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Pd-catalyzed Heck arylation of cycloalkenes—studies on selectivity comparing homogeneous and heterogeneous catalysts

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Abstract

Heck reactions of aryl bromides with cyclohexene and cyclopentene catalyzed by typical homogeneous as well as heterogeneous Pd catalysts (Pd/C, Pd/SiO_2, Pd/MgO, Pd/Al_2O_3, and Pd(0), Pd(II) and $[Pd(NH_3)_4]^{2+}$ in zeolites Y or ZSM-5) have been studied in order to get detailed information on the reaction mechanism with regard to the catalyst. The focus of the present investigation was on correlations between selectivity (Heck products: double bond isomers of arylcycloalkenes, dehalogenation and double arylation products) and nature of the catalyst or active Pd species, respectively. The results indicate that dissolved molecular Pd species are responsible for the Heck coupling for both homogeneous and heterogeneous (solid) catalysts, whereas dehalogenation is due to a mechanism involving the surface of solid Pd metal particles and radical processes. The selectivity of the reactions can be controlled by the choice of catalyst and reaction conditions (base, solvent, temperature).

Keywords: Heck arylation; Homogeneous catalyst; Heterogeneous catalyst; Dehalogenation; Mechanism

1. Introduction

The Heck reaction, a palladium-catalyzed arylation or vinylation of olefines, has become one of the most important and powerful transition-metal-catalysed transformations in organic synthesis to generate new carbon–carbon bonds [1–8]. Nowadays, this reaction has found several commercial applications for the production of fine chemicals on multi-ton scale/year [9–11]: e.g. the Herbicide Prosulfuron™ [12], the anti-inflammatory Naproxen™ [13] or the anti-asthma agent Singulair™ [14].

During the last decade, important advancements have been reported in homogeneous and heterogeneous Heck catalysis. Independent of the nature of the catalyst (homogeneous or heterogeneous) it is generally reported that the Heck reaction is catalyzed by Pd(0)-species generated from Pd(0)- or Pd(II)-catalyst precursors [4], however the mechanism in particular with heterogeneous catalysts is still under debate.

For homogeneously catalyzed Heck reactions, a well accepted mechanism involving a coordinatively unsaturated 14-electron Pd(0)-species coordinated with donor ligands such as triarylphosphines (PdL_2) was early proposed. The 14-electron Pd(0)-species, is thought to be in general the active species, which undergoes oxidative addition to give a *trans*-palladium(II) complex $[ArPdXL_2]$ [4]. However, this "traditional" mechanism is still under discussion and the "real" mechanism seems to be dependent on the ligand, the base, and the solvent used during the reaction [15]. Amatore et al. [16–19] have shown that anionic species (L_2PdX^-) may be the catalytically active species for the Heck reaction when strong donor anions are present. Herrmann and Beller et al. [20–25] reported for the first time palladacycles as active catalysts in Heck reactions. Initially it was assumed that the active species is based on a Pd(II)/Pd(IV) catalytic cycle, however later on it was proposed that Pd(0)-species are the actual catalysts in the reaction medium. Nevertheless, a Pd(II)/Pd(IV) mechanistic approach was reported by Milstein et al. [26] and Shaw et al. [27] for other cyclometallated

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palladium catalysts precursors [28]. Recently, Evans et al. [29] have shown that anionic palladium species $[Pd_2X_6]^{2-}$ may be the catalytically active species for Heck reactions catalyzed by phosphine free systems.

Concerning heterogeneously catalyzed Heck reaction, several papers discussed mechanistic aspects. Up to now there is no clear evidence concerning structure-activity relationships. As for homogeneous systems, it seems that the authentic mechanism depends on the preparation of the heterogeneous palladium catalyst, the nature of the support (carbon, metal oxide, micro or mesoporous support, etc.) and on the catalytic system used: i.e. the solvent and the base. Augustine et al. [30,31] proposed, based on single turn-over hydrogenation experiments, that the activity of Pd-metal supported catalysts for the Heck reaction is directly related to the number of low-coordination or "defect" palladium surface atoms. This mechanistic approach was recently supported by Blackmond et al. [32] for colloidal palladium particles stabilized by various homo-polymers for the Heck arylation and Choudary et al. [33] for supported nanopalladium catalysts on layered double hydroxides. Kaneda et al. [34] proposed on analogy with the well known π-aryl-chromium complexes that the activation of aryl halides during the Heck reaction results from a flat π-adsorption of the aromatic ring over a "large" palladium particle. In this mechanism, after activation of the C–X bond, the adsorbed aryl halide gives a σ-aryl–palladium complex at the metallic surface by palladium insertion. However, for several authors the activity of the heterogeneous palladium catalysts (Pd/C, Pd/MO_x) is related to palladium species leached into solution, resulting in a mechanism very similar to that of homogeneous systems involving a Pd(0)/Pd(II) catalytic cycle [35–41]. Based on our results for Pd-zeolite (Pd(0)/NaY, Pd(II)/NaY and $[Pd(NH_3)_4]^{2+}$/NaY) and Pd/MO_x catalyzed Heck reactions, we strongly support such a mechanism and propose that the overall activity of these catalysts results from dissolved Pd-species [42–50]. These Pd-species could be retained in the zeolite pores or re-adsorbed at the surface through a dissolution–readsorption equilibrium. Recently, Dams et al. [51,52] revisited the Heck reaction catalyzed by Pd-zeolite and proposed that the activity of these heterogeneous catalysts depends on the thermal treatment. The Pd(II)-species surrounded by oxygen inside the zeolites pores are prone to leaching, the leached Pd-species reflecting the overall activity of the catalyst through a homogeneous cycle whereas the $[Pd(NH_3)_4]^{2+}$-species or the Pd(0)-particles entrapped in the zeolite pores would remain true heterogeneous systems.

Most of the past studies focussed on the relation between the activity and the catalyst's structure/nature, but selectivity issues of Heck reactions were usually not taken into account. Generally, when using typical (non-problematic) olefins, e.g. styrene, acrylates no differences in selectivity are observed both for homogeneous or heterogeneous Pd catalysts used in these Heck reactions. These observations would support that the same or a very similar mechanism occurred for both catalytic systems. Nevertheless, in some heterogeneously catalyzed reactions, a moderate to strong dehalogenation of the aryl halides is observed, whereas it is not as typical for homogeneous systems, suggesting that a different mechanism would operate for heterogeneous catalysts.

In order to achieve deeper insight into the mechanism of heterogeneous catalysts Heck reactions sensitive toward the selectivity should be studied. Among them, the Heck arylation of cyclic olefins is probably the most appropriated as a mixture of double-bond regioisomers is often obtained under standard Heck conditions (125 °C or 140 °C for, respectively, homogeneous or heterogeneous catalysts; polar aprotic solvents; NaOAc or NR_3) [53–66]. From literature results one can conclude that the regioselectivity depends on the palladium source and electronic factors (essentially the ligand field) [67–70]. Thus, one could expect effects related to the reaction mechanisms (homogeneous/heterogeneous) by detailed analysis of (regio- and chemo-) selectivity variations. For this purpose, we have chosen the arylation of cyclic olefins, known to be difficult substrates toward the Heck arylation as a model system.

In the present contribution, we describe the Heck arylation of cyclohexene and cyclopentene [53] by bromoacetophenone catalyzed both by homogeneous and heterogeneous systems. Particular attention toward the selectivity of the reaction was paid in order to get deeper insights into the reaction mechanism.

2. Experimental

All preparations, manipulations and reactions were carried out under argon, including the transfer of the catalysts to the reaction vessel. All glassware was base- and acid-washed and oven dried.

The toluene used for the synthesis of the "palladacyle" catalyst $\{Pd[P(o\text{-}C_6H_4CH_3)_2\text{-}(o\text{-}C_6H_4CH_2)(CH_3CO_2)]\}_2$ was distilled under argon before use over sodium from purple benzophone ketyl. The supports (TiO_2 {P25}, SiO_2 {Aerosil 200}, Al_2O_3 {aluminium oxide C}), and the zeolite (HY and ZSM-5) were donated by Degussa AG. The NaY zeolite (LZ-Z-52) was purchased from Sigma–Aldrich. Silica Aerosil 200 was agglomerated prior to use by treatment with water. After evaporation and drying at 120 °C for 3 days the resulting material was crushed and sieved to give a selected fraction with a particle size of 40–60 mesh. BET of a silica sample dehydroxylated at 500 °C under 10^{-5} mmHg for 6 h gave the following characteristics: specific surface $= 240 \pm 4\,m^2/g$, pore diameter = 32–36 nm. All catalyst supports were dried before use at 120 °C for 48 h under 5.10^{-2} mmHg. The Pd/C catalyst (5 wt.% on dry basis, 52% water) was purchased from Aldrich. The other chemicals (organic reagents and solvents) were deaerated by an argon flow before they were used.

NMR spectra were recorded with a Bruker AM 400 spectrometer (^{1}H NMR were referenced to the residual protio-solvent: $CDCl_3$, $\delta = 7.25$ ppm; ^{13}C NMR were referenced to the C-signal of the deutero solvent: $CDCl_3$, $\delta = 77$ ppm). The palladium content determination of the catalysts (Pd/MO_x or Pd-loaded zeolites) was performed by AAS spectroscopy from a solution obtained by treatment of the catalysts with a 40% HF commercial solution for the Pd/MO_x catalysts or by treatment with a mixture of HBF_4, HNO_3 and HCl in a Teflon reactor at 180 °C for the Pd-zeolites after calcination and reduction (in order to remove all organic materials). Gas–liquid chromatograms were performed on a HP 6890 series chromatograph equipped with a FID detector and a HP-1 column (cross-linked methylsiloxane, 30 m × 0.25 mm × 0.25 μm film thickness) using He as carrier gas. Alternatively, a HP 5970 series chromatograph equipped with a selective mass-spectrometer detector HP 5970 and a BGB-1 column from SCP-Seitz GmbH (95% methylpolysiloxane + 5% phenylpolysiloxane, 25 m × 0.32 mm × 0.52 μm) using He as carrier gas was used.

2.1. Catalyst preparations

All catalysts (homogeneous "palladacycle" and heterogeneous catalysts) were prepared according procedures previously described in the literature.

2.1.1. Preparation of the "palladacycle" {*Pd[P(o-C$_6$H$_4$CH$_3$)$_2$-(o-C$_6$H$_4$CH$_2$)(CH$_3$CO$_2$)]*}$_2$ [25]

$Pd(OAc)_2$ (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 (rt) 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.

2.1.2. Preparation of the $Pd_2(dba)_3$·dba catalyst precursor [71,72]

Dibenzylidenacetone (2.30 g, 9.8 mmol) and sodium acetate (1.95 g, 23.8 mmol) were dissolved in 75 mL of absolute methanol at 50 °C under argon. Palladium chloride (0.53 g, 2.96 mmol) was added to the reaction mixture. The solution was heated at 40 °C for 4 h to give a purple precipitate. The reaction mixture was cooled to 0 °C and the precipitate was filtered off, then washed with water (2 × 15 mL) and acetone (3 × 10 mL) to give 1.67 g of $Pd_2(dba)_3$·dba as a microcrystalline purple compound (97% yield). All data were in accordance with literature.

2.1.3. Preparation of MgO [73]

1 mole of $MgSO_4$ (120.3 g) was dissolved in distilled water (1 L) at 30 °C. Then, 400 mL of a 25% ammonia solution were added over 100 min under agitation. The resulting mixture was left for 20 h in order to allow the formed $Mg(OH)_2$ to precipitate. The $Mg(OH)_2$ was then filtered off and washed with distilled water until the filtrate is neutral (pH 7). The resulting material was then dried at 130 °C to give 33.9 g of a white powder (58% yield).

In a second period, 10 g of $Mg(OH)_2$ were activated by the "addition" of a 1.4 M solution of $Mg(NO_3)_2$ in distilled water (12 mL). Then the "wet" material was calcinated at air at 600 °C for 6 h to give 7.25 g of a fine white powder (99% yield). The MgO thus obtained present a specific surface of $S = 44.2\ m^2/g$.

2.1.4. Preparation of the Pd(0)/MO_x catalysts [34]

A solution of $Pd(acac)_2$ in benzene (made from 143.1 mg of $Pd(acac)_2$ in 15 mL of benzene) was added to 1.0 g of MO_x. After stirring the mixture for 1 h at rt, the benzene is evaporated to give a slightly yellow material. This was reduced under H_2 flow (150 mL/min) in a U-reactor at 70 °C for 2 h to give the desired Pd/MO_x catalyst as grey materials.

2.1.5. Preparation of the $[Pd(NH_3)_4]^{2+}$ modified zeolites [46,50,74,75]

A 0.1 M ammonia solution of $[Pd(NH_3)_4]Cl_2$-prepared from $PdCl_2$ and a commercial ammonia solution (4 mL/g zeolite, corresponding to approximately 5% 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 rt and the exchanged zeolite was filtered off and washed until no trace of chloride was detected in the filtrate ($AgNO_3$ test). Then the zeolite was allowed to dry at rt to give the entrapped $[Pd(NH_3)_4]^{2+}$ zeolite as a slightly yellow material.

2.1.6. Preparation of the [Pd(II)] modified zeolites [46,50,74,75]

The Pd(II) exchanged zeolite was obtained by calcination of the entrapped $[Pd(NH_3)_4]^{2+}$ zeolite in a U-reactor under a pure oxygen flow (180 mL/min) using a heating rate of 2 K/min from rt to 500 °C. The temperature was maintained at 500 °C for 30 min and the reactor was cooled to rt under a flow of argon to give the modified Pd(II) zeolite as a tabac-colored powder. The Pd(II) loaded zeolite was then stored under an Ar atmosphere to prevent hydration.

2.1.7. Preparation of the [Pd(0)] modified zeolites [46,50,74,75]

The Pd(0) exchanged zeolite was obtained by reduction of the Pd(II) zeolite in a U-reactor under a pure hydrogen flow (70 mL/min) using a heating rate of 8 K/min from rt to 350 °C. The temperature was maintained at 350 °C for 15 min and the reactor was cooled to rt under a flow of argon to give the Pd(0) modified zeolite as a black powder. The

Table 1
AAS analysis of the heterogeneous catalysts

Catalyst	Pd (wt.%)
$[Pd(NH_3)_4]/HY$	6.8 ± 0.2
$[Pd(NH_3)_4]/NaY$	4.0 ± 0.2
$[Pd(NH_3)_4]/ZSM\text{-}5$	5.2 ± 0.2
Pd(II)/HY	6.2 ± 0.2
Pd(II)/NaY	4.7 ± 0.2
Pd(II)/ZSM-5	4.9 ± 0.2
Pd(0)/HY	6.0 ± 0.2
Pd(0)/NaY	4.8 ± 0.2
Pd(0)/ZSM-5	5.0 ± 0.2
$Pd(0)/TiO_2$	4.6 ± 0.2
$Pd(0)/SiO_2$	4.3 ± 0.2
Pd(0)/MgO	4.7 ± 0.2

Pd(0) loaded zeolite was then stored under an Ar atmosphere to prevent re-oxidation.

2.1.8. Elemental analysis of the heterogeneous catalysts

Summary of the elemental analysis of the heterogeneous palladium catalysts is presented in Table 1.

2.2. Catalytic test reactions

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 (GLC). Conversion and yields were determined by GLC based on the relative area of GLC-signals referred to an internal standard (diethylene glycol di-*n*-butyl ether) calibrated to the corresponding pure compound ($\Delta_{rel} = \pm 5\%$). Selectivity is represented by product distribution based on the relative area of GLC-signals. In the text and tables, Pd(II) refers to Pd species immobilized in zeolite by ion-exchange subsequently treated by calcination under O_2 flow and Pd(0) refers to Pd species immobilized in zeolite by ion-exchange subsequently treated by calcination under O_2 flow followed by reduction with H_2. All catalysts were handled and transferred under Ar.

2.2.1. General procedure for the Heck reaction

10 mmol of 4-bromoacetophenone, 15 mmol of cyclic alkene, 15 mmol of base and 0.1 mol% of [Pd] (for heterogeneous catalysts, the amount in grams of catalysts depending of the palladium concentration) were introduced in a pressure tube under argon. 10 mL of solvent (DMAc or DMF 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 or 120 °C for 20 h with vigorous stirring and then cooled to rt before the reaction mixture was analyzed by GLC.

2.2.2. GLC analysis

A 3 mL sample of the reaction mixture was quenched with 3 mL of water in a test tube. The mixture was extracted with 2 mL of CH_2Cl_2 and the organic layer was filtered through a $MgSO_4$ pad. The resulting dry organic layer was then analyzed by GLC. GLC-rate program: 2 min at 100 °C, heating 15 K/min up to 170 °C, 2 min at 170 °C, heating 35 K/min up to 240 °C, 10 min at 240 °C, heating 50 K/min up to 270 °C and 2 min at 270 °C.

2.3. Preparation of the Heck products

2.3.1. Preparation of 4-(1-cyclohexenyl)acetophenone **1**, 4-(2-cyclohexenyl)acetophenone **2**, 4-(3-cyclohexenyl)acetophenone **3**, 1,4-bis(4-acetylphenyl)-1-cyclohexene **5**

5 mmol (1.0 g) of 4-bromoacetophenone, 25 mmol (2.5 mL) of cyclohexene, 6 mmol (0.49 mg) NaOAc, 0.1 mol% (1.12 mg) $Pd(OAc)_2$ and 0.2 mol% (2.63 mg) PPh_3 were added to 10 mL of a mixture DMSO/DMAc (1:4). The reaction mixture was heated at 150 °C for 20 h to give 728 mg (73% yield) of a mixture of compounds **1**–**3** as a colorless oil by distillation under 0.05 mbar: bp (0.05 mmbar) = 104–107 °C. From the remaining residue, compound **5** was isolated by flash chromatography on silica gel (Merck 230–400 mesh ASTM) eluting with a mixture of hexane/ethyl acetate (10:1). $R_f = 0.03$. **5** was further purified by crystallization from hexane as a yellow microcrystalline compound (9% yield).

*2.3.1.1. Data for **1**.* ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 7.88 (m, 2H, *o*–$C_6\underline{H}_4$); 7.45 (m, 2H, *m*–$C_6\underline{H}_4$); 6.24 (m, ^{1}H, C$\underline{H}$=C); 2.58 (s, 3H, C$\underline{H}_3$); 1.45–2.43 (m, 8H, C$\underline{H}_2$).

^{13}C NMR ($CDCl_3$, 100.61 MHz): δ = 197.4 (*C*=O); 145.1 (*C*=CH); 139.2 (*p*-C_q *C*$_6$H$_4$); 136.2 (*ipso*-C_q C_6H_4); 128.6 (*o*-C_6H_4); 126.4 (*m*-*C*$_6$H$_4$); 123.7 (C=*C*H); 34.9 (CH_2–*C*H_2–C=CH); 31.8 (CH_2–*C*H_2–CH_2); 28.7 (CH_2–*C*H_2–CH_2); 28.1 (*C*H_2–CH=C); 25.3 (*C*H_3).

$C_{14}H_{16}O$, molecular weight: 200.29, MS = *m*/*z* (%): [$M^{\bullet+}$] 200 (100); [$M^{\bullet+}$–CH_3] 185 (53); [$M^{\bullet+}$–$COCH_3$] 157 (72); [$CH_3CO^{\bullet+}$] 43 (15).

*2.3.1.2. Data for **2**.* ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 7.88 (m, 2H, *o*–$C_6\underline{H}_4$); 7.29 (m, 2H, *m*–$C_6\underline{H}_4$); 5.91 (qd, ^3J(H, H) = 10.1 Hz, ^3J(H, H) = 2.5 Hz, 1H, CH^a=CH^b); 5.67 (qd, ^3J(H, H) = 10.1 Hz, ^3J(H, H) = 2.5 Hz, 1H, CH^a=CH^b); 3.44 (pseudo-octet, ^3J(H, H) = 2.5 Hz, 1H, CH); 2.55 (s, 3H, C$\underline{H}_3$); 1.45–2.30 (m, 6H, CH_2).

^{13}C NMR ($CDCl_3$, 100.61 MHz): δ = 197.8 (*C*=O); 152.4 (*p*-C_q *C*$_6$*H*$_4$); 129.1 (*C*H^a=CH^b); 129.0 (CH^a=*C*H^b); 128.4 (*ipso*-C_q *C*$_6$*H*$_4$); 128.4 (*o*-*C*$_6$H$_4$); 127.9 (*m*-*C*$_6$H$_4$); 41.8 (*C*H); 32.3 (*C*H_2–CH=CH); 29.6 (*C*H_3); 24.9 (*C*H_2-CH); 21.0 (*C*H_2).

$C_{14}H_{16}O$, molecular weight: 200.29, MS = *m*/*z* (%): [$M^{\bullet+}$] 200 (100); [$M^{\bullet+}$–CH_3] 185 (28); [$M^{\bullet+}$–$CH_2 = CH_2$] 172 (37); [$M^{\bullet+}$–$COCH_3$] 157 (72); [$M^{\bullet+}$–$COCH_3$–CH_2=CH_2] 129 (39); [$CH_3CO^{\bullet+}$] 43 (24).

*2.3.1.3. Data for **3**.* ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 7.88 (d, ^3J(H, H) = 8.5 Hz, 2H, *o*−$C_6\underline{H}_4$); 7.29 (d, ^3J(H, H) = 8.5 Hz, 2H, *m*−$C_6\underline{H}_4$); 5.75 (m, 2H, C*H*^{a}=C*H*^{b}); 2.85 (m, 1H, C*H*); 2.55 (s, 3H, C$\underline{H}_3$); 1.45–2.30 (m, 6H, CH_2).

^{13}C NMR ($CDCl_3$, 100.61 MHz): δ = 197.8 (*C*=O); 153.0 (*p*-C_q *C*$_6$H$_4$); 135.2 (*ipso*-C_q *C*$_6$H$_4$); 128.5 (*o*-C_6H_4); 127.1 (*m*−*C*$_6$H$_4$); 127.0 (*C*H^a=CH^b); 126.3 (CH^a=*C*H^b); 40.2 (*C*H); 32.9 (CH–*C*H$_2$–CH=CH); 29.3 (CH–*C*H$_2$–CH$_2$); 26.5 (*C*H$_3$); 25.5 (CH$_2$–*C*H$_2$–CH=CH).

$C_{14}H_{16}O$, molecular weight: 200.29, MS = *m*/*z* (%): [*M*$^{\bullet+}$] 200 (80); [*M*$^{\bullet+}$–CH_3] 185 (28); [*M*$^{\bullet+}$–$COCH_3$] 157 (100); [*M*$^{\bullet+}$– CH_2=CH−CH=CH_2] 146 (43); [*M*$^{\bullet+}$–CH_2=CH−CH=CH_2–CH_3] 131 (57); [*M*$^{\bullet+}$–CH_2=CH−CH=CH_2–$COCH_3$] 103 (86); [$CH_3CO^{\bullet+}$] 43 (24).

*2.3.1.4. Data for **5**.* ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 7.92 (d, ^3J(H, H) = 8.0 Hz, 2H, *o*−$C_6\underline{H}_4$); 7.91 (d, ^3J(H, H) = 8.0 Hz, 2H, *o*−$C_6\underline{H}_4$); 7.48 (d, ^3J(H, H) = 8.0 Hz, 2H, *m*−$C_6\underline{H}_4$); 7.35 (d, ^3J(H, H) = 8.0 Hz, 2H, *m*−$C_6\underline{H}_4$); 6.33 (m, 1H, C*H*=C); 2.96 (m, 1H, C*H*); 2.58 (s, 6H, C$\underline{H}_3$); 2.51–2.65 (m, 2H, CH_2–C*H*$_2$–C=CH); 2.55–.37 (m, 2H, CH_2–C*H*$_2$–CH); 2.14–.95 (m, 2H, CH-C*H*$_2$–CH=C).

^{13}C NMR ($CDCl_3$, 100.61 MHz): δ = 197.6 (*C*=O); 197.4 (*C*=O); 152.1 (*p*-C_q *C*$_6$H$_4$); 146.4 (*C*=CH); 136.0 (*ipso*-C_q *C*$_6$H$_4$); 135.6 (*p*-C_q *C*$_6$H$_4$); 135.5 (*ipso*-C_q *C*$_6$H$_4$); 128.7 (*o*−*C*$_6$H$_4$); 128.5 (*m*−*C*$_6$H$_4$); 127.1 (*o*−*C*$_6$H$_4$); 126.2 (C=*C*H); 125.0 (*m*−*C*$_6$H$_4$); 39.7 (*C*H); 33.7 (CH_2–*C*H$_2$–C=CH); 29.7 (CH–*C*H$_2$–CH=C); 27.5 (CH_2–*C*H$_2$–CH); 26.5 (*C*H$_3$).

$C_{22}H_{22}O_2$, molecular weight: 318.41, MS = *m*/*z* (%): [*M*$^{\bullet+}$] 318 (100); [*M*$^{\bullet+}$–CH_3] 303 (72); [$C_6H_5^{\bullet+}$] 77 (18).

*2.3.2. Preparation of 4-(1-cyclopentenyl)acetophenone **6**, 4-(2-cyclopentenyl)acetophenone **7**, 4-(3-cyclopentenyl)acetophenone **8***

5 mmol (1.0 g) of 4-bromoacetophenone, 25 mmol (2.2 ml) of cyclopentene, 6 mmol (0.49 mg) NaOAc, 0.1 mol% (1.12 mg) $Pd(OAc)_2$ and 0.2 mol% (2.63 mg) PPh_3 were added to 10 ml of a mixture DMSO/DMAc (1:4). The reaction mixture was heated at 150 °C for 20 h to give 856 mg (92% yield) of a mixture of compounds **6–8** as a colorless oil by distillation under 0.05 mbar: bp (0.05 mmbar) = 91–93 °C. From the mixture, compound **6** was isolated by crystallization from a mixture of acetone/water (9:1) as a colorless microcrystalline compound in 11% yield.

*2.3.2.1. Data for **6**.* ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 7.88 (d, ^3J(H, H) = 8.5 Hz, 2H, *o*−$C_6\underline{H}_4$); 7.47 (d, ^3J(H, H) = 8.5 Hz, 2H, *m*−$C_6\underline{H}_4$); 6.33 (*pseudo*-quintet, ^3J(H, H) = ^4J(H, H) = 0 Hz, 1H, C*H*=C); 2.72 (td, ^3J(H, H) = 5 Hz, ^4J(H, H) = 2.0 Hz, 2H, C*H*$_2$=C); 2.57 (s, 3H, C$\underline{H}_3$); 2.55 (m, 2H, C*H*$_2$–CH=C); 2.02 (quin, ^3J(H, H) = 7.5 Hz, 2H, C*H*$_2$).

^{13}C NMR ($CDCl_3$, 100.61 MHz): δ = 197.7 (*C*=O); 141.8 (*C*=CH); 141.4 (*p*-C_q *C*$_6$H$_4$); 135.3 (*ipso*-C_q *C*$_6$H$_4$); 129.6 (C=*C*H); 128.5 (*o*−*C*$_6$H$_4$); 125.6 (*m*−*C*$_6$H$_4$); 33.6 (*C*H$_2$–CH=C); 33.0 (*C*H$_2$–CH=C); 26.5 (*C*H$_3$); 23.3 (CH$_2$–*C*H$_2$–CH$_2$).

$C_{13}H_{14}O$, molecular weight: 186.25, MS = *m*/*z* (%): [*M*$^{\bullet+}$] 186 (86); [*M*$^{\bullet+}$–CH_3] 171 (62); [*M*$^{\bullet+}$–$COCH_3$] 143 (52); [$CH_3CO^{\bullet+}$] 43 (23).

*2.3.2.2. Data for **7**.* ^{1}H NMR ($CDCl_3$, 400.13MHz): δ = 7.86 (d, ^3J(H, H) = 8.5 Hz, 2H, *o*−$C_6\underline{H}_4$); 7.23 (d, ^3J(H, H) = 8.5 Hz, 2H, *m*−$C_6\underline{H}_4$); 5.96 (m, 1H, CH-C*H*=CH); 5.73 (m, 1H, CH–CH=C*H*); 3.92 (m, 1H, C*H*–CH=CH); 2.56 (s, 3H, C$\underline{H}_3$); 1.60–2.55 (m, 4H, C*H*$_2$–C*H*$_2$).

^{13}C NMR ($CDCl_3$, 100.61 MHz): δ = 197.7 (*C*=O); 152.2 (*p*-C_q *C*$_6$H$_4$); 135.1 (*ipso*-C_q *C*$_6$H$_4$); 133.2 (CH–*C*H=CH); 132.7 (CH–CH=*C*H); 128.5 (*o*−C_6H_4); 127.3 (*m*−*C*$_6$H$_4$); 51.2 (*C*H–CH=CH); 33.5 (*C*H$_2$–CH=CH); 32.4 (CH–*C*H$_2$–CH$_2$); 26.4 (*C*H$_3$).

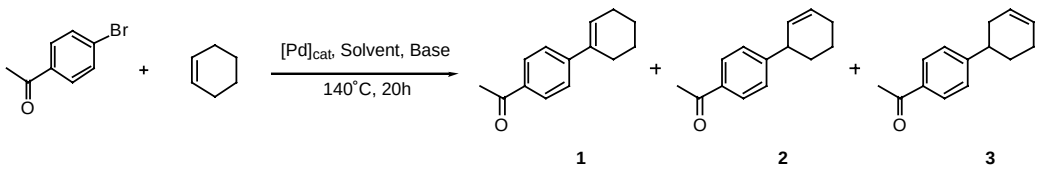
$C_{13}H_{14}O$, molecular weight: 186.25, MS = *m*/*z* (%): [*M*$^{\bullet+}$] 186 (100) [*M*$^{\bullet+}$–CH_3] 143 (67) [*M*$^{\bullet+}$–$COCH_3$] 143 (37) [$CH_3CO^{\bullet+}$] 43 (24).

*2.3.2.3. Data for **8**.* ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 7.86 (d, ^3J(H, H) = 8.5 Hz, 2H, *o*−*C*$_6$H$_4$); 7.30 (d, ^3J(H, H) = 8.5 Hz, 2H, *m*−*C*$_6$H$_4$); 5.76 (s, 2H, C*H*=C*H*); 3.47 (m, 1H, C*H*); 2.55 (s, 3H, C$\underline{H}_3$); 1.60–2.55 (m, 4H, C*H*$_2$–C*H*$_2$).

^{13}C NMR ($CDCl_3$, 100.61 MHz): δ = 197.5 (*C*=O); 153.3 (*p*-C_q *C*$_6$H$_4$); 135.0 (*ipso*-C_q *C*$_6$H$_4$); 129.5 (*C*H=*C*H); 128.4 (*o*−*C*$_6$H$_4$); 127.0 (*m*−*C*$_6$H$_4$); 42.9 (*C*H); 41.2 (*C*H$_2$); 26.4 (*C*H$_3$). $C_{13}H_{14}O$, molecular weight: 186.25, MS = *m*/*z* (%): [*M*$^{\bullet+}$] 186 (80); [*M*$^{\bullet+}$–CH_3] 171 (48); [*M*$^{\bullet+}$–$COCH_3$] 143 (100); [*M*$^{\bullet+}$–$COCH_3$–CH = CH] 115 (16); [$CH_3CO^{\bullet+}$] 43 (24).

3. Results and discussion

Initially, we studied the Heck arylation of cyclohexene with 4-bromoacetophenone as a model reaction (Scheme 1). Cyclohexene is known to be a difficult substrate in the Heck reaction leading generally to a mixture of regioisomers with a slow kinetic [53]. These problems make this reaction particularly interesting for the observation of effects related to the palladium source and the nature/structure of the active species. As catalytic systems $Pd(OAc)_2/PPh_3$ or $Pd_2(dba)_3$·dba/PCy_3 and the "palladacycle" {Pd[P(*o*-$C_6H_4CH_3)_2$-(*o*-$C_6H_4CH_2$)(CH_3CO_2)]}$_2$ were used as homogeneous catalysts. In addition Pd/C (Aldrich), Pd/SiO_2, Pd/MgO, Pd/Al_2O_3, Pd(0)/Z, Pd(II)/Z and $[Pd(NH_3)_4]^{2+}$/Z (Z = zeolites NaY, HY or



Scheme 1. Heck arylation of cyclohexene with 4-bromoacetophenone. Reaction conditions: 10 mmol 4-bromoacetophenone, 15 mmol cyclohexene, 0.1 mol% $[Pd]_{cat}$, 15 mmol NaOAc, 10 mL solvent, 140 °C, 20 h.

Table 2
Heck reaction of cyclohexene with 4-bromoacetophenone (Scheme 1)

Entry	Catalyst	Solvent	Additive	Conversion[a]	Yield (**1**+**2**+**3**)(%)[a]	Selectivity **1**:**2**:**3**[b]	Yield 4%[a]	Yield 5%[a]
1	$Pd_2(dba)_3$·dba/PCy_3	DMAc	–	94	75	6:16:78	2	8
2	Palladacycle	DMAc	–	>99	89	7:15:78	<1	5
3	$Pd(OAc)_2/PPh_3$	DMAc	–	96	78	4:17:79	1	8
4	$Pd(OAc)_2/PPh_3$	DMF	–	57	50	4:18:78	1	3
5	$[Pd(NH_3)_4]$/HY	DMAc	–	29	12	1:17:83	17	0
6	$[Pd(NH_3)_4]$/HY	DMF	–	22	14	1:21:79	8	0
7	$[Pd(NH_3)_4]$/NaY	DMAc	–	29	14	1:15:84	15	0
8	$[Pd(NH_3)_4]$/NaY	DMF	–	46	45	0:19:81	<1	0
9	$[Pd(NH_3)_4]$/ZSM-5	DMAc	–	29	28	2:16:82	1	2
10	$[Pd(NH_3)_4]$/ZSM-5	DMF	–	51	47	0:19:81	1	3
11	Pd(II)/HY	DMAc	–	55	14	1:14:85	41	0
12	Pd(II)/HY	DMF	–	37	24	0:17:83	13	0
13	Pd(II)/NaY	DMAc	–	53	12	1:17:82	40	0
14	Pd(II)/NaY	DMF	–	38	25	0:17:83	12	0
15	Pd(II)/ZSM-5	DMAc	–	40	11	1:18:81	29	2
16	Pd(II)/ZSM-5	DMF	–	33	22	0:18:82	11	3
17	Pd(0)/TiO_2	DMAc	–	100	7	2:14:83	93	0
18	Pd(0)/TiO_2	DMF	–	33	21	5:16:79	8	2
19	Pd(0)/C	DMAc	–	77	15	2:14:84	60	1
20	Pd(0)/C	DMAc	RT[c]	55	33	7:14:78	5	8
21	Pd(0)/C	DMF	–	50	38	5:16:79	5	4
22	Pd(0)/C	DMF	RT[c]	82	57	6:15:78	6	10
23	Pd(0)/SiO_2	DMAc	–	70	5	0:11:89	63	1
24	Pd(0)/MgO	DMAc	–	100	7	2:18:80	87	2
25	Pd(0)/Al_2O_3	DMAc	–	59	7	0:13:87	52	1
26	Pd(0)/HY	DMAc	–	40	8	1:12:87	32	0
27	Pd(0)/HY	DMF	–	43	30	0:17:83	13	1
28	Pd(0)/NaY	DMAc	–	50	11	1:18:81	39	0
29	Pd(0)/NaY	DMF	–	51	40	1:22:75	9	1
30	Pd(0)/ZSM-5	DMAc	–	48	15	0:27:73	29	2
31	Pd(0)/ZSM-5	DMF	–	59	44	0:16:84	7	4

[a] Conversions and yields were determined by GC with an internal standard (diethylene glycol di-*n*-butyl ether) ($\Delta_{rel} = \pm 5\%$).
[b] Selectivities were determined by GC on the basis of area percentage.
[c] RT: radical trap: 2,6-di-*tert*-butyl-4-methylphenol (ca. 5 mol%) was used as radical trap in these experiments.

ZSM-5) were used as heterogeneous catalysts. All catalysts (homogeneous or heterogeneous) were prepared according to procedures previously described in the literature [25,34,46,50,71,72,74,75].

Table 2 describes the results obtained with homogeneous catalysts (entries 1–4), molecular species entrapped in zeolites (entries 5–10) and heterogeneous catalysts (entries 11–31) using standard reaction conditions (polar solvent, NaOAc, 140 °C, 20 h, 0.1 mol% Pd).

Generally, only small differences are observed in terms of selectivity: almost all catalysts gave an average "Heck-product" distribution of roughly 3:17:80 for the products **1:2:3**, respectively, independent on the catalysts and the solvent used for the reaction. This product distribution can be explained to some extend by molecular mechanics calculations, which indicate that isomer **3** represents the thermodynamically most stable isomer (Fig. 1).[1]

However, clear differences are observed for the selectivity to Heck products **1–3** versus the dehalogenation reaction to give acetophenone **4** (Scheme 2). This chemoselectivity was found to be strongly dependent on the nature of the palladium catalysts, the solvent and the catalyst support.

[1] CAChe version 4.1.1 for Macintosh from Oxford Molecular Ltd. was used for the molecular modeling using MM2 extended parameters.

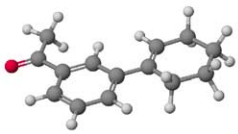
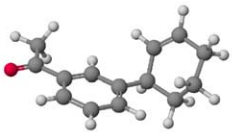
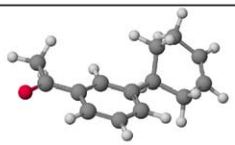
Product	1	2	3
Structure			
Energie kcal/mol[1]	17.02	2.54	4.99

Fig. 1. Molecular mechanics calculation for the different regio-isomers obtained from the Heck arylation of cyclohexene by 4-bromoacetophenone. The thermodynamically most stable structure for each isomer is represented.

While dehalogenation can be neglected when using homogenous catalysts (Table 2, entries 1–4), with heterogeneous catalysts it can represent up to 93% of the product distribution (Table 2, entry 17). Generally, less dehalogenation is observed for zeolite entrapped molecular Pd-species (i.e. $[Pd(NH_3)_4]^{2+}$) than for supported Pd(0) particles (Table 2, entries: 5–10 versus entries 26–31). Interestingly, the solvent was found to be an important parameter too: using DMF instead of DMAc reduces strongly the dehalogenation side reaction (for example compare in Table 2 entries 5 versus 6, 7 versus 8, 11 versus 12, 13 versus 14, 17 versus 18, 19 versus 21). We attribute this observation to the formation of molecular Pd-species in solution that catalyze efficiently the Heck arylation. The formation of such species dissolved in the reaction media is favoured in DMF, since it is able to stabilize ionic species as those involved in the Heck catalytic cycle. Interestingly, the chemoselectivity of the reaction was also found to be strongly dependent on the catalyst support: some heterogeneous catalysts like Pd supported on ZSM-5 and C seem to give lower dehalogenation rates than the others (Table 2, entries 9, 10, 15, 16, 21). It is important to note that these catalysts showed the highest content of palladium leached into solution (up to 16% of the total palladium used for ZSM-5).

In addition, the ratio of formation of the double-arylated Heck product **5** (Scheme 2) compared to the mono-arylated Heck products, was investigated with regard to the different catalysts. Double arylation of cyclohexene is comparatively pronounced when using homogeneous catalysts (Table 2, entries 1–4) or heterogeneous catalysts that show strong leaching (Table 2, entries 9–10, 15–16, 19–22). This behavior is easily explained by the higher activity of molecular dissolved palladium complexes compared to heterogeneous palladium particles. These results also support our conclusion toward the molecular nature of the active species in the Heck reaction due to dissolved Pd-species. Generally, the double arylation is not observed when using Pd-species supported on zeolites probably due to shape selectivity, except for ZSM-5 as support for which a strong leaching is observed.

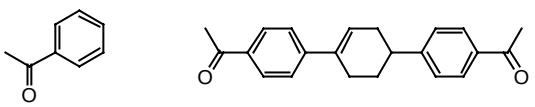
Next, the arylation of cyclopentene was studied. Compared to cyclohexene, cyclopentene is much more reactive toward the Heck arylation with 4-bromoacetophenone (Scheme 3) giving high conversions, and generally leading to the formation of three isomers with "poor" selectivity [53]. This rather equal distribution of the three Heck products can be expected from molecular mechanics calculations indicating that all three arylcyclopentene isomers have approximately the same thermodynamic stability.[2] Nevertheless, some of us have demonstrated that highly selective arylations of cyclopentene toward the conjugated isomer **6** can be achieved using optimized reaction conditions [53].

Table 3 describes the results obtained with homogeneous catalysts (entries 1–4), molecular species entrapped in zeolites (entries 5–8) and classical heterogeneous catalysts (entries 9–16).

Following the results previously reported [53], a strong influence of the reaction conditions was observed for homogeneous catalysts (Table 3, entries 1–4). While isomer **7** is obtained as the main product (45–72%) with NaOAc as base, a complete inversion toward the conjugated Heck product **6** is attained using Na_2CO_3. It is important to note that such an influence of the base in Heck reactions was never observed using heterogeneous catalysts. Using molecular palladium species ($[Pd(NH_3)_4]^{2+}$ or Pd(II)) entrapped inside the zeolite pores resulted in a high selectivity (>80%) toward isomer **7**, independent of the reaction conditions (Table 3, entries 5–10).

Contrarily, using supported Pd(0) particles in presence of NaOAc at 140 °C gave a poor selectivity (Table 3, entries 11 and 15). These results can be compared to that of the Pd(0) homogeneous catalyst, namely the $Pd_2(dba)_3$ × dba/PCy_3 catalytic system (Table 3, entry 1), suggesting that dissolved Pd(0)-species act as the active species for these Heck reactions.

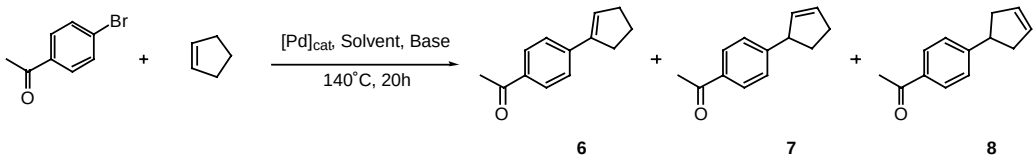
As for the reactions with cyclohexene, the ratio of double arylation observed during some reactions (Table 3, entries 11–12) supports the homogeneous aspect of the Heck re-



4 **5**

Scheme 2. Heck arylation of cyclohexene with 4-bromoacetophenone: side products of the reaction.

[2] Energy (kcal/mol): 6.76, 5.92, 5.28 for **6**, **7**, **8**, respectively. MM2 extended parameters implemented in CAChe version 4.1.1 for Macintosh were used to perform the calculations.



Scheme 3. Heck arylation of cyclopentene with 4-bromoacetophenone. Reaction conditions: 10 mmol 4-bromoacetophenone, 15 mmol cyclopentene, 0.1 mol% $[Pd]_{cat}$, 15 mmol base, 10 mL DMAC, 120 °C or 140 °C, 20 h.

Table 3
Heck reaction of cyclopentene with 4-bromoacetophenone (Scheme 3)

Entry	Catalyst	Base	T (°C)	Conversion[a]	Yield (6+7+8) (%)[a]	Selectivity 6:7:8[b]	Yield 4%[a]	Yield 9%[a]
1	$Pd_2(dba)_3$·dba/PCy_3	NaOAc	140	>99	98	39:45:16	0	0
2	$Pd_2(dba)_3$·dba/PCy_3	Na_2CO_3	140	>99	>99	91:7:2	0	0
3	$Pd(OAc)_2$/PPh_3	NaOAc	140	>99	94	17:72:11	0	2
4	$Pd(OAc)_2$/PPh_3	Na_2CO_3	140	>99	98	83:13:4	0	0
5	$[Pd(NH_3)_4]$/NaY	NaOAc	140	>99	96	9:83:8	0	0
6	$[Pd(NH_3)_4]$/NaY	Na_2CO_3	140	>99	97	12:81:7	0	0
7	$[Pd(NH_3)_4]$/ZSM-5	NaOAc	140	>99	98	10:83:7	0	0
8	$[Pd(NH_3)_4]$/ZSM-5	Na_2CO_3	140	>99	99	12:80:8	0	0
9	Pd(II)/NaY	NaOAc	140	>99	97	11:82:7	0	0
10	Pd(II)/NaY	Na_2CO_3	140	>99	98	10:84:6	0	0
11	Pd(0)/C	NaOAc	140	>99	70	27:58:15	0	15
12	Pd(0)/C	Na_2CO_3	140	>99	11	0:100:0	2	43
13	Pd(0)/C	NaOAc	120	33	32	8:81:11	0	0
14	Pd(0)/C	Na_2CO_3	120	6	4	8:76:15	0	0
15	Pd(0)/NaY	NaOAc	140	>99	96	16:47:37	0	0
16	Pd(0)/NaY	Na_2CO_3	140	>99	98	8:72:20	0	0

[a] Conversions and yields were determined by GC with an internal standard (diethylene glycol di-*n*-butyl ether) ($\Delta_{rel} = \pm 5\%$).
[b] Selectivities were determined by GC on the basis of area percentage.

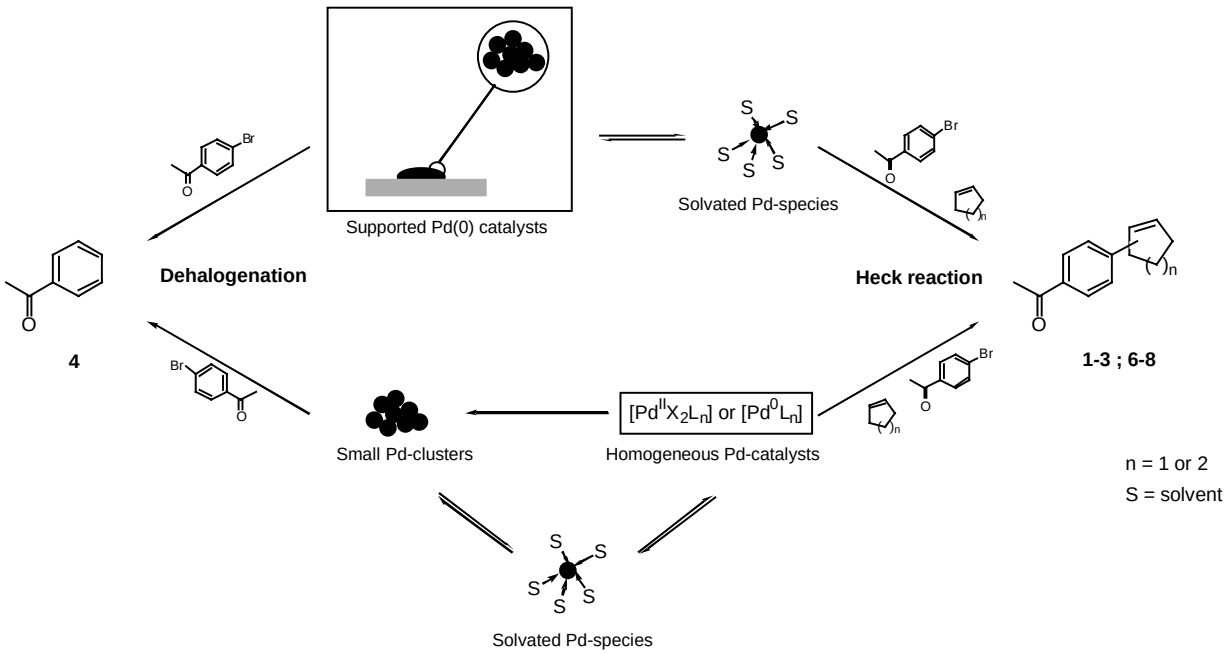
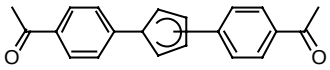


Fig. 2. Proposed routes to the formation of the different products observed for the Heck arylation of cyclic olefines using homogeneous or heterogeneous Pd-catalysts.



9

Scheme 4. Heck arylation of cyclopentene with 4-bromoacetophenone: side products of the reaction.

actions catalyzed by supported metal as the Pd/C catalysts (Scheme 4). Probably due to the shape selectivity, double arylations are not observed with zeolite catalysts. Nevertheless, using Pd/C at 120 °C instead of 140 °C avoids the double arylation of the initial Heck product (Table 3, entries 11 versus 13 and 12 versus 14). A second effect attributed to the lower reaction temperature is a simultaneous significant lowering of the conversion (33% instead of >99%) and an improvement of the selectivity (81% instead of 58%) toward **7** (Table 3, entry 13 versus 11).

Using Pd/C or Pd(0)/NaY as catalyst in the presence of Na_2CO_3 instead of NaOAc resulted in improved selectivity (>72%) for isomer **7**, which is in contrast to homogeneous catalysts. These results make it likely that different Pd species of molecular nature are active as catalysts in this reaction.

Based on the results reported above, we conclude that different Pd-species are involved in the Heck arylation on one hand and the aryl dehalogenation reaction on the other hand. Molecular Pd species dissolved in the reaction medium (for zeolites this can be inside the pores) are most likely the active Pd-species for the Heck arylation while Pd metal particles (or clusters) are responsible for the dehalogenation reaction. The last hypothesis is further supported by additional experiments in which a radical trap was appplied (Table 1, entry 20 versus 19). Indeed when 2,6-di-*tert*-butyl-4-methylphenol is added to the catalytic reactions, the rate of dehalogenation strongly decreased indicating that a radical mechanism occurs possibly at the palladium surface. Fig. 2 summarizes the most likely reaction pathways.

4. Conclusion

The Heck arylation of activated and deactivated cyclic olefins (cyclohexene and cyclopentene) is found to be particularly suitable for studies of correlations between the selectivity and the nature of the catalyst or active Pd species, respectively, since the formation of the different products and regioisomers (Heck products: double bond isomers of arylcycloalkenes, dehalogenation and double arylation products) is significantly dependent on the active catalyst species.

The comparative interpretation of selectivities obtained for homogeneous and heterogeneous catalysts under strictly the same reaction conditions indicates the following conclusions:

- The (most) active Pd centres for the Heck arylation are molecular Pd species dissolved in solution.
- Applying truely heterogeneous catalysts in the Heck arylation of cyclic olefins the formation of acetophenone (from 4-bromoacetophenone) by dehalogenation is increased. Radical species seem to be involved in this side reaction. It is indicated that this side reaction proceeds on the surface of metallic Pd particles.

In general, our studies have shown that during Heck reactions of aryl halides with olefins concurrent homogeneous and heterogeneous mechanisms occur to activate the aryl halides. These mechanisms have to be taken in account in order to optimize the preparation of improved catalysts toward high activity and selectivity in the Heck arylation of olefins.

Acknowledgements

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