

Heck Arylation of α,β -Unsaturated Aldehydes

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Received: November 4, 2002; Accepted: February 2, 2003

Abstract: The Heck arylation of α,β -unsaturated aldehydes is strongly dependent on the catalyst, the solvent and the base. Optimized conditions yielded either selectively cinnamyl derivatives (83%) or double arylation products (88% based on aryl con-

version). A new α -arylation of β,β -disubstituted acrolein is also realized.

Keywords: acrolein; arylation; catalysis; cinnamic compounds; Heck reaction; α,β -unsaturated aldehydes

Introduction

Cinnamyl derivatives are an interesting class of compounds, which find industrial application as UV-adsorbers and anti-oxidants in plastics. Furthermore, they are valuable starting materials and intermediates for the preparation of pharmaceuticals, agrochemicals and fragrances.^[1]

Several methods have been reported for the synthesis of cinnamyl derivatives at the industrial scale based on the Perkin and Claisen condensations of aromatic aldehydes.^[2] However, the applicability of these methods remains limited due to the difficult and costly synthesis of the corresponding aldehydes.^[3] A convenient approach could be a direct C–C coupling reaction between an aromatic halide and an acrylic compound.

The palladium-catalyzed carbon–carbon bond formation between aryl halides and olefins (Heck reaction) is probably one of the most effective tools for the synthesis of elaborated styrene derivatives due to its tolerance for a wide variety of substituents and the broad availability of aryl bromides and chlorides.^[4]

Except for intramolecular Heck cyclization reactions, the Heck reaction is limited to the arylation of styrene, acrylic, or vinyl ether derivatives.^[4,5] Few reports in the literature provide references concerning the use of the synthetically interesting acrolein as the olefin, probably due to its rapid polymerization under the reaction conditions. Continuing the development of synthetic methods for fine chemicals we studied in detail the reactivity of α,β -unsaturated aldehydes in the Heck C–C coupling reaction, paying particular attention to the selectivity of the reaction.

The present paper describes the reactivity of acrolein and its derivatives in the Heck reaction with aryl bromides in homogeneous and heterogeneous systems.

Results and Discussion

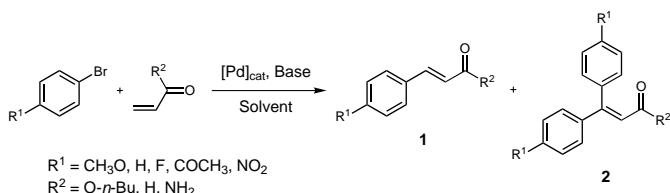
Catalysts

The well-known homogeneous palladacycle $\{Pd[P(o-C_6H_4CH_3)_2(C_6H_4CH_2)][OCOCH_3]\}_2$ catalyst^[7] or the $Pd(OAc)_2/PPPh_3$ catalytic system were tested in this reaction. Previously, as a part of our studies, we reported the preparation and use of efficient, easily separable and reusable heterogeneous Pd-catalysts using zeolite as support for C–C bond-forming reactions.^[6] Such heterogeneous catalysts are valuable for industrial applications of the Heck reaction, and we extended the study to $[Pd(NH_3)_4]^{2+}$ -NaY prepared by an ion-exchange process,^[6] as well as Pd/SiO₂ prepared by impregnation and the commercially available Pd/C (Aldrich).

Heck Reactions

Influence of the Vinylic Group

As a preliminary work, the influence of the vinylic group on the Heck reaction of acrylic compounds with bromobenzene was studied (Scheme 1, R¹ = H) with both homogeneous and heterogeneous catalysts.



Scheme 1. Reaction conditions: 10 mmol aryl bromide, 15 mmol olefin, 15 mmol base, 0.1 mol % [Pd]_{cat}, 8 mL solvent, 140 °C, 20 h.

Table 1. Influence of the vinylic group on the Heck arylation of acrylic compounds (Scheme 1, $R^1 = H$, $R^2 = O-n\text{-Bu}$, H , NH_2). Reaction conditions: 10 mmol bromobenzene, 15 mmol olefin, 15 mmol NaOAc, 0.1 mol % [Pd].., 8 mL DMAc, 140 °C, 20 h).

R^2	Catalyst	Product Yields [%] ^[a]		Conversion [%] ^[b]
		1	2	
$O-n\text{-Bu}$	Palladacycle	98 [86]	–	100
	$[\text{Pd}(\text{NH}_3)_4]^{2+}\text{-NaY}^{[c]}$	65 [58]	–	73
NH_2	Palladacycle	69 [62]	–	77
	$[\text{Pd}(\text{NH}_3)_4]^{2+}\text{-NaY}^{[c]}$	13	–	18
H	Palladacycle	33 [21]	25 [16]	90
	$[\text{Pd}(\text{NH}_3)_4]^{2+}\text{-NaY}^{[c]}$	12	–	15

^[a] GLC yields and when available [isolated yields] are given ($\Delta_{\text{rel}} = \pm 5\%$).

^[b] Based on the unreacted bromobenzene determined by GLC.

^[c] 1.0 wt % Pd.

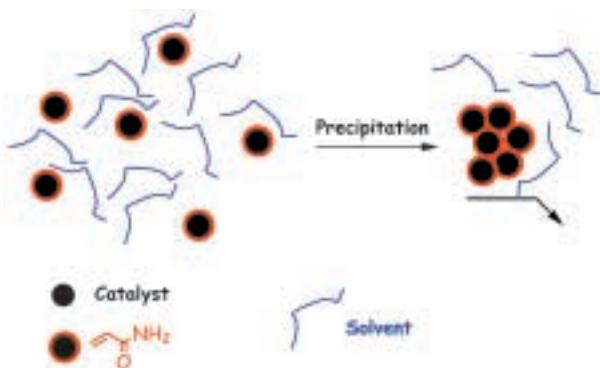


Figure 1. Hypothesis for inactivation of the heterogeneous catalyst during the Heck arylation of acrylamide.

The results reported in Table 1 show that the nature of the vinylic R^2 group has a strong influence on the yield of the reaction. Using acrolein (Scheme 1, $R^2 = H$) or acrylamide (Scheme 1, $R^2 = NH_2$), we observed lower yields than with *n*-butyl acrylate (Scheme 1, $R^2 = O-n\text{-Bu}$) and these results were in agreement with those reported in the literature.^[4,6] These lower yields are probably due to the lower reactivity of acrolein and acrylamide in the Heck reaction with bromobenzene.

Furthermore, Table 1 shows that for acrylamide and acrolein, heterogeneous catalysts lead to a very low conversion of bromobenzene.

When acrylamide was used as substrate, we did observe a strong precipitation of materials in the reaction media. This phenomenon could be attributed to the trapping of the inorganic materials by acrylamide *via* the formation of an adsorption layer at the surface through the polar groups ($CONH_2$) leading to the expulsion of the polar solvent and precipitation (Figure 1).

For acrolein, the lower reactivity is accompanied by a slight polymerization of the olefin as evidenced by a

viscous solution at the end of the reaction. However, this cannot be quantified as acrolein was not analyzed by GC. As a main consequence we did obtain a low conversion of bromobenzene due to the resulting low concentration of acrolein.

When homogeneous palladium complex was engaged as catalyst, we observed by GC-mass chromatography the formation of the supplementary product **2** that we attributed to a double Heck arylation of acrolein. This product was independently synthesized by Heck arylation of cinnamaldehyde using $Pd(OAc)_2/PPh_3$ and was obtained with 90% yield after purification. The structure of the product was assigned as 3,3-diphenylpropanal by 1H and ^{13}C NMR. This product was not observed using the heterogeneous $[\text{Pd}(\text{NH}_3)_4]^{2+}\text{-NaY}$ catalyst.

To our knowledge, double Heck arylation of an olefin was not reported previously, except in the case of cyclopentene using an excess of aryl halide,^[8a] whereas in our experiments a slight excess of olefin was employed. Recently, after our work on previously unknown inter- β,β -diarylation had been completed, specific cases of double arylations were described by an inter- followed by an intra- β,β -diarylation of α,β -unsaturated olefins.^[8b]

Figure 2 shows selectivity of mono- vs. diarylation of acrolein as a function of time. As suggested, cinnamaldehyde **1** is formed at the beginning of the reaction in up to 28% yield after 750 min of reaction. The formation of cinnamaldehyde is accompanied after 500 min by the formation of product **2** resulting from a double arylation of acrolein. As the reaction time became longer, the complete transformation of the cinnamaldehyde into **2** was achieved.

Influence of the Solvent

The Heck arylation of an olefin generates a large amount of salts that have generally low solubility in the reaction media. This remains a major problem since the

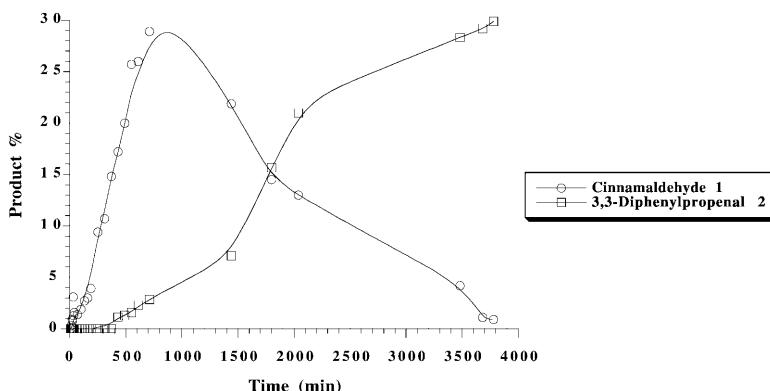


Figure 2. Mono- vs. diarylation during the Heck arylation of acrolein. Reaction conditions: 50 mmol bromobenzene, 75 mmol acrolein, 75 mmol NaOAc, 0.1 mol % palladacycle, 60 mL DMAc, reflux.

Table 2. Influence of the solvent on the Heck arylation of acrolein (Scheme 1, $R^1=R^2=H$. Reaction conditions: 10 mmol bromobenzene, 15 mmol acrolein, 15 mmol NaOAc, 0.1 mol % $[Pd]_{cat}$ palladacycle, 8 mL Solvent, 140 °C, 20 h).

Solvent	Product Yield (Selectivity) [%] ^[a]		Conversion [%] ^[b]
	1	2	
DMAc	33 [21] (36)	25[16] (56)	90
DMF	12 (39)	7 (45)	31
DMSO	19 (39)	11 (45)	49
NMP	89 [83] (89)	5 (10)	100
CH ₃ CN	9 (45)	5 (45)	22

^[a] GLC yields ($\Delta_{rel}=\pm 5\%$); and, when available, [isolated yields] are given; Selectivity **1**=Yield **1**/Conversion; Selectivity **2**=2 × Yield **2**/Conversion.

^[b] Based on unreacted bromobenzene determined by GLC ($\Delta_{rel}=\pm 5\%$).

precipitation of salts often trapped the heterogeneous catalysts or co-precipitated the homogeneous catalysts. Therefore, the solvent used for the reaction plays a major role. We have studied this parameter in more detail for the Heck arylation of acrolein by the bromobenzene using the homogeneous palladacycle as catalyst (Scheme 1, $R^1=R^2=H$).

Polar solvents were tested for this reaction. In DMF, DMSO or CH₃CN, lower conversion of the aromatic bromide was achieved. The selectivity of mono- and diarylated products was similar to that observed with DMAc. Surprisingly, the use of NMP modifies dramatically the activity and the selectivity of the reaction. The conversion was complete after 20 h, which is attributed to high solubility of base and formed salts in the reaction media. This allows a rapid arylation of acrolein and few diarylated compounds are formed. Such a higher activity of Pd-catalysts for the Heck arylation of olefin was reported in the literature, also with modifications of the selectivity.^[9a]

Influence of the Catalyst

Results described in Table 1 indicate that the double arylation of acrolein is strongly dependent on the nature of the catalysts used: while 25–28% were achieved with the homogeneous palladacycle catalyst (corresponding to 50–56% aromatic conversion), only monoarylation was observed with the heterogeneous supported Pd-species in the NaY zeolite. Complementarily, we found that the selectivity is also very dependent on the solvent media for similar conversions: 55% of double arylation were obtained in DMAc vs. 10% in NMP. To optimize the reaction, the influence of catalysts on the Heck reaction was studied in DMAc and NMP in more detail (Table 3).

Using heterogeneous catalysts, very low conversion of the bromobenzene was achieved. Whatever the catalyst, the conversion was significantly lower when DMAc was used as solvent compared to NMP. Carbon and silica supported palladium catalysts exhibit similar behaviors; not only small yields of Heck coupling products were attained, but also benzene was detected (3–6% yield). This product emerged from a dehalogenation reaction, that can be performed only with metallic catalysts.^[9]

The $[Pd(NH_3)_4]^{2+}$ -NaY catalyst yielded higher conversion of bromobenzene and in NMP double arylated product **2** was observed. Slight leaching of the metal under the reaction conditions cannot be excluded.

When homogeneous catalysts were employed in the reaction very high conversions were observed after 20 h. With $Pd(OAc)_2/PPh_3$ catalyst similar selectivities were obtained in both solvents and the double arylated product **2** was formed predominantly. With the palladacycle catalyst, the selectivity of the reaction is strongly dependent to the nature of the solvent. While in NMP the monoarylated product **1** was mainly formed (89%), in DMAc higher selectivity in the double arylated product **2** was observed (55%). However, whatever the solvent, the selectivity in double arylation was lower with the palladacycle compared to the $Pd(OAc)_2/PPh_3$

Table 3. Influence of the catalyst on the Heck arylation of acrolein (Scheme 1, $R^1=R^2=H$. Reaction conditions: 10 mmol bromobenzene, 15 mmol acrolein, 15 mmol NaOAc, 0.1 mol % [Pd], 8 mL solvent, 140 °C, 20 h).

Catalyst	Solvent	Product Yield (selectivity) [%] ^[a]		Conversion [%] ^[b]
		1	2	
Pd(OAc) ₂ /PPh ₃	DMAc	11 (13)	36 (85)	85
	NMP	19 (20)	35 (74)	95
Palladacycle	DMAc	33 (37)	25 (55)	90
	NMP	89 (89)	5 (10)	100
[Pd(NH ₃) ₄] ²⁺ -NaY (5.1 wt % Pd)	DMAc	12	—	15
	NMP	26 (71)	4 (22)	37
Pd/C (5 wt % Pd on wet catalyst)	DMAc	3	<2	8 ^[c]
	NMP	8 (44)	<2	18 ^[d]
Pd/SiO ₂ (5 wt % Pd)	DMAc	3	<2	8 ^[c]
	NMP	3	<1	11 ^[e]

^[a] GLC yields are given ($\Delta_{rel}=\pm 5\%$).^[b] Based on unreacted bromobenzene determined by GLC. Side products. ^[c] 3% benzene; ^[d] 4% benzene and ^[e] 6% benzene.**Table 4.** Influence of the base on the Heck arylation of acrolein (Scheme 1, $R^1=R^2=H$. Reaction conditions: 10 mmol bromobenzene, 15 mmol acrolein, 15 mmol base, 0.1 mol % [Pd]_{cat}, palladacycle, 8 mL solvent, 140 °C, 20 h).

Base	Solvent	Product Yield (Selectivity) [%] ^[a]		Conversion [%] ^[b]
		1	2	
NaOAc	DMAc	33 (37)	25 (55)	90
	NMP	85 (85)	5 (10)	100
Na ₂ CO ₃	DMAc	16 (23)	22 (65)	68
	NMP	0 (0)	36 (72)	76
K ₂ CO ₃	DMAc	8 (22)	12 (65)	37
	NMP	0 (0)	44 (88)	100
(n-Bu) ₃ N	DMAc	2	—	3
	NMP	7 (87)	—	8

^[a] GLC yields are given ($\Delta_{rel}=\pm 5\%$); Selectivity **1**=Yield **1**/Conversion; Selectivity **2**=2 × Yield **2**/Conversion.^[b] Based on unreacted bromobenzene determined by GLC.

system. This result could be correlated with a stronger steric hindrance in the transition state when the palladacycle is used, disfavoring the double arylation.

Influence of Bases

The influence of bases on the yield and the selectivity of the arylation of acrolein by the bromobenzene (Scheme 1, $R^1=R^2=H$) was studied using the palladacycle as catalyst.

The results reported in Table 4 show that bases influenced the conversion of the bromobenzene and the selectivity of mono- and di-arylated compounds. With carbonate base, the results depend on the solvent used: in DMAc a higher selectivity in diarylated compound **2** (65%) is observed while it is formed exclusively in NMP. The modification of the selectivity of the Heck arylation of olefins when carbonate was used as base was already described in the literature.^[10] Generally, the conversion of bromobenzene is lower

with Na₂CO₃ or K₂CO₃ than with NaOAc because of a lower solubility of carbonates in the solvents, with a positive effect on the use of NMP instead of DMAc. With an organic base, such as the tri-n-butylamine, very low conversions of bromobenzene are observed (3–8%) and only the monoarylated product is detected. This result could be compared to other data reported in the literature.^[4,11]

Influence of the Substituent on the Aromatic Ring

As is known that the electronic nature of the educts, particularly the nature of the substituent on the aromatic ring, has a strong influence on the Heck reaction,^[4] the arylation of acrolein using differently substituted bromoarene was studied (Scheme 1, $R^2=H$) using the palladacycle.

When *para*-substituted aromatic compounds with electron-withdrawing groups ($R^1=F$, COCH₃ or NO₂) were used, high yields in monosubstituted compound

Table 5. Influence of the substituent on the aromatic ring on the Heck arylation of acrolein (Scheme 1, R¹ = OCH₃, H, F, NO₂, COCH₃; R² = H. Reaction conditions: 10 mmol aryl bromide, 15 mmol acrolein, 15 mmol NaOAc, 0.1 mol % [Pd]_{cat.} palladacycle, 8 mL DMAc, 140 °C, 20 h).

R ¹	Product	Yield [%] ^[a]	Conversion [%] ^[b]
	1	2	
OCH ₃	11 [7]	6	24
H	33 [21]	25 [16]	90
F	95 [76]	—	100
COCH ₃	92 [64]	—	100
NO ₂	95 [78]	—	100

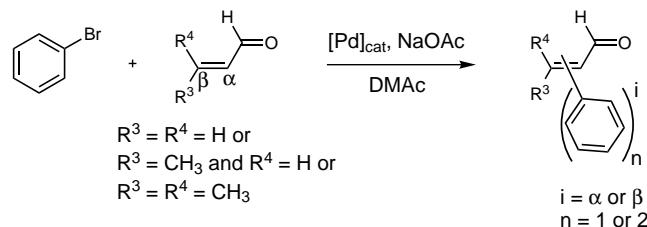
^[a] GLC yields ($\Delta_{\text{rel}} = \pm 5\%$) and [isolated yields] are given.

^[b] Based on unreacted aryl halides determined by GLC.

were achieved. In these cases the conversion of the aromatic compound is complete and as a consequence no double arylated products were observed. On the contrary, using electronically neutral (bromobenzene, R¹ = H) or electron-rich (*p*-bromoanisole, R¹ = OCH₃) aromatic halides, we observed a smaller conversion of aromatic bromide and the product from a double arylation of acrolein was detected together with the monoarylated olefin. In NMP, better conversion of bromoanisole is obtained (38%) together with a higher selectivity in monarylated product **1** (76%).

Regioselectivity of the Arylation

Typically, the regioselectivity of the Heck reaction was directed by the electronic structure of the substituted olefin. Only β -substitution was observed with acrylic ester, while α - and β -substitutions were achieved using enol ether.^[5,13] Due to high reactivity of acrolein, we investigated the reaction with substituted α,β -unsaturated aldehydes, namely methacrolein and prenol.



Scheme 2. Reaction conditions: 10 mmol bromobenzene, 15 mmol olefin, 15 mmol NaOAc, 0.1 mol % [Pd]_{cat.}, 8 mL DMAc, 140 °C, 20 h.

Methacrolein reacts similarly to acrolein: in the case of a heterogeneous catalyst, monoarylation is achieved at low yield. Using a palladacycle catalyst, mono- and diarylated products are formed, the monoarylated being the main compound. Interestingly, when methacrolein is the substrate, the second arylation occurs at the α position to the carbonyl group with a moderate yield (8% with homogeneous catalyst) whereas this position is unfavored considering the electronic point of view.

When the two β positions are already occupied by alkyl groups only one arylation is possible: naturally and directly at the carbon α to the carbonyl group. The α -arylation of the β,β -disubstituted olefin is observed for the first time with high yield (41% with homogenous catalyst and 30% with heterogeneous catalysts) regarding the lack of reactivity of such olefins in the Heck reaction. A similar functionalization was reported in the case of vinyl ethers using silver or thallium salts to enhance the selectivity of the reaction *via* an ionic mechanism.^[12]

This arylation at the α -carbon by the Heck reaction opens the route to a Pd-catalyzed 1,3-addition to α,β -unsaturated carbonyl compounds, a reaction very similar to the well-documented Baylis–Hilman reaction.^[13] Further experiments are currently in progress to direct the selectivity of the Heck arylation of acrylic derivatives to the α -position.

Table 6. Influence of the steric hindrance on the double bond for the Heck arylation of acrylic compounds (Scheme 2. Reaction conditions: 10 mmol bromobenzene, 15 mmol olefin, 15 mmol NaOAc, 0.1 mol % [Pd]_{cat.}, 8 mL DMAc, 140 °C, 20 h).

R ³	R ⁴	Catalyst	First Arylation		Second Arylation		Conversion [%] ^[b]
			Position	Yield [%] ^[a]	Position	Yield [%] ^[a]	
H	H	Palladacycle	β	33	β	25	90
		[Pd(NH ₃) ₄] ²⁺ -NaY ^[c]	β	12	—	—	15
CH ₃	H	Palladacycle	β	20	α	8	43
		[Pd(NH ₃) ₄] ²⁺ -NaY ^[c]	β	13	—	—	15
CH ₃	CH ₃	Palladacycle	α	41	—	—	45
		[Pd(NH ₃) ₄] ²⁺ -NaY ^[c]	α	30	—	—	34

^[a] GLC-Yields are given ($\Delta_{\text{rel}} = \pm 5\%$).

^[b] Based on unreacted aryl halides.

^[c] 1.0 wt % Pd.

Conclusion

While the Heck arylation of alkyl acrylate derivatives is well documented, arylation of acrolein was not well studied.

While the yields are in some cases limited, we have demonstrated for the first time that the arylation of acrolein by the Heck reaction is possible and under certain reaction conditions can give high yields of cinnamaldehydes. It was observed that this reaction is strongly dependent on the catalyst, the solvent and the base. Depending on the catalytic system used, we could obtain quite cleanly the mono- or the diarylated product of acrolein. For the monoarylation, the optimum reaction was obtained at 140 °C for 20 h using the homogeneous palladacycle catalyst, NaOAc as the base and *N*-methylpyrrolidinone (NMP) as the solvent. Under these reaction conditions, the cinnamaldehyde was obtained in 83% isolated yield. Changing the base to K₂CO₃, the exclusive double arylation of acrolein to afford 3,3-diphenylpropenal in 44% yield was observed. Of particular interest was also the clean α -arylation of β,β -disubstituted acrolein.

As was previously described for the Heck reactions, the electronic nature of the aryl bromide has a dominating effect on the reaction yield. The activated aryl bromides react nearly quantitatively under standard reaction conditions.

Current investigations focus on the regioselectivity of the Pd-catalyzed arylation/functionalization of α,β -unsaturated carbonyl compounds, as this reaction can be of interest for fine chemicals.

Experimental Section

All preparations, manipulations and reactions were carried out under argon, including the transfer of the catalyst to the reaction vessel. All glassware was base-, acid- and water-washed and oven dried. Toluene and heptane were freshly distilled under argon over sodium before use. The zeolite NaY was purchased from Sigma-Aldrich Chemical (LZ-Z-52) and dried under 5 × 10⁻² mm Hg at 120 °C for 48 h before use. All other chemicals (organic reagents and solvents) were deaerated by an argon flow before they were used. The Pd-loaded zeolites were stored after drying under Ar atmosphere.

Solution NMR spectra of the organic products were recorded with a Bruker AM 250 spectrometer (¹H NMR were referenced to the residual protio-solvent: CDCl₃, δ = 7.25 ppm; ¹³C NMR were referenced to the C-signal of the deutero solvent: CDCl₃, δ = 77 ppm). Gas chromatography was performed on a Shimazu 14A chromatograph equipped with a FID detector and an HP-5 column (cross-linked methylsiloxane – 5% phenylsiloxane, 30 m × 0.25 mm × 0.25 mm film thickness).

The absolute palladium content of the catalysts was determined by ICP-AES for the Pd-complex loaded zeolites after drying and calcination (in order to remove all organic material) from a solution obtained by treatment with a mixture of HBF₄, HNO₃ and HCl in a Teflon reactor at 180 °C.

Preparation of the Catalysts

Procedure for the Preparation of the [Pd(NH₃)₄]²⁺-NaY^[6]

A 0.1 M ammonia solution of [Pd(NH₃)₄]Cl₂ – prepared from PdCl₂ and a commercial ammoniac solution – (0.95 or 5 mL/g zeolite, corresponding respectively approximately to 1 wt % and 5 wt % Pd in the final catalyst) was added dropwise to a suspension of the zeolite Na-Y in bidistilled water (100 mL/g zeolite). The mixture was stirred for 24 h at room temperature and the exchanged zeolite was filtered off and washed until no trace of chloride was detected in the filtrate (AgNO₃ test). Then the zeolite was allowed to dry at room temperature to give the entrapped [Pd(NH₃)₄]²⁺ zeolite as a slightly yellow material. The AAS gave respectively 1.0 ± 0.2 wt % Pd and 5.1 ± 0.2 Wt % Pd.

Procedure for the Preparation of the Pd(0)/SiO₂^[9b]

Before the preparation of the Pd/SiO₂ catalyst, the silica Aerosil 200 was agglomerated. It was added in water (100 mL/g SiO₂) in a round-bottomed flask under vigorous stirring. After 2 h water was evaporated. The silica was then dried in air at 120 °C, then slightly crushed and sifted. For the following experiment, we selected the particle sizes 40–60 mesh (250–400 nm) that allows easy handling of the material.

A solution of Pd(acac)₂ in toluene [made from 143.1 mg of Pd(acac)₂ in 15 mL of toluene] was added to 1 g of agglomerated silica. The mixture was then stirred for 1 h at room temperature under argon, before the toluene was evaporated to give a slightly yellow material. This was calcinated under air flow (100 mL/min) at 300 °C for 2 h then reduced under an H₂ flow (80 mL/min) in a U-reactor at 300 °C for 2 h to give the desired Pd(0)/SiO₂ catalyst as a black material. AAS determination gave 4.9 ± 0.1 wt % Pd.

Preparation of the Palladacycle Catalyst {Pd[P(o-C₆H₄CH₃)₂(C₆H₄CH₂)][OCOCH₃]}₂^[7]

Pd(OAc)₂ (4.5 g, 20 mmol) was dissolved in freshly distilled toluene (500 mL) under argon to give a reddish brown solution. Tri(*o*-tolyl)phosphine (8.0 g, 26.3 mmol) was added under argon. The resulted mixture was shortly (1 min) heated at 50 °C then rapidly cooled to room temperature to give a bright orange solution. The volume was reduced under vacuum to about 1/3 (160 mL) and freshly distilled hexane (500 mL) was added which causes the palladacycle to precipitate. After filtration and drying under vacuum the palladium complex was recrystallized from toluene/hexane to give the product as a microcrystalline yellow compound in 83% yield. All data were in accordance with literature reports.

Catalytic Runs

The catalytic reactions were carried out in pressure tubes under argon. The qualitative and quantitative analysis of the reactants and the products was made by gas liquid chromatography (GC). Conversion and selectivity were represented by product distribution based on GC yields (= relative area of GC signals

referred to an internal standard calibrated to the corresponding pure compound, $\Delta_{\text{rel}} = \pm 5\%$). When available, yields in isolated products are given in brackets.

General Procedure for the Catalytic Runs

10 mmol of aryl halide, 15 mmol of olefin, 15 mmol of base and 0.1 mol % of Pd (as homogeneous or heterogeneous catalysts, for which the mass of catalyst depends on the palladium concentration) were introduced in a pressure tube under argon. 8 mL of solvent p.a. previously deaerated were added and the mixture was deaerated by an argon flow for 5 min. The reactor was then placed in a pre-heated oil bath at 140 °C for 20 h with vigorous stirring and then cooled to room temperature before the reaction mixture was analyzed by GC.

GC analysis

A homogeneous 3 mL sample of the reaction mixture was sampled and quenched with 3 mL of water in a test tube. The mixture was extracted with 2 mL of CH₂Cl₂ and the organic layer was filtered through an MgSO₄ pad. The resulting dry organic layer was then analyzed by GC.

Purification of the Styrene Derivatives **1**, **2** or **3**

At the completion of the reaction, the reaction mixture was poured in water (60 mL), then extracted with CH₂Cl₂ (4 × 20 mL). The organic layer was then washed with brine (15 mL), dried over MgSO₄ and evaporated. The residue was further evaporated under vacuum to remove almost all DMAc, and purified by flash chromatography on silica gel 60 (Merck 230–400 mesh ASTM) eluting with a mixture CH₂Cl₂/petroleum ether (35–60 °C) 80–20% or with CH₂Cl₂.

Compound 1 with R¹=H and R²=O-n-Bu: ¹H NMR (CDCl₃, 250 MHz): δ = 7.68 (d, ³J = 16 Hz, 1H, CH=CH-CO), 7.51 (m, 2H, m-C₆H₅), 7.37 (m, 3H, o-C₆H₅ and p-C₆H₅), 6.44 (d, ³J = 16 Hz, 1H, CH=CH-CO), 4.20 (t, ³J = 6.7 Hz, 2H, CH₂O), 1.68 (m, 2H, CH₂), 1.45 (m, 2H, CH₂), 0.96 (t, ³J = 3.6 Hz, 3H, CH₃); ¹³C NMR (CDCl₃, 62.9 MHz): δ = 166.97 (CHO), 144.43 (CH=CH-CHO), 134.31 (C_q-C₆H₅), 130.19 (p-C₆H₅), 129.14 (o-C₆H₅), 128.04 (m-C₆H₅), 118.13 (CH=CH-CHO), 64.28 (CH₂O), 21.41 (CH₂), 19.18 (CH₂), 13.19 (CH₃); C₁₃H₁₆O₂, mol. wt.: 204.26, MS: m/z (%) = [M⁺] 204 (100), [M⁺-C₄H₉O] 131 (22), [M⁺-C₄H₉O-CO] 103 (42), [M⁺-C₄H₉O-CH=CHCHO + H] 77 (38).

Compound 1 with R¹=H and R²=H: ¹H NMR (CDCl₃, 250 MHz): δ = 9.68 (d, ³J = 7.9 Hz, 1H, CHO), 7.57 (m, 2H, m-C₆H₅), 7.50 (d, ³J = 15.3 Hz, 1H, CH=CH-CHO), 7.44 (m, 3H, o-C₆H₅ and p-C₆H₅), 6.69 (dd, ³J = 7.7 Hz, ³J_{2,3} = 15.8 Hz, 1H, CH=CH-CHO); ¹³C NMR (CDCl₃, 62.9 MHz): δ = 193.46 (CHO), 147.31 (CH=CH-CHO), 133.83 (C_q-C₆H₅), 131.08 (p-C₆H₅), 128.35 (o-C₆H₅), 128.95 (m-C₆H₅), 128.32 (CH=CH-CHO); C₉H₈O, mol. wt.: 132.05; MS: m/z (%) = [M⁺] 132 (100), [M⁺-CO] 104 (62), [M⁺-CH=CHCHO + H] 78 (58).

Compound 1 with R¹=H and R²=NH₂: ¹H NMR (CDCl₃, 250 MHz): δ = 7.60 (d, 1H, ³J = 15.8 Hz, CH=CH-CO), 7.58 (m, 2H, m-C₆H₅), 7.44 (m, 3H, o-C₆H₅ and p-C₆H₅), 6.54 (d, 1H, ³J = 15.8 Hz, CH=CH-CO), 5.91 (broad d, 2H, NH₂); ¹³C NMR (CDCl₃, 62.9 MHz): δ = 167.77 (CONH₂), 142.36 (CH=CH-

CO), 134.32 (C_q-C₆H₅), 129.84 (p-C₆H₅), 128.70 (o-C₆H₅), 127.78 (m-C₆H₅), 119.35 (CH=CH-CO); C₉H₉NO, mol. wt.: 147.07; MS: m/z (%) = [M⁺] 147 (100), [M⁺-NH₂] 131 (42), [M⁺-NH₂-CO] 103 (36), [M⁺-NH₂-CH=CHCHO + H] 77 (29).

Compound 2 with R¹=H and R²=H: ¹H NMR (CDCl₃, 250 MHz): δ = 9.48 (d, ³J = 7.9 Hz, 1H, CHO), 7.42 (m, 4H, m-C₆H₅), 7.28 (m, 6H, o-C₆H₅ and p-C₆H₅), 6.56 (d, ³J = 7.9 Hz, 1H, C=CH-CHO); ¹³C NMR (CDCl₃, 62.9 MHz): δ = 193.37 (CHO), 162.14 (C=CH-CHO), 139.57 and 136.54 (C_q-C₆H₅), 130.61 (o-C₆H₅), 130.38 (p-C₆H₅), 128.22 (o-C₆H₅), 129.33 (p-C₆H₅), 129.55 (m-C₆H₅), 128.49 (m-C₆H₅), 127.15 (C=CH-CHO); C₁₅H₁₂O, mol. wt.: 208.08; MS: m/z (%) = [M⁺] 208 (100), [M⁺-CO] 178 (52), [M⁺-CO-C₆H₅] 102 (41), [M⁺-C=CHCHO-C₆H₅+H] 77 (58).

Compound 1 with R¹=CH₃O and R²=H: ¹H NMR (CDCl₃, 250 MHz): δ = 9.68 (dd, ³J = 7.8 Hz, 1H, CHO), 7.56 (d, ³J = 15.9 Hz, 1H, CH=CH-CHO), 7.27 (d, ³J = 9.04 Hz, 2H, o-CH₃O-C₆H₄), 6.86 (d, ³J = 9.04 Hz, 2H, m-CH₃O-C₆H₄), 6.61 (dd, ³J = 15.8 Hz, ³J = 7.5 Hz, 1H, CH=CH-CHO), 3.68 (s, 3H, CH₃O); ¹³C NMR (CDCl₃, 62.9 MHz): δ = 193.26 (CHO), 159.74 (C_q-CH₃O-C₆H₄), 150.31 (CH=CH-CHO), 134.23 (C_q-C₆H₄), 127.35 (o-C₆H₄), 116.65 (m-C₆H₅), 129.52 (CH=CH-CHO), 55.87 (CH₃O); C₁₀H₁₀O₂, mol. wt.: 162.07; MS: m/z (%) = [M⁺] 162 (100), [M⁺-CH₃] 147 (90), [M⁺-CH₃O] 131 (80), [M⁺-CH₃O-CO] 103 (60), [M⁺-CH₃O-CH=CHCHO + H] 77 (35).

Compound 1 with R¹=F and R²=H: ¹H NMR (CDCl₃, 250 MHz): δ = 8.98 (dd, ³J = 7.7 Hz, 1H, CHO), 6.98 (m, 4H, C₆H₄), 6.44 (d, ³J = 16.9 Hz, 1H, CH=CH-CHO), 5.94 (dd, ³J = 15.8 Hz, ³J = 7.5 Hz, 1H, CH=CH-CHO); ¹³C NMR (CDCl₃, 62.9 MHz): δ = 192.96 (CHO), 161.24 (C_q-FC₆H₄), 151.01 (CH=CH-CHO), 134.63 (C_q-C₆H₄), 127.85 (o-C₆H₄), 115.38 (m-C₆H₅), 129.67 (CH=CH-CHO); C₉H₇OF, mol. wt.: 150.05; MS: m/z (%) = [M⁺] 150 (100), [M⁺-CO] 122 (56), [M⁺-CH=CHCHO + H] 96 (38).

Compound 1 with R¹=NO₂ and R²=H: ¹H NMR (CDCl₃, 250 MHz): δ = 9.10 (d, ³J = 7.5 Hz, 1H, CHO), 7.55 (d, ³J = 8.7 Hz, 2H, o-NO₂-C₆H₄), 7.28 (d, ³J = 8.5 Hz, 2H, m-NO₂-C₆H₄), 7.19 (d, ³J = 16.2 Hz, 1H, CH=CH-CHO), 6.17 (dd, ³J = 15.8 Hz, ³J = 7.3 Hz, 1H, CH=CH-CHO); ¹³C NMR (CDCl₃, 62.9 MHz): δ = 192.96 (CHO), 151.02 (CH=CH-CHO), 143.94 (C_q-NO₂C₆H₄), 139.53 (C_q-C₆H₄), 129.81 (CH=CH-CHO), 127.62 (m-C₆H₅), 122.95 (o-C₆H₄); C₉H₇NO₃, mol. wt.: 177.04; MS: m/z (%) = [M⁺] 177 (100), [M⁺-NO₂] 130 (90), [M⁺-NO₂-CO] 102 (68), [M⁺-NO₂-CH=CHCHO + H] 77 (51).

Compound 1 with R¹=CH₃CO and R²=H: ¹H NMR (CDCl₃, 250 MHz): δ = 9.74 (d, ³J = 7.5 Hz, 1H, CHO), 8.00 (d, ³J = 7.9 Hz, 2H, o-CH₃CO-C₆H₄), 7.65 (d, ³J = 8.3 Hz, 2H, m-CH₃CO-C₆H₄), 7.51 (d, ³J = 16.0 Hz, 1H, CH=CH-CHO), 6.78 (dd, ³J = 16.0 Hz, ³J = 7.5 Hz, 1H, CH=CH-CHO), 2.63 (s, 1H, CH₃CO); ¹³C NMR (CDCl₃, 62.9 MHz): δ = 197.02 (CO), 193.06 (CHO), 151.32 (CH=CH-CHO), 136.94 (C_q-CH₃CO-C₆H₄), 139.32 (C_q-C₆H₄), 128.62 (m-C₆H₅), 126.15 (o-C₆H₄), 129.68 (CH=CH-CHO), 25.96 (CH₃); C₁₁H₁₀O₂, mol. wt.: 174.07; MS: m/z (%) = [M⁺] 174 (100), [M⁺-CH₃] 159 (90), [M⁺-CH₃CO] 131 (100), [M⁺-CH₃CO-CO] 103 (60), [M⁺-CH₃CO-CH=CHCHO + H] 77 (45).

Compound 3 with R³=CH₃, R⁴=H, β and n=1: ¹H NMR (CDCl₃, 250 MHz): δ = 9.58 (d, ³J = 7.8 Hz, 1H, CHO), 7.33 (m, 2H, o-C₆H₅), 7.22 (m, 3H, m-C₆H₅ and p-C₆H₅), 6.19 (d, ³J = 7.8 Hz, 1H, C=CH-CHO), 2.85 (s, 3H, CH₃); ¹³C NMR

(CDCl₃, 62.9 MHz): δ = 195.49 (CHO), 156.23 (C=CH-CHO), 136.73 (C_q, C₆H₅), 127.95 (m-C₆H₅), 127.08 (p-C₆H₅), 126.35 (o-C₆H₅), 121.82 (C=CH-CHO), 21.94 (CH₃); C₁₀H₁₀O, mol. wt.: 146.07; MS: m/z (%) = [M⁺] 146 (100), [M⁺ - CO] 118 (82), [M⁺ - CO - CH₃] 103 (71), [M⁺ - C=CHCHO - CH₃] 77 (58).

Compound 3 with R³ = CH₃, R⁴ = H, α and β and n = 2: ¹H NMR (CDCl₃, 250 MHz): δ = 9.62 (s, 1H, CHO), 7.38 (m, 4H, o-C₆H₅), 7.21 (m, 6H, m-C₆H₅ and p-C₆H₅), 3.02 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 62.9 MHz): δ = 197.23 (CHO), 149.21 (C=C-CHO), 135.93 (C_q, C₆H₅), 132.76 (C=C-CHO), 128.01 (m-C₆H₅), 127.72 (p-C₆H₅), 126.15 (o-C₆H₅), 20.14 (CH₃); C₁₆H₁₄O, mol. wt.: 222.10; MS: m/z (%) = [M⁺] 222 (50), [M⁺ - CO] 194 (100), [M⁺ - CO - CH₃] 179 (10), [M⁺ - C=CCHO - CH₃] 77 (28).

Compound 3 with R³ = R⁴ = CH₃, β and n = 1: ¹H NMR (CDCl₃, 250 MHz): δ = 9.57 (s, 1H, CHO), 7.33 (m, 2H, o-C₆H₅), 7.20 (m, 3H, m-C₆H₅ and p-C₆H₅), 2.22 (s, 6H, CH₃); ¹³C NMR (CDCl₃, 62.9 MHz): δ = 196.53 (CHO), 146.21 (C=C-CHO), 136.02 (C_q, C₆H₅), 133.24 (C=C-CHO), 128.42 (m-C₆H₅), 127.03 (p-C₆H₅), 125.98 (o-C₆H₅), 19.36 (CH₃); C₁₁H₁₂O, mol. wt.: 160.08; MS: m/z (%) = [M⁺] 160 (72), [M⁺ - CHO] 131 (100), [M⁺ - CO - 2 × CH₃ + 2 H] 103 (45), [M⁺ - C=CCHO - 2 CH₃] 77 (35).

References and Notes

- [1] a) Kirk-Othmer, *Encyclopedia of Chemical Technology*, Wiley Interscience, New York, **1999**, Vol. 7, 153ff; b) D. Garbe, in *Ullmann's Encyclopedia*, **1992**, Vol. A 7, 99ff; c) H. Gregger, O. Hoffer, H. Kählig, G. Wurz, *Tetrahedron* **1992**, 48, 1209.
- [2] a) T. Rosen in *Comprehensive Organic Synthesis*, (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, Vol. 4, 395 ff.
- [3] D. Garbe, in *Ullmann's Encyclopedia*, **1992**, Vol. A 7, 99ff.
- [4] For general reviews see: a) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, 100, 3009; b) A. de Meijere, S. Bräse, *J. Organomet. Chem.* **1999**, 576, 88; c) S. Bräse, A. de Meijere, in *Metal Catalyzed Cross-Coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH Weinheim, **1998**, 99ff; d) M. Beller, T. H. Riermeier, G. Stark, in *Transition Metals for Organic Synthesis*, Vol. 1, (Eds.: M. Beller, C. Bolm), VCH, Weinheim, **1998**, pp. 208; e) R. A. DeVries, P. C. Vosejpk, M. L. Ash, in *Catalysis of Organic Reactions* (Ed.: F. E. Herkes), Marcel Dekker, Basel, **1998**, pp. 467; f) A. Eisenstadt, in *Catalysis of Organic Reactions*, Vol. 1, (Ed.: F. E. Herkes), Marcel Dekker, Basel, **1998**, pp. 415; g) O. Loiseleur, M. Hayashi, N. Schmees, A. Pfaltz, *Synthesis* **1997**, 1338; h) A. de Meijere, F. E. Meyer, *Angew. Chem.* **1994**, 106, 2473; i) R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press Inc, London, **1985**.
- [5] a) C.-M. Andersson, A. Hallberg, *J. Org. Chem.* **1988**, 53, 235; b) W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, 28, 2; c) W. Cabri, I. Candiani, A. Bedeschi, S. Penco, *J. Org. Chem.* **1992**, 57, 1481.
- [6] a) L. Djakovitch, H. Heise, K. Köhler, *J. Organomet. Chem.* **1999**, 584, 16; b) L. Djakovitch, K. Koehler, *J. Mol. Catal. A: Chem.* **1999**, 142, 275; c) L. Djakovitch, K. Koehler, *J. Am. Chem. Soc.* **2001**, 123, 5990.
- [7] a) M. P. Muñoz, B. Martín-Matute, C. Fernández-Rivas, D. J. Cárdenas, A. M. Echavarren, *Adv. Synth. Catal.* **2001**, 343, 338; b) W. A. Herrmann, V. P. W. Böhm, C.-P. Reisinger, *J. Organomet. Chem.* **1999**, 576, 23; c) W. A. Herrmann, C. Broßmer, C.-P. Reisinger, T. H. Riermeier, K. Öfele, M. Beller, *Chem. Eur. J.* **1997**, 1357; d) W. A. Herrmann, C. Broßmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem.* **1995**, 107, 1989; e) W. A. Herrmann, C. Broßmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1844.
- [8] a) M. Prashad, J. C. Tomesch, J. R. Wareing, H. C. Smith, S. H. Cheon, *Tetrahedron Lett.* **1989**, 30, 2877; b) Recently some authors reported a double Heck arylation of olefin by consecutive inter- plus intra-molecular reactions, see: M. Prashad, Y. Liu, X. Y. Mak, D. Har, O. Repic, T. J. Blacklock, *Tetrahedron Lett.*, **2002**, 43, 8559.
- [9] a) R. G. Heidenreich, J. G. E. Krauter, J. Pietsch, K. Köhler, *J. Mol. Catal. A: Chem.* **2002**, 182–183, 499; b) K. Köhler, M. Wagner, L. Djakovitch, *Catal. Today*, **2001**, 66, 105; c) K. Köhler, M. Wagner, L. Djakovitch, in *European Conference Series on Catalysis – 3rd G.-M. Schwab Symposium – Catalysis for Organic Synthesis*, DecHEMA, Berlin, **1997**, p. P 39.
- [10] C. G. Hartung, K. Köhler, M. Beller, *Org. Lett.* **1999**, 1, 709.
- [11] a) F. Zhao, B. M. Bhanage, M. Shirai, M. Arai, *Chem. Eur. J.* **2001**, 6, 843; b) A.-S. Carlström, T. Frejd, *Acta Chem. Scand.* **1992**, 46, 163; c) A. F. Shmidt, L. V. Mametova, T. V. Dmitrieva, E. Y. Shmidt, V. S. Tkach, *Izv. Akad. Nauk. SSSR* **1991**, 40, 190.
- [12] a) S. Sjövall, M. H. Johansson, C. Andersson, *Eur. J. Inorg. Chem.* **2001**, 2907; b) C.-M. Andersson, A. Hallberg, *J. Org. Chem.* **1988**, 53, 235; c) C.-M. Andersson, A. Hallberg, *J. Org. Chem.* **1987**, 52, 3529; d) K. Karabelas, C. Westerlund, A. Hallberg, *J. Org. Chem.* **1985**, 50, 3896; e) C.-M. Andersson, K. Karabelas, A. Hallberg, *J. Org. Chem.* **1985**, 50, 3891.
- [13] a) D. Basavaiah, R. M. Reddy, N. Kumaragurubaran, D. S. Sharada, *Tetrahedron* **2002**, 58, 3693; b) C. Yu, L. Hu, *J. Org. Chem.* **2002**, 67, 219.