba) at 100–140°C [12](a). Hence not the lower rate of oxidative addition but rather isomerizations at the Pd^{II} center (aryl–aryl exchange, phosphine scrambling) and ligand degradation (PC bond cleavage + vinylic substitution) account for early catalyst deactivation.

The extremely nucleophilic ligands dippp and dippb mentioned in the introduction show a tendency of attacking electron-poor olefins (e.g. acrylates) in the Heck reaction. Especially the dimerization of olefinic compounds is noticed as a major side reaction. Milstein's catalyst system is yet limited to the use of styrenes [7]. Another remarkable feature concerns the reaction temperature: although aryl chlorides easily add to $Pd(dippp)_2$ and $Pd(dippb)_2$ at 60–80°C [18](a,b), a reaction temperature of 150°C was reported to allow for successful Heck coupling [7]. This discrepancy between activation step and overall reaction illustrates the importance of other elemental steps in the catalytic cycle, namely olefin insertion, β-H elimination and reductive HCl elimination [18](c).

Further studies aimed at an activation of aryl chlorides in the Heck reaction should concentrate on temperature-stable catalysts and measures to inhibit metal precipitation. Promising new catalytic concepts will be reported in due course [22–24].

4. Experimental

Palladium(II) acetate was purchased from Degussa AG. Phosphines were either prepared by literature methods [9](a),[20] or were obtained from Aldrich, Fluka or Strem. Other chemicals were from Fluka or Aldrich. The palladium complexes $Pd(PPh_3)_4$ [25], $Pd(PPh_3)_2(Ar)X$ (X = Br, Cl) [12],[21](c) and $Pd[P(o\text{-}Tol)_3]_2$ [13](b),[14] were synthesized according to literature methods. NMR spectra (^1H, ^{31}P, ^{13}C) were recorded on a JEOL JMX-GX 400 instrument. GC–MS spectra were measured on a Hewlett Packard gas chromatograph GC 5890 A equipped with a mass selective detector MS 5970 B. Elemental analyses were carried out by the Microanalytical Laboratory at the Technische Universität München. All products were fully characterized (GC–MS, ^1H-, ^{13}C-, ^{31}P-NMR, EA), yields were determined by gas chromatography. Quantitative GC analyses were performed with a Hewlett Packard 5980 A instrument using a 12.5 m HP-1 capillary column in conjunction with a flame ionisation detector (GC/FID).

Except for the work-up of reaction mixtures, all operations were carried out under argon. *N,N*-dimethyl acetamide was distilled prior to use. Catalyst solutions were freshly prepared for each reaction and only used once.

4.1. General procedure

Catalyst solutions: To *N,N*-dimethyl acetamide (20 ml) was added under argon palladium acetate

(225 mg, 1 mmol) and triarylphosphine (4 mmol) or diphosphine (2 mmol) respectively (P/Pd = 4). The mixture was stirred at room temperature until homogeneous and degased several times prior to use.

Reaction mixture: In a 100 ml three-necked flask equipped with a septum inlet, a thermometer and a reflux condenser (Hg bubbler) were placed aryl halide (50 mmol), anhydrous sodium acetate (4.51 g, 55 mmol), diethylene glycol di-*n*-butyl ether (1 g, GC standard) and *N*,*N*-dimethyl acetamide (30 ml). The reaction mixture was degased under vacuum and argon was passed over the condenser for 5 min to ensure an inert reaction atmosphere. *N*-butyl acrylate (10 ml, 70 mmol) was then added last because of possible losses by evaporation. The reaction mixture was stirred vigorously and heated to the appropriate reaction temperature. After thermostating for 10 min the catalyst solution was injected by syringe ($t = 0$). Circa 0.5 ml samples were continuously removed, washed with 5 ml 5% hydrochloric acid and extracted with 3.5 ml methylene chloride. The organic phases were removed and sealed in GC vials for the gas chromatographic determination of the yield.

Work-up was achieved by pouring the reaction mixture at room temperature into an excess of water, extracting with methylene chloride or diethyl ether, and drying with magnesium sulphate. After removal of the extraction solvent and DMA, the products were purified by distillation or recrystallisation.

For the gas chromatographic determination of reaction profiles (concentration vs. time diagrams) reactant amounts were doubled in order to ensure an approximately constant reaction volume.

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