Palladium-Catalyzed Reactions for Fine Chemical Synthesis, 4[◇]

Phosphapalladacycle-Catalyzed Heck Reactions for Efficient Synthesis of Trisubstituted Olefins: Evidence for Palladium(0) Intermediates

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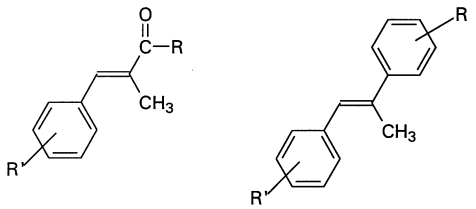
The coupling reaction of 1,1-disubstituted olefins (α-methylstyrene, *n*-butyl methacrylate) with various aryl bromides (Heck reaction) has been studied as a new concept to synthesize trisubstituted olefins. Surprisingly, the nature of the base dramatically influences the product distribution. Thus, a systematic investigation on the role of base in Heck reactions of 1,1-disubstituted olefins was performed. Less coordinating bases like NaOAc, NaOBz or Na_2CO_3 yield a statistical distribution of regioisomers with the terminal olefin **10** as the major product. However, by using amines like Bu_3N or diisopropylethylamine (DIPEA) as base internal olefins can be synthesized with high selectivities. With phosphapalladacycle **3** as catalyst precursor, we were able to obtain catalyst turnover numbers up to 1000, while $Pd(OAc)_2/2PPh_3$ was one order of magnitude less active. Analysis of the reaction profile by kinetic investigations led to the postulation of a reduction and subsequent oxidative addition of the catalyst precursor **3** to form **12** as catalytically active intermediate.

Introduction

Trisubstituted, arylated olefins of the type **A** or **B** display interesting pharmacological or physical properties.[2]

Figure 1. Trisubstituted aromatic olefins



A **B**

In this respect derivatives of α-methylcinnamic acids display hypolipidemic activities.[2a] Further, the substructure is found in active substances such as the antibiotic hygromycin A.[2b] In addition, certain α-methylstilbenes can be used as nematic liquids[2c] with interesting retinoidal properties.[2d] Despite of their broad applications the stereodefined synthesis of trisubstituted alkenes is still a challenge of modern synthetic organic chemistry. Although a number of methodologies have been reported in the literature[3] the problems in synthesizing highly substituted alkenes, e.g. by Wittig reaction are well documented.[4] Thus, the search for alternative methodologies is ongoing.[5]

In this respect, the palladium-catalyzed Heck reaction is a powerful tool for the construction of aryl- and vinyl-substituted carbon−carbon double bonds as it does not interfere with a broad range of functional groups (for reviews see ref.[6]). Recently, we have developed cyclometallated palladium complexes as a new type of efficient catalysts for Heck and related reactions.[7][8] Obviously, olefins **A** or **B** should be available by Heck olefination. However, the low regioselectivity in the formation of the C=C double bond using disubstituted as well as aliphatic olefins is still a major disadvantage for the application of Heck reactions. The low regioselectivity can be explained either by unselective β-hydride elimination during the catalytic cycle, and/or by the tendency of the eliminated HPdX species to undergo readdition and subsequent β-hydride elimination to different hydrogen atoms, thus resulting in isomerization reactions.

As a concept for controlling regioselective olefin formation Tietze et al. have shown that silyl groups in allylsilanes act as terminating group in intramolecular Heck reactions enabling regio- and enantioselective construction of triple-substituted double bonds.[9] More recently, Ricci et al. reported a stereo- and regiocontrolled synthesis of di- and trisubstituted olefins starting from vinylsilanes by a Heck reaction and Pd-catalyzed desilylation reaction sequence.[10] Despite the high selectivities for specific double-bond isomers using silyl-substituted olefins it is obvious that control of the double-bond formation in Heck reactions using simple disubstituted alkenes by other means is a very attractive goal.

Results and Discussion

The interesting properties of α-methylcinnamic acid derivatives[2a][2b][11] prompted us to study regioselective Heck reactions of various aryl bromides **1** with *n*-butyl methacry-

[◇] Part 3: Ref.[1].

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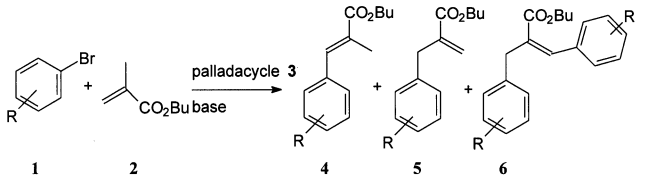
late (**2**) as model reaction.[12] Clearly, after insertion of the olefin into the Ar−Pd−Br complex there are two possibilities for β-hydride elimination: it can proceed towards the methyl or the benzylic methylene group. The former reaction leads to α-benzylacrylates **5** with a terminal double bond, the latter to α-methylcinnamic acid esters **4** with an internal double bond. Because of the reactivity of terminal olefins **5** the doubly arylated product **6** can subsequently be formed. In addition, *E* and *Z* isomers of **4** and **6** could be formed. Due to the importance of the β-hydride elimination for determining the double-bond selectivity we anticipitated that the nature of the base will be of major influence for the product distribution. Thus, various bases were examined for the reaction of *n*-butyl methacrylate with 1-bromo-4-fluorobenzene using the phosphapalladacycle catalyst **3** {*trans*-di(μ-acetato)bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II)[13]}. The results are sumarized in Table 1.

Table 1. Heck reaction of *n*-butyl methacrylate with aryl bromides



1 **2** **4** **5** **6**

Run	R	Base	Time [h]	Conversion aryl bromide [a] [%]	TON	Internal olefin[b] [%]	Terminal olefin[b] [%]	Double arylated[b] [%]
1	4-F	NaOAc	24	83	8300	39	28	33
2	4-F	Bu_3N	24	36	3600	76	20	4
3	4-F	Bu_3N	24	92	920	79	8	13
4	4-F	DIPEA	24	90	900	82	5	13
5	4-$COCH_3$	NaOAc	18	> 98	980	42	9	49
6	4-$COCH_3$	Bu_3N	4	> 98	980	79	7	14
7	4-OCH_3	NaOAc	18	40	400	45	40	15
8	4-OCH_3	Bu_3N	24	25	250	82	17	1
9	4-Cl	NaOAc	18	> 98	980	38	18	44
10	4-Cl	Bu_3N	4	> 98	980	76	8	16

Reaction: 15 mmol of aryl bromide with 22.5 mmol of butyl methacrylate in the presence of 18 mmol of base and 0.1 or 0.01 mol% of phosphapalladacycle catalyst **3** in 15 ml of DMAc at 135−140°C. − [a] Conversions of the aryl bromides have been determined by GC with internal standard (diethylene glycol dibutyl ether). − [b] Selectivities have been determined by GC on the basis of area percentage.

Indeed, the nature of base significantly influences the regioselectivity of the double bond. Sodium acetate favors the formation of terminal olefin **5**, thus leading to a relatively large extent of doubly arylated products **6** (Table 1, run 1). In contrast, in the presence of 1.2 equiv. of tributylamine the internal olefin **4** is formed as major product (runs 2 and 3). Further improvement of selectivity towards the internal olefin **4** was achieved using the sterically hindered base *N,N*-diisopropylethylamin (DIPEA) which gives so far the best selectivities for this reaction (internal olefin/terminal products, 82:18, run 4). Interestingly, the productivity of the catalyst system is reduced by a factor of 3 in the presence of amines compared to NaOAc (0.01 mol% Pd, runs 1 and 2) which is explained by enhanced stabilization of Pd^{II} intermediates. While the selectivity in the presence of NaOAc is only moderate the catalyst productivity (TON = 8300) is about two orders of magnitude higher compared to previous data of similar reactions.[14]

In order to distinguish between thermodynamic or kinetic control of the double-bond formation the terminal olefin **5** was isolated and treated with NaOAc and Bu_3N under reaction conditions in the presence of the palladium catalyst. Only a negligable amount of isomerization of **5** to the more stable internal olefin **4** was detected. Thus, we assume that the formation of the double bond occurs under kinetic control.

Comparison of the phosphapalladacycle **3** with conventional palladium phosphane complexes which were tested as in situ catalysts shows the superiority of **3**. Significantly lower conversions (16% and < 5%) were obtained in the presence of tributylamine as base and 0.1 mol% $Pd(OAc)_2$/PPh_3 (1:2) or $Pd(OAc)_2$/P(*o*-tolyl)$_3$ (1:2), respectively.

In agreement with previous results[6] the electronic nature of the aryl bromide has dominating effect on the yield of the reaction (runs 5−10). Here, electron-withdrawing substituents enhance the productivity. It is noteworthy that, in all cases where amine is used as base, the ratio of internal olefin to terminal and doubly arylated olefin is approximately 80:20, while with NaOAc as base the ratio is about 40:60. Therefore, we conclude that the electronic nature of the aryl bromide has just a minor effect on the selectivity.

As a suitable candidate for further evaluation of the influence of base on the regioselectivity of Heck reactions with 1,1-disubstituted olefins we considered α-methylstyrene (**8**) which is available on large scale.[15] Here, the olefination of 1-bromo-4-chlorobenzene (**7**) was performed in the presence of 8 different bases. As shown in Scheme 1 five different Heck products can in principle arise from the reaction of **7** and **8** (both *E* and *Z* isomers are possible).

To suppress formation of doubly arylated Heck products an excess of α-methylstyrene **8** (5 equiv.) was used. The results of the model reaction are summarized in Table 2.

Using the phosphapalladacycle *trans*-di(μ-acetato)bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II) (**3**) as catalyst under standard reaction conditions (dimethylacetamide, NaOAc, 0.1 mol% **3**, 135−140°C, 24 h; run 1) the coupling products were isolated in excellent yield (94%). Analogous to the reactions with *n*-butyl methacrylate the highest selectivity for the terminal olefin **10** is observed with NaOAc (**9**/**10**, 35:65). Only a small amount of the doubly arylated product **11** is formed (4% yield). Comparison of the phosphapalladacycle **3** with a classical catalyst system [0.1 mol% $Pd(OAc)_2$/2 PPh_3] gave similar results (run 10). The same regioselectivity (**9**/**10**, 37:63), albeit a lower total yield (66%) was obtained with sodium benzoate as base (run 2). Using inorganic salts such as sodium carbonate (run 3) or sodium hydrogen carbonate (run 4) excellent total yields (97% and 95%) were obtained, but the selectivity towards the terminal product is slightly lower (**9**/**10**, 38:62 and 46:54, respectively). On the other hand high selectivities up to 95:5 towards the internal olefin **9** are observed using tertiary amines as bases. Again, best results were obtained using the sterically hindered amine *N,N*-diisopropylethylamine (DIPEA, run 9, 65% total yield). A slightly lower regiose-

Scheme 1. Heck reaction of 1-bromo-4-chlorobenzene with α-methylstyrene

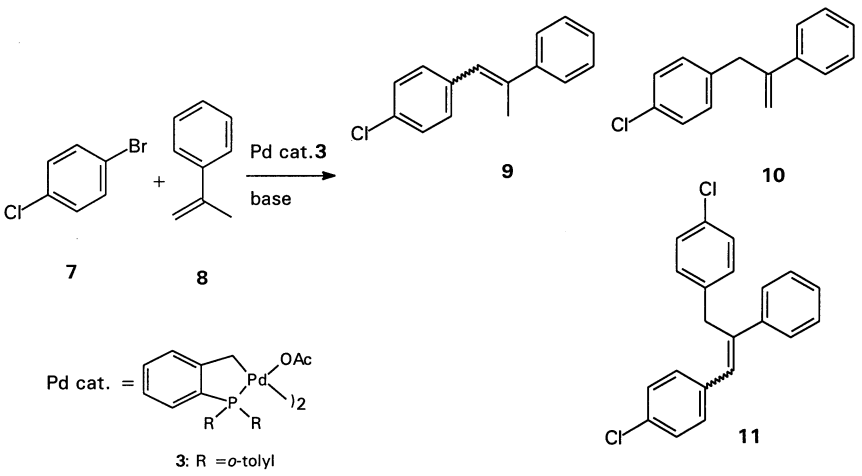
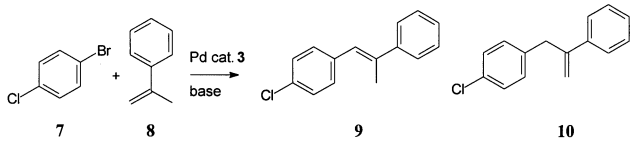


Table 2. Heck reaction of α-methylstyrene with aryl bromides



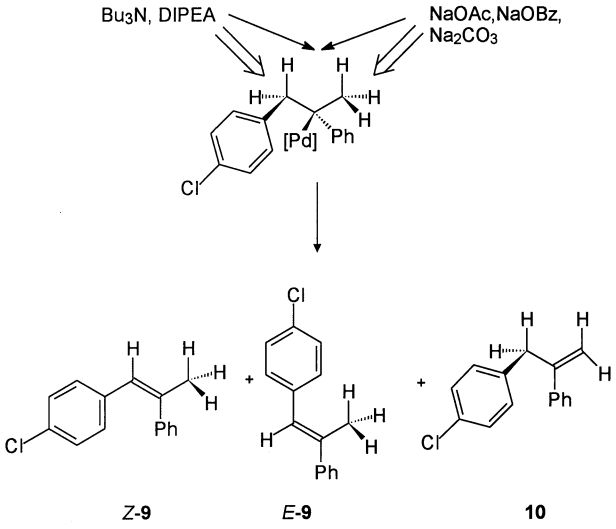
Run	Base	Yield[a] [%]	Internal[b] [%]	Terminal[b] [%]	Double[b] [%]	*E*/*Z*[b]	TON[c]
1	NaOAc	94	35	61	4	17	940
2	PhCOONa	66	37	60	3	18	660
3	Na_2CO_3	97	38	57	5	12	970
4	$NaHCO_3$	95	46	50	4	6.7	950
5	DABCO	69	53	46	1	26	690
6	0.8 NaOAc/0.2 DIPEA	96	61	35	4	4.3	960
7	proton sponge[d]	40	88	12	–	1.6	400
8	Bu_3N	66	89	11	–	2.6	660
9	DIPEA	65	95	5	–	2.5	650
$Pd(OAc_2)/2PPh_3$ (0.1 mol%) as catalyst:							
10	NaOAc	97	37	58	5	11	970
11	DIPEA	14	93	7	–	12	140

Reaction: 15 mmol of 4-bromo-1-chlorobenzene with 75 mmol of α-methylstyrene in the presence of 18 mmol of base and 0.1 mol% of phosphapalladacycle catalyst **3** in 15 ml of DMAc at 135−140°C. After 24 h, the reaction mixture was extracted and the solvent and not converted starting materials were removed in vacuo. The remaining reaction mixture was analyzed by GC, GC/MS, and ^{1}H NMR. − [a] Isolated yields. − [b] Selectivities have been determined by NMR of the isolated products. − [c] TON = mol product/mol catalyst. − [d] 1,8-Bis(dimethylamino)naphthalene.

lectivity (**9**/**10**, 89:11) is observed using tributylamine as base (66% total yield). Other bases or mixtures of bases gave results inbetween sodium acetate and DIPEA. No reaction is observed using chelating amines like TMEDA.

In the presence of amine as base the phosphapalladacycle catalyst **3** was found to be superior in productivity compared to classical catalyst precursors. Thus, the use of 0.1 mol% $Pd(OAc)_2$/2 PPh_3 led to a significantly lower total yields of **9** and **10** (14%, run 11). The selectivity towards the internal olefin is similar to the phosphapalladacycle catalyst **3** (**9**/**10**, 93:7), but there is a clear difference in the *E*/*Z* selectivity (*E*/*Z* = 12).

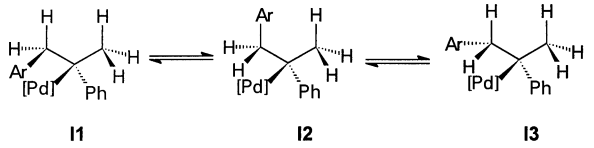
Scheme 2. Regiochemistry of the β-hydride elimination



Next we investigated whether an isomerization of the terminal olefin **10** to the internal olefin **9** in the presence of amine is possible. Neither heating of the terminal olefin **10** with catalyst **3** and DIPEA, nor heating of the internal olefin **9** with **3** and sodium acetate results in significant isomerization (< 10%). In addition, a thermodynamic isomerization would not explain the observed amount of the *Z* isomer *Z*-**9**. Thus, we propose a kinetic control for the reaction. In order to explain the different regio- and stereoselectivities (Scheme 2) we propose different mechanism for the proton abstraction (β-hydride elimination) depending on the base. Unfortunately, the β-hydride elimination and reductive elimination of HX from "H−Pd−X" have been scarcely investigated in the literature.[16] Based on simple conformation analysis the stereochemical outcome of the products is explained by β-hydride elimination from the possible intermediates **I1** (leading to **10**), **I2** (leading to *E*-**9** and **10**) and **I3** (leading to *Z*-**9** and **10**) (Scheme 3).

In the presence of less basic salts like NaOAc, NaOBz direct elimination of "H−Pd−X" will occur from inter-

Scheme 3. Conformational analysis of the β-hydride elimination



mediates **I1**, **I2** and **I3**. Because of the nearly statistical product ratio (terminal/internal, 3:2) we assume that the less coordinating bases are not involved in the elimination step of "H−Pd−X". However, the amine-assisted elimination takes place towards the most acidic protons (Scheme 2). A direct abstraction of the more acidic benzylic protons would explain for the low selectivity for the *E* isomer ***E*-9** because of a similar acidity of both benzylic protons. Thus, we believe that the base is involved in the β-hydride elimination by proton abstraction. Support for the direct abstraction of the proton may also result from the fact that the amine is blocking coordination sites on the metal centre, which are esssential for β-hydride elimination.

To obtain further mechanistic information about the system concentration vs. time diagrams for the reaction of 1-bromo-4-chlorobenzene (**7**) with α-methylstyrene (**8**) in the presence of NaOAc and DIPEA were compared (Figure 2).

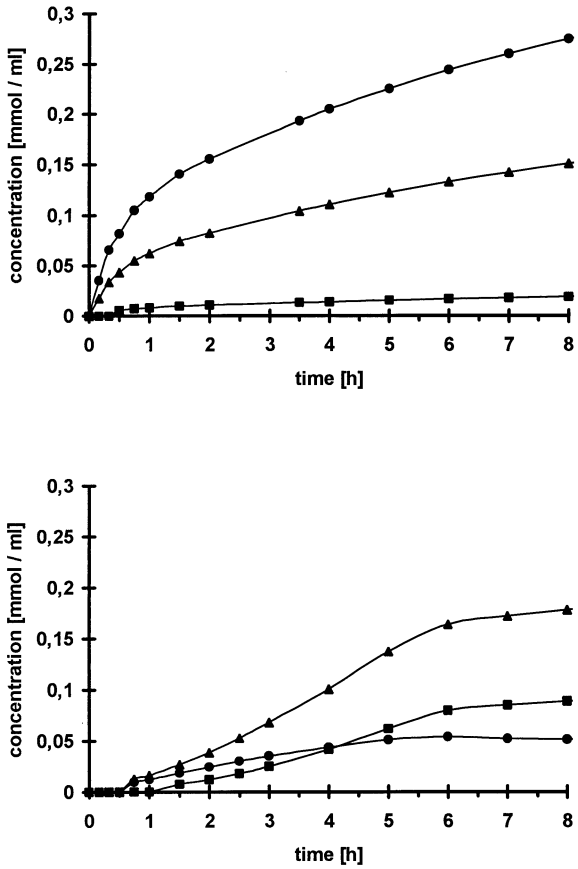
As shown in Figure 2 the base influences the reaction profile dramatically. In the presence of NaOAc the reaction starts immediately leading to the terminal olefin **10** as the major isomer. If the concentration of **10** is high enough (after ca. 5 h) the doubly arylated product **11** (not shown in Figure 2) is produced in small quantities by a consecutive Heck reaction. No initial catalyst activation is observed. However, the reaction with DIPEA as base (Figure 2, lower diagram) shows a sigmoidal concentration vs. time diagram indicating preformation of the active catalyst species. The induction period might be explained by a slowly occurring reduction of the phosphapalladacycle **3**[17] to a monophosphanepalladium(0) compound. Immediately, this species would undergo oxidative addition to 1-bromo-4-chlorobenzene (**7**) to give the palladium complex **12** (Scheme 4). To proof this assumption the oxidative addition product **12** was prepared independently from $Pd[P(o\text{-tolyl})_3]_2Cl_2$ and **7** in a total yield of 66% according to a procedure described by J. F. Hartwig et al.[18]

The concentration vs. time diagrams for the Heck reaction of 1-bromo-4-chlorobenzene (**7**) with α-methylstyrene (**8**) in the presence of 0.1 mol% **12** as catalyst with NaOAc and DIPEA as base are shown in Figure 3.

No induction period is observed in both cases! In the presence of NaOAc as base the reaction catalyzed by **12** starts faster compared to the reaction catalyzed by **3** and a similar product distribution is observed. Also using DIPEA as base the raction starts immediately. The ratio of products initially formed is comparable to the ratio of the different isomers obtained in the phosphapalladacycle-catalyzed reaction. However, after several hours ***E*-9** is formed preferentially with **12** as catalyst yielding in a higher *E*/*Z* ratio.

This findings are rationalized as follows: As shown in Scheme 4 the phosphapalladacycle **3** is reduced to a monophosphanepalladium(0) species. The nature of the reducing agent is not clear in detail. Coordination of amines stabilizes the phosphapalladacycle **3** slowing down the formation of a palladium(0) compound. This results in an induction

Figure 2. Concentration vs. reaction time diagrams; top: NaOAc as base; bottom: DIPEA as base; ● terminal olefin **10**; ■ **Z-9**; ▲ E-**9**[a]



[a] Reaction conditions: 15 mmol of 1-bromo-4-chlorobenzene, 75 mmol of α-methylstyrene, 18 mmol of base and 2 ml of diethylene glycol dibutyl ether were heated in 15 ml of DMAc at 135°C. At $t = 0$ a solution of 0.1 mol% of the phosphapalladacycle **3**, dissolved in 1 ml of DMAc, was added. The course of the reaction was monitored by removing 0.1-ml samples of the reaction mixture. These were washed with 5% HCl solution, then extracted with 1.5 ml of dichloromethane and analyzed by GC.

Scheme 4. Postulated formation of **12** from the phosphapalladacycle **3** (R = *o*-tolyl)

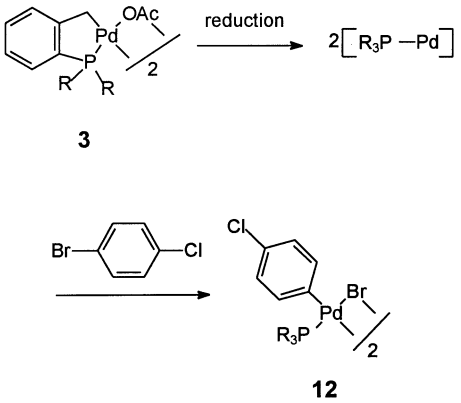
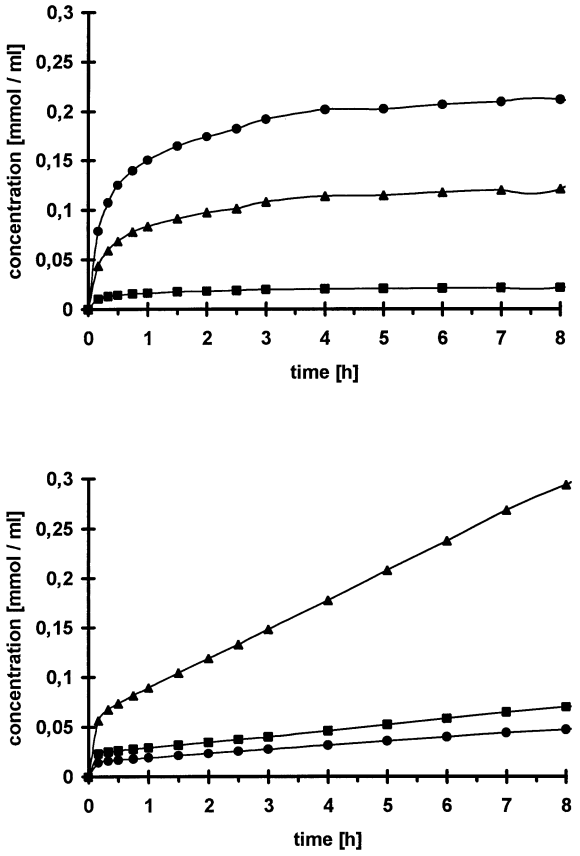


Figure 3. Concentration vs. reaction time diagrams; top: NaOAc as base; bottom: DIPEA as base; ● terminal olefin **10**; ■ Z-**9**; ▲ E-**9**[a]



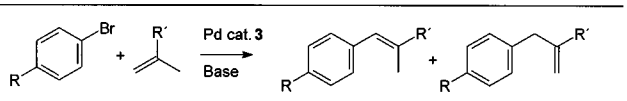
[a] Reaction conditions: 15 mmol of 1-bromo-4-chlorobenzene, 75 mmol of α-methylstyrene, 18 mmol of base and 2 ml of diethylene glycol dibutyl ether were heated in 15 ml of DMAc at 135°C. At $t = 0$ a solution of 0.1 mol% of **12**, dissolved in 1 ml of DMAc, was added. The course of the reaction was monitored by removing 0.1-ml samples of the reaction mixture. These were washed with 5% HCl solution, then extracted with 1.5 ml of dichloromethane and analyzed by GC.

period for the proper catalyst. Furthermore, the rate of oxidative addition is decreased in the presence of amines by blocking of free coordination sites on the Pd^0 species. On the other hand it is known, that the coordination of NaOAc to phosphanepalladium(0) complexes increases the rate of oxidative addition for haloarenes.[19] This explains in general the higher catalyst activity in the presence of NaOAc.

Further evidence for the discussed transformation of the phosphapalladacycle **3** to **12** is obtained by comparing the *E*/*Z* ratio for the different catalysts (**3** and **12**) using DIPEA as base. As a matter of fact the *E*/*Z* ratio produced by **12** in the first hour is identical to that of the phosphapalladacycle **3** during the whole reaction time. Due to side-reactions in the formation of **12** from **3** the productivity of **3** is lower.

In order to demonstrate that the determination of the regiochemistry by the base is a general principle for Heck reactions of 1,1-disubstituted olefins we studied coupling reactions of **2** and **8** with various other aryl bromides (Table 3). As can be seen from Table 3 4-bromotoluene and 1-bromo-4-fluorobenzene behave in a similar manner as described for 1-bromo-4-chlorobenzene. In contrast to Table 1 the coupling reactions with *n*-butyl methacrylate were performed in the presence of five equivalents of the olefin. Thus, the amount doubly arylated products could be minimized.

Table 3: Heck reaction of 1,1-disubstituted olefins with various aryl bromides



Run	R	R'	Base	Yield[a] [%]	Internal[b] [%]	Terminal[b] [%]	Double[b] [%]	*E*/*Z*[b]	TON[c]
1	CH_3	Ph	NaOAc	62	39	59	2	38	620
2	CH_3	Ph	DIPEA	58	97	3	–	2.2	580
3	F	Ph	NaOAc	96	39	56	5	9	960
4	F	Ph	DIPEA	82	96	4	–	1.6	820
5	Cl	COOBu	NaOAc	99[d]	47[d]	36[d]	17[d]	22[d]	990
6	Cl	COOBu	DIPEA	84[d]	88[d]	7[d]	5[d]	23[d]	840

Reaction: 15 mmol of aryl halide with 75 mmol of olefin in the presence of 18 mmol of base and 0.1 mol% of phosphapalladacycle catalyst **3** in 15 ml of DMAc at 135−140°C (24 h). − [a] Total isolated yields. − [b] Selectivities have been determined by NMR of the isolated products. − [c] TON = mol product/mol catalyst. − [d] Determined by GC analysis.

In conclusion we have demonstrated that the nature of base significantly influences the regiochemistry of the double bond in certain types of Heck reactions. Based on this finding we have developed a new and general valid concept to determine the regiochemistry of Heck reactions of 1,1-disubstituted olefins simply by changing the added base. Moreover, by using phosphapalladacycle **3** as catalyst precursor we have been able to improve the catalyst productivity for Heck coupling reactions of 1,1-disubstituted olefins by at least one order of magnitude. Comparison of the concentration vs. time diagrams for Heck reactions with the phosphapalladacycle **3** and the oxidative addition product **12** as catalysts provides evidence that **3** is a catalyst precursor with **12** as active species.

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Experimental Section

Chemicals were obtained from Aldrich and Fluka. NMR spectra (^1H,^{13}C,^{31}P) were recorded with a Jeol JMX-GX 400 or a Bruker AM 360 instrument. GC-MS spectra were measued with 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 TU München. Quantitative analyses were performed with a Hewlett Packard 6890 instrument using a HP-5 capillary column in conjunction with a flame ionization detector (GC/FID). − Except for the work-up of reaction mixtures, all operations were carried out under nitrogen. Solvents were carefully dried according to standard procedures.

1. *Heck Reactions with n-Butyl Methacrylate:* 15 mmol of aryl halide, 22.5 mmol of *n*-butyl methacrylate (3.58 ml), 18 mmol of tri-*n*-butylamine (4.29 ml), 0.1 mg of 2,6-di-*tert*-butyl-4-methyl-

phenol and 7.0 mg of the phosphapalladacycle **3** were dissolved in 15 ml of *N,N*-dimethylacetamide and stirred at 135−140°C (reaction time as indicated). After cooling, the reaction mixture was extracted with diethyl ether and 5% aqueous HCl for three times. The combined organic phases were neutralized with 10% aqueous $NaHCO_3$ and dried with $MgSO_4$. After removal of the solvent and starting materials in vacuo the products were isolated as colourless oils by distillation or by column chromatography.

n-Butyl 3-(4-Fluorophenyl)-2-methylpropenoate: Isolated by distillation (60%, b.p. 95−100°C/1 mbar). − ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.64 (s, 1 H, C*H*=C), 7.36 (dd, 2 H, $^3J_{HH}$ = 8.6 Hz, $^4J_{FH}$ = 5.5 Hz), 7.06 (dd, $^3J_{HH}$ = 8.6 Hz, $^3J_{FH}$ = 8.6 Hz, 2 H), 4.21 (t, $^3J_{HH}$ = 6.6 Hz, 2 H, COOCH_2), 2.10 (s, 3 H, = C−CH_3), 1.71 (tt, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 6.7 Hz, 2 H, COOCH$_2$CH_2) 1.46 (tt, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 7.3 Hz, 2 H, COOCH$_2$CH$_2$CH_2), 0.97 (t, $^3J_{HH}$ = 7.3 Hz, 3 H, CH$_2$CH_3). − MS (70 eV); *m/z*: 236 [M$^+$], 180, 134, 109.

n-Butyl 3-(4-Acetylphenyl)-2-methylpropenoate: Isolated by column chromatography (ethyl acetate/hexane, 1:8, 74%). − ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.97 (d, 2 H, $^3J_{HH}$ = 8.3 Hz, 3-Ph-H, 5-Ph-H), 7.67 (s, 1 H, C*H*=C), 7.46 (d, 2 H, $^3J_{HH}$ = 8.3 Hz, 2-Ph-H, 6-Ph-H), 4.23 (t, $^3J_{HH}$ = 6.6 Hz, 2 H, COOCH_2), 2.60 (s, 3 H, COCH_3), 2.12 (s, 3 H, =C−CH_3), 1.73 (tt, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 6.6 Hz, 2 H, COOCH$_2$CH_2) 1.47 (tt, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 7.4 Hz, 2 H, COOCH$_2$CH$_2$CH_2), 0.98 (t, $^3J_{HH}$ = 7.4 Hz, 3 H, CH$_2$CH_3). − MS (70 eV); *m/z*: 260 [M$^+$], 245, 204, 189, 161, 145, 115.

n-Butyl 3-(4-Methoxyphenyl)-2-methylpropenoate: Isolated by column chromatography (ethyl acetate/hexane, 1:10, 20%). − ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.64 (s, 1 H, C*H*=C), 7.37 (d, 2 H, $^3J_{HH}$ = 8.3 Hz, 2-Ph-H, 6-Ph-H), 6.91 (d, 2 H, $^3J_{HH}$ = 8.3 Hz, 3-Ph-H, 5-Ph-H), 4.18 (t, $^3J_{HH}$ = 6.6 Hz, 2 H, COOCH_2), 3.82 (s, 3 H, OCH_3), 2.13 (s, 3 H, =C−CH_3), 1.65 (tt, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 6.6 Hz, 2 H, COOCH$_2$CH_2) 1.44 (tt, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 7.4 Hz, 2 H, COOCH$_2$CH$_2$CH_2), 0.97 (t, $^3J_{HH}$ = 7.4 Hz, 3 H, CH$_2$CH_3). − MS (70 eV); *m/z*: 248 [M$^+$], 192, 146, 115, 91.

n-Butyl 3-(4-Chlorophenyl)-2-methylpropenoate: Isolated by distillation (55%, b.p. 120−125°C/1 mbar). − ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.63 (s, 1 H, C*H*=C), 7.38−7.32 (m, 4 H), 4.23 (t, $^3J_{HH}$ = 6.6 Hz, 2 H, COOCH_2), 2.10 (s, 3 H, =C−CH_3), 1.74 (tt, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 6.6 Hz, 2 H, COOCH$_2$CH_2) 1.44 (tt, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 7.4 Hz, 2 H, COOCH$_2$CH$_2$CH_2), 0.98 (t, $^3J_{HH}$ = 7.4 Hz, 3 H, CH$_2$CH_3). − MS (70 eV); *m/z*: 252 [M$^+$], 196, 179, 150, 115, 89.

n-Butyl 3-(4-Nitrophenyl)-2-methylpropenoate: Isolated by column chromatography (ethyl acetate/hexane, 1:15, 75%). − ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 8.25 (d, 2 H, $^3J_{HH}$ = 8.9 Hz, 3-Ph-H, 5-Ph-H), 7.70 (s, 1 H, C*H*=C), 7.54 (d, 2 H, $^3J_{HH}$ = 8.9 Hz, 2-Ph-H, 6-Ph-H), 4.25 (t, $^3J_{HH}$ = 6.6 Hz, 2 H, COOCH_2), 2.12 (s, 3 H, =C−CH_3), 1.72 (tt, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 6.6 Hz, 2 H, COOCH$_2$CH_2) 1.47 (tt, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 7.4 Hz, 2 H, COOCH$_2$CH$_2$CH_2), 0.98 (t, $^3J_{HH}$ = 7.4 Hz, 3 H, CH$_2$CH_3). − MS (70 eV); *m/z*: 263, [M$^+$], 207, 190, 161, 115, 89.

2. *Heck Reactions with α-Methylstyrene:* 15 mmol of the aryl bromide, 75 mmol of α-methylstyrene (8.86 g, **2**), 18 mmol of the base and 7.0 mg of the phosphapalladacycle **3** (0.1 mol% Pd) were dissolved in 15 ml of *N,N*-dimethylacetamide and stirred under a gentle stream of nitrogen at 135−140°C for 24 h. After cooling, the reaction mixture was extracted with dichloromethane and 5% aqueous HCl for three times. The combined organic phases were neutralized with 10% aqueous $NaHCO_3$ and dried with $MgSO_4$. The solvent and starting materials were removed in vacuo. The ratio of the regioisomers was calculated by the relative intensities of the typical signals in the ^{1}H-NMR spectrum ($CDCl_3$, TMS as internal standard). Total yields for different bases are given in Tables 2 and 3.

(E)-4-Chloro-α-methylstilbene (*E*-**4**): ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.5−7.0 (m, 9 H, aromatic protons), 6.76 (s, 1 H, C= C*H*), 2.25 (s, 3 H, −CH_3). − MS (70 eV); *m/z*: 228, [M$^+$], 211, 193, 178.

(Z)-4-Chloro-α-methylstilbene (*Z*-**4**): ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.5−7.0 (m, 9 H, aromatic protons), 6.40 (s, 1 H, C= C*H*), 2.19 (s, 3 H, −CH_3). − MS (70 eV); *m/z*: 228, [M$^+$], 211, 193, 178.

3-(4-Chlorophenyl)-2-phenyl-1-propene (**5**): ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.5−7.0 (m, 9 H, aromatic protons), 5.48 (s, 1 H, C=C*H*), 5.01 (s, 1 H, C=C*H*), 3.79 (s, 2 H, −CH$_2$Ar). − MS (70 eV); *m/z*: 228, [M$^+$], 193, 103.

(E)-4-Fluoro-α-methylstilbene: ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.5−7.0 (m, 9 H, aromatic protons), 6.78 (s, 1 H, C= C*H*), 2.24 (s, 3 H, −CH_3). − MS (70 eV); *m/z*: 212, [M$^+$], 197, 177, 133.

(Z)-4-Fluoro-α-methylstilbene: ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.5−7.0 (m, 10 H, aromatic and olefinic protons), 2.18 (s, 3 H, −CH_3). − MS (70 eV); *m/z*: 212, [M$^+$], 197, 177, 133.

3-(4-Fluorophenyl)-2-phenyl-1-propene: ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.5−7.0 (m, 9 H, aromatic protons), 5.48 (s, 1 H, C=C*H*), 5.01 (s, 1 H, C=C*H*), 3.79 (s, 2 H, −CH_2Ar). − MS (70 eV); *m/z*: 212, [M$^+$],197, 134, 103.

(E)-4-Methyl-α-methylstilbene: ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.5−6.8 (m, 9 H, aromatic protons), 6.43 (s, 1 H, C= C*H*), 2.36 (s, 3 H, Ar-CH_3), 2.28 (s, 3 H, -CH_3). − MS (70 eV); *m/z*: 208, [M$^+$], 193, 178, 115.

(Z)-α,4-Dimethylstilbene: ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.5−6.8 (m, 10 H, aromatic and olefinic protons), 2.18 (s, 3 H, Ar-CH_3), 2.22 (s, 3 H, −CH_3). − MS (70 eV); *m/z*: 208, [M$^+$], 193, 178, 115.

3-(4-Methylphenyl)-2-phenyl-1-propene: ^{1}H NMR (360 MHz, 20°C, $CDCl_3$): δ = 7.5−6.8 (m, 9 H, aromatic protons), 5.44 (s, 1 H, C=C*H*), 4.77 (s, 1 H, C=C*H*), 3.74 (s, 2 H, −CH_2Ar), 2.38 (s, 3 H, Ar-CH_3). − MS (70 eV); *m/z*: 208, [M$^+$], 193, 178, 130, 115, 103.

3. *Synthesis of {Pd[P(o-tolyl)$_3$](p-ClC$_6$H$_4$)(Br)}$_2$* (**12**): 1.21 g (1.54 mmol) of Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$ and 0.54g (1.78 mmol) of P(*o*-tolyl)$_3$ were suspended in 8 ml of toluene. To this suspension NaOH (0.14 g) in 8 ml of ethanol was added. The reaction mixture was heated at 90°C for 5 h. After cooling, the yellow precipitate was filtered off and washed several times with water, ethanol and diethyl ether. After drying in vacuo, 1.06 g of crude Pd[P(*o*-tolyl)$_3$]$_2$ was obtained. This product was stirred with 1.60 g of 1-bromo-4-chlorobenzene in 20 ml of benzene at room temp. overnight. The suspension was filtered and concentrated. After addition of 20 ml of diethyl ether and cooling to −30°C 0.60 g (66%) of **12** precipitated. − ^{1}H NMR (400 MHz, 80°C, [D$_8$]toluene): δ = 7.03−6.45 (br. m, 32 H), 2,14 (br. s, 18 H). − ^{31}P{^{1}H} NMR (162 MHz, 80°C, [D$_8$]toluene): δ = 26.8. − IR (KBr): $\tilde{\nu}$ = 3054 (m), 2970 (m), 2922 (m), 2861 (m), 1589 (m), 1566 (w), 1467 (vs), 1449 (s), 1200 (w), 1088 (s), 1004 (vs), 807 (vs), 752 (vs), 717 (s), 680 (m), 561 (m), 534 (s), 466 (s). − FAB MS; *m/z*: 520 [M$^+$ − HBr], 430 [M$^+$ − Br−tolyl]. − $C_{54}H_{50}Br_2C_{12}P_2Pd_2 \cdot Et_2O$ (1278.6): calcd. C 54.48, H 4.73, P 4.84; found C 54.66, H 4.44, P 4.88.

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