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Efficient Heterogeneously Palladium-Catalysed Heck Arylation of Acrolein Diethyl Acetal. Selective Synthesis of Cinnamaldehydes *or* 3-Arylpropionic Esters

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Abstract: A heterogeneous tetrakis(ammine)palladium-NaY zeolite {[Pd(NH_3)$_4$]/NaY} catalyst was applied successfully to the Heck arylation of acrolein diethyl acetal using a large variety of aryl and heteroaryl bromides. Depending on the reaction conditions (Heck *versus* Cacchi) good to high selectivities toward the 3-arylpropionic esters or to the cinnamaldehydes were achieved, respectively. Under classical Heck conditions, while the catalyst was found to be stable over the two first runs, it showed significant loss of activity from the third cycle. Under Cacchi conditions, the catalyst could not be reused as it led to high dehalogenation rates. All results indicate that the reactions proceed through dissolved palladium species in the bulk solution (leaching). As observed by transmission electronic microscopic (TEM) analyses, while these species can be trapped and stabilised by the zeolite framework under the Heck conditions, they tend to form large palladium(0) aggregates under the Cacchi conditions leading to dehalogenation rather than to the expected Heck coupling.

Keywords: acrolein diethyl acetal; condensed aryl and heteroaryl halides; Heck reaction; homogeneous and heterogeneous palladium catalysts; zeolite supports

Introduction

Both cinnamaldehyde derivatives and 3-arylpropionic acids are important intermediates for fine chemistry. Cinnamaldehyde compounds have found wide applications in food, cosmetic[1,2] or agrochemical[3–6] and pharmaceutical industries.[7–12] Some cinnamaldehyde derivatives exhibit non-linear optical properties.[13–20]

Several methods based on the Perkin and Claisen condensations of aromatic aldehydes have been reported for the synthesis of cinnamaldehyde derivatives on the industrial scale.[21] However, the applicability of these methods remains limited due to the difficult and costly synthesis of the starting materials.[22] Several palladium-catalysed syntheses of such products have been reported in the literature. An α,β-unsaturated aldehyde was obtained as a major product of a pallado-catalysed coupling reaction of an aryl halide with allyl alcohol either under an air atmosphere or in the presence of Cu(OTf)$_2$.[23–25] But few examples were reported and the selectivity was not complete. Alternatively, direct Heck coupling of aryl halides with acrolein resulted in the formation of these products.[26–28] However, some polymerisation of the olefin occurred during the reaction. Under solid-liquid phase transfer conditions, Jeffery obtained high yields of *trans*-α,β-unsaturated aldehydes at room temperature starting from an aryl iodide but this approach was not general.[29] To avoid the degradation of acrolein, Zebovitch and Heck developed the coupling reaction of acrolein dialkyl acetal with aryl halides.[26] The reaction was not selective and mixtures of aldehyde and ester were obtained. As an alternative, Santelli reported the preparation of cinnamaldehydes derivatives by coupling aryl iodides and bromides with 3,3-diacetoxypropene.[30] However, the procedure was limited to activated aryl halides, and gave generally low yields with heteroaryl halides. Recently, the group of Cacchi reported the selective synthesis of cinnamaldehyde derivatives by accurate adjustment of reaction conditions based on the Jeffery procedure.[31] In the presence of Pd(OAc)$_2$, Bu_4NOAc, K_2CO_3, KCl in DMF at 90°C, the aldehyde was formed selectively. We extended this approach to a

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large variety of condensed aryl and heteroaryl substrates.[28] Under similar conditions but using a well defined dimeric 4-hydroxyacetophenone oxime-derived palladacycle as catalyst, Najera and Botella reported the preparation of cinnamaldehyde derivatives from iodo-, bromo-, and chloroarenes in high yield.[32]

On the other hand, 3-arylpropionic acids are common building blocks in organic synthesis and an important intermediates in the preparation of biologically active compounds such as in the synthesis of 3-amino-3-arylpropionic acids (TNF-α inhibitors, lactam antibodies etc.).[33–40] Therefore, their selective synthesis using simple methods from commercially available substrates represents an important industrial challenge since it generally requires several reaction steps. As mentioned previously, Zebovitch and Heck reported the formation of arylpropionic esters by arylation of acrolein acetal with aryl halides using the $Pd(OAc)_2/P(o\text{-}Tol)_3$ catalytic system, in the presence of NEt_3 as base, but mixtures were obtained.[26] The group of Cacchi reported a very efficient procedure [$Pd(OAc)_2$, *n*-Bu_4NCl, *n*-Bu_3N, DMF, 90 °C] to prepare selectively the ester.[41] More recently, the selective syntheses of aryl propionates catalysed by different palladacycle complexes were reported.[28,32] To date, the most efficient synthesis of 3-arylpropionic acid was described by the group of Santelli and Doucet: a catalyst/substrate loading as low as 1/10 000 allowed the coupling of aryl iodides and some activated aryl bromides with acrolein ethylene acetal in 20 h.[42] In that study, the outstanding performances of the catalyst was attributed to the tetradentate ligand Tedicyp [1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane]. Unfortunately, this ligand is not commercially available.

While successful, theses methods suffer from the use of soluble palladium catalysts, sometimes with high palladium loading (2–5 mol%), that could not be recovered and could result in high palladium contamination of the products (up to 2%). Such Pd contaminations are regarded as a severe limitation to the use of these methodologies for producing fine chemicals. To overcome these difficulties, the use of heterogeneous palladium catalysts remains a method of choice. Several supports were used to immobilise palladium complexes or to support palladium particles for the Heck reaction: ligand-protected palladium nanoparticles,[43–49] palladium on active carbon[50–53] or carbon nanotubes,[54] palladium on metal oxides[27,55–74] or palladium on functional polymers.[75–79] Among them the zeolites showed exceptional activity and stability.[62,69,70,73] Most of the work reported in this area concerned mainly model reactions, reacting aryl iodides and bromides with styrene or acrylates. Few reports concern the reaction of aryl chlorides with styrene.[69,70]

As a part of our studies in developing synthetic methods for fine chemical synthesis, we decided to evaluate several palladium catalytic systems for the arylation of acrolein diethyl acetal, especially, heterogeneous systems.

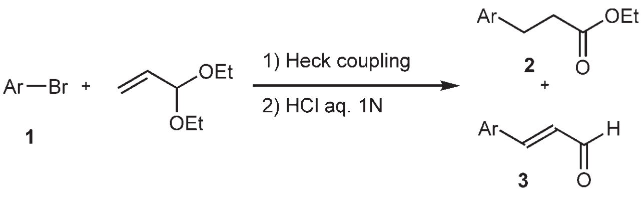
In this contribution, we report the Heck arylation of acrolein diethyl acetal with a large variety of aryl and heteroaryl bromides using a $[Pd(NH_3)_4]/NaY$ heterogeneous catalyst. The results are compared to those obtained from homogeneously catalysed reactions under strictly the same reaction conditions. A mechanism to account for the results observed is proposed.

Results and Discussion

Several palladium catalysts and palladium catalytic systems were used in this study in order to compare both the activity and the selectivity of the heterogeneous Pd-exchanged zeolite to those of different homogeneous systems. The heterogeneous $[Pd(NH_3)_4]/NaY$ zeolite was prepared, according to procedures reported in the literature, by ion exchange of a NaY zeolite using a 0.1 M aqueous solution of $[Pd(NH_3)_4]^{2+}$, $2Cl^-$.[62] After a period of 24 h, the exchanged $[Pd(NH_3)_4]/NaY$ catalyst was obtained. The absolute palladium content of the catalyst was determined by ICP-AES as $1.0\%_{wt}$ Pd. The homogeneous "palladacycle" $\{Pd[P(o\text{-}C_6H_4CH_3)_2(C_6H_4CH_2)[OCOCH_3]\}_2$ catalyst was prepared from $Pd(OAc)_2$ and tris(*o*-tolyl)phosphine following the procedure reported by Herrmann et al.[80,81]

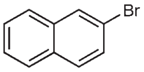
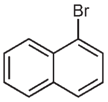
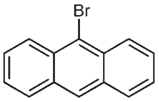
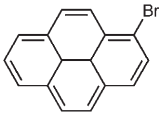
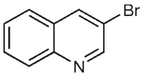
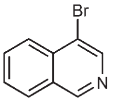
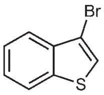
Initially, the Heck arylation of acrolein diethyl acetal with various aryl and heteroaryl halides was studied using reaction conditions previously optimised for the Heck reaction of aryl bromides with styrene using heterogeneous $[Pd(NH_3)_4]/NaY$ catalyst (2.4 mmol aryl bromide, 7.2 mmol acrolein diethyl acetal, 2 mol% Pd catalyst, 3.6 mmol NaOAc, 8 mL NMP, 140 °C) (Scheme 1).[62] The results are reported in Table 1.

As expected, after hydrolysis, the reaction gave a mixture of aldehyde **3** and ester **2**, the latter being in every cases formed as the predominant product (>65%). Generally, after 6 h, full conversions of aryl and heteroaryl bromides **1** are observed, except for the 4-bromoisoquinoline **1f** and the 3-bromobenzo-



Scheme 1.

Table 1. Heck arylation of acrolein diethyl acetal with various aryl and heteroaryl halides using the [Pd(NH_3)$_4$]/NaY catalyst.[a]

Entry	Substrate		Time [h]	Conversion [%][b]	Selectivity (**2**/**3**) [%][c]	Yield **2** [%][d]
1	**1a**		6	100	72/28	63
2	**1b**		6	100	75/25	43
3	**1c**		6	93	94/6	79
4	**1d**		6	87	88/12	71
5	**1e**		6	100	65/35	51
6	**1f**		24	100	82/18	66
7	**1g**		24	63	72/28	23

[a] *Reaction conditions:* 2.4 mmol aryl bromide, 7,2 mmol acrolein diethyl acetal, 2 mol% Pd catalyst, 3.6 mmol NaOAc, 8 mL NMP, 140 °C.

[b] Conversions based on unreacted aryl bromide were determined by GC.

[c] Selectivities were determined by GC on the basis of area percentage.

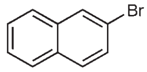
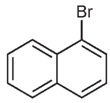
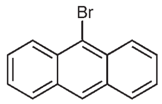
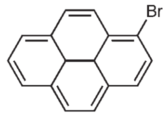
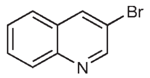
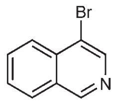
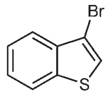
[d] Isolated yields are reported.

thiophene **1g** that required 24 h reaction time to achieve, respectively, 100% and 63% conversion (Table 1, entries 6 and 7). Using a heterogeneous catalyst, no significant influence of the size of the polyaromatic moiety was observed, even the highly hindered bromopyrene **1d** was converted to the corresponding ester in 87% conversion after 6 h reaction time (Table 1, entry 4). At this stage of the study, it was interesting to compare the performances of the [Pd(NH_3)$_4$]/NaY catalyst to those of different homogeneous [namely, Herrmann's palladacycle, Pd(OAc)$_2$/PPh$_3$ and ligand-free Pd(OAc)$_2$] catalytic systems (Table 2), the reaction conditions being identical in other respects. The selectivity was not significantly affected by the nature of the catalyst, the ester **2** being in every case the main product. Moderate to high conversions were achieved with these homogeneous catalysts. The ligand-free catalytic system [Pd(OAc)$_2$] exhibited the lowest activity in this reaction except in the case of the 3-bromoquinoline substrate **1e** (Table 2, entry 5) for which complete conversion was achieved after 6 h. We may assume that the substrate played also the role of a ligand towards the palladium that modified its reactivity. Surprisingly, these homogeneous catalysts showed lower activities, compared to the heterogeneous [Pd(NH_3)$_4$]/NaY catalyst, requiring up to 24 h to achieve complete conversions for most of the aryl bromides. Similar observations were made by De Vries and co-workers, while developing the ligand-free Pd(OAc)$_2$-catalyzed Heck reactions, for which, generally, most ligands retard the reactions.[82]

Regarding the high activity of the [Pd(NH_3)$_4$]/NaY catalyst, better insights could be obtained from kinetic experiments. We compared the heterogeneous [Pd(NH_3)$_4$]/NaY catalyst to the homogeneous Herrmann palladacycle catalyst, both affording similar selectivities under standard reaction conditions. The arylation of acrolein diethyl acetal with the 2-bromonaphthalene **1a** and the 3-bromoquinoline **1e** were chosen for this purpose (Figure 1).

With both substrates, the heterogeneous [Pd(NH_3)$_4$]/NaY catalyst showed higher activity than the homogeneous palladacycle. In the presence of Pd-exchanged zeolite catalyst, complete conversions were obtained after, respectively, 240 min and 30 min, for the 2-bromonaphthalene **1a** and the 3-bromoquinoline **1e**. On the other hands, using Herrmann's palladacy-

Table 2. Heck arylation of acrolein diethyl acetal with various aryl and heteroaryl halides using the homogeneous catalytic systems.[a]

Entry	Substrate		Catalyst	Time [h]	Conversion [%][b]	Selectivity (**2**/**3**) [%][c]
1	**1a**		Palladacycle	24	75	73/27
			$Pd(OAc)_2/PPh_3$	24	100	80/20
			$Pd(OAc)_2$	24	42	100/0
2	**1b**		Palladacycle	24	75	84/16
			$Pd(OAc)_2/PPh_3$	24	100	74/24
			$Pd(OAc)_2$	24	49	71/29[d]
3	**1c**		Palladacycle	6	95	94/6
			$Pd(OAc)_2/PPh_3$	24	100	100/0
			$Pd(OAc)_2$	6	87	100/0
4	**1d**		Palladacycle	24	100	100/0
			$Pd(OAc)_2/PPh_3$	24	97	100/0
			$Pd(OAc)_2$	6	88	93/7
5	**1e**		Palladacycle	24	100	75/25
				6	95	68/32
			$Pd(OAc)_2/PPh_3$	24	75	72/28
			$Pd(OAc)_2$	6	100	78/22
6	**1f**		Palladacycle	24	100	77/23
			$Pd(OAc)_2/PPh_3$	24	71	63/37
			$Pd(OAc)_2$	24	72	100/0
7	**1g**		Palladacycle	24	54	80/20
			$Pd(OAc)_2/PPh_3$	24	100	87/13
			$Pd(OAc)_2$	24	26	60/40

[a] *Reaction conditions:* 2.4 mmol aryl bromide, 7,2 mmol acrolein diethylacetal, 2 mol% Pd catalyst, 3.6 mmol NaOAc, 8 mL NMP, 140 °C.

[b] Conversions based on unreacted aryl bromide were determined by GC.

[c] Selectivities were determined by GC on the basis of area percentage.

[d] Dehalogenation was observed in this experiment, giving 21% naphthalene. The selectivity did not account for dehalogenation rate.

cle as catalyst, the conversion of 2-bromonaphthalene **1a** reached 75% after 24 h reaction (Table 2, entry 1), while the conversion of 3-bromoquinoline **1c** attained 95% after 6 h (Table 2, entry 5). These differences of catalytic activities are well represented through the corresponding initial activities: for the reaction of 2-bromonaphtalene **1a** with acroleine diethyl acetal, the heterogeneous catalyst showed an initial activity of $Ai_1 = 38$ mmol/g_{Pd}/min while the palladacycle catalyst showed only an activity of $Ai_2 = 6$ mmol/g_{Pd}/min. Similarly, for the reaction of 3-bromoquinoline **1e**, the heterogeneous catalyst showed an apparent initial activity of $Ai_3 = 31$ mmol/g_{Pd}/min whereas the homogeneous palladacycle catalyst showed an activity of $Ai_4 = 13$ mmol/g_{Pd}/min. However, for this reaction, one could note that, before being active, the heterogeneous $[Pd(NH_3)_4]$/NaY catalyst exhibited a period of inactivity for about 5 min that was reasonably attributed to the time required to generate in bulk solution active species through leaching (*vide infra*). Such an activation period was also observed for the reaction of 2-bromonaphthalene **1a** with acrolein diethyl acetal (see Figure 3 for details).

As previously mentioned, both catalytic systems afforded the same selectivities (within the error limits of the analytical method) that were found stable all over the reaction time.

When using heterogeneous $[Pd(NH_3)_4]$/NaY catalysts, the questions regarding the reuse and the leaching of active Pd species in solution were addressed. The recycling was examined for the coupling reaction of 2-bromonaphthalene **1a** and acrolein diethyl acetal under optimised reaction conditions (2.4 mmol 2-bromonaphthalene, 7.2 mmol acrolein diethyl acetal, 2 mol% $[Pd(NH_3)_4]^{2+}$/NaY, 3.6 mmol NaOAc, 8 mL NMP, 140 °C) over 6 h. The following procedure was performed: after the first run of the catalyst, the reaction mixture was allowed to cool to room temperature and the catalyst was separated by centrifugation, washed twice with NMP and allowed to dry under vacuum at room temperature overnight. The recycled palladium catalyst was then used without any regener-

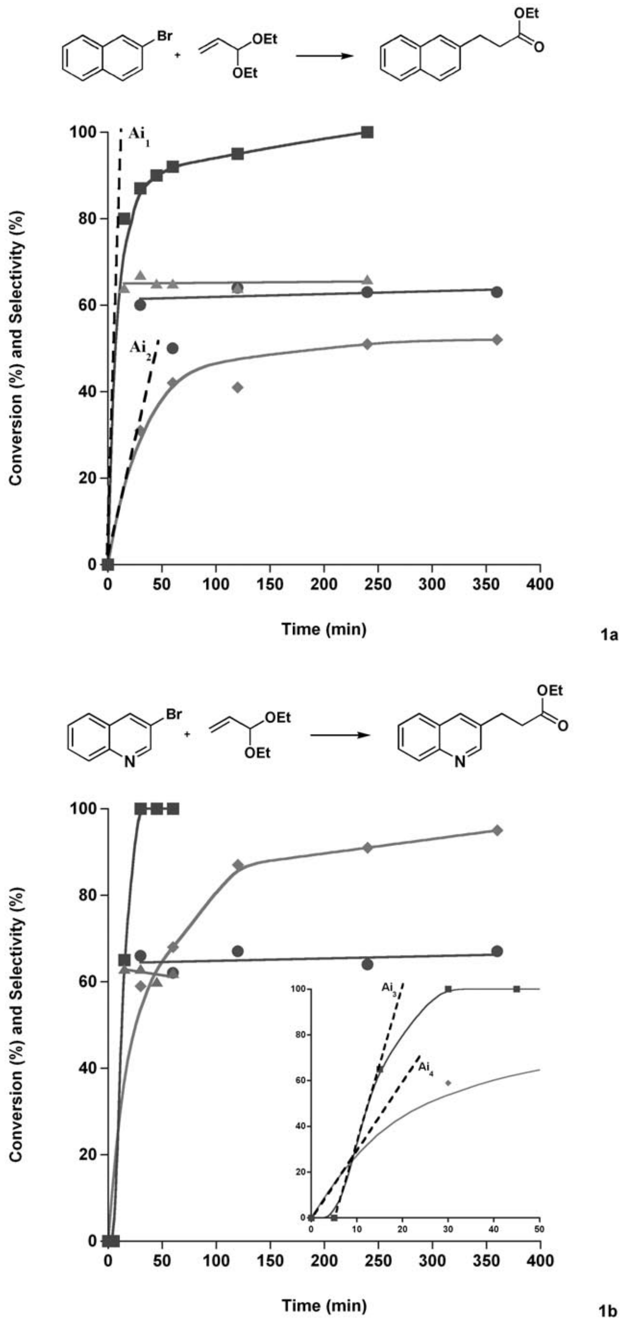


Figure 1. Conversions and selectivities *versus* the time for the coupling reaction of 2-bromonaphtalene or 3-bromoquinoline with the acrolein diethyl acetal using the "palladacycle" (◆ and ●, respectively), or the $[Pd(NH_3)_4]/NaY$ (■ and ▲, respectively). Reaction conditions: 2,4 mmol aryl bromide, 7,2 mmol acrolein diethyl acetal, 2 mol% [Pd], 8 mL NMP, 140 °C.

Table 3. Influence of the recycling of the heterogeneous catalysts.

Run	Heck conditions[a]		Cacchi conditions[b]	
	Conversion [%]	Selectivity **2**/**3** [%]	Conversion [%]	Selectivity **2/3** [%][d]
1	100	72/28	100	0/100
2	100	73/27	38 (27)[c]	0/100
3	67	70/30		
4	45	71/29		
5	< 5%	n.d.		

[a] Coupling reaction of 2-bromoquinoline **1a** with acrolein diethyl acetal under standard Heck conditions (2.4 mmol aryl bromide, 7.2 mmol acrolein diethyl acetal, 2 mol% Pd catalyst, 3.6 mmol NaOAc, 8 mL NMP, 140 °C).

[b] Coupling reaction of 3-bromoquinoline **1e** with acrolein diethyl acetal under standard Cacchi conditions (2.4 mmol aryl bromide, 7.2 mmol acrolein diethyl acetal, 2 mol% Pd catalyst, 4.8 mmol n-Bu_4NOAc, 2.4 mmol KCl, 3.6 mmol K_2CO_3, 8 mL DMF, 110 °C).

[c] GC yield in quinoline (dehalogenation).

[d] The selectivity did not account for dehalogenation rate.

ation under the same reaction conditions as the fresh catalyst. The procedure was repeated up to 5 runs, giving respectively conversions of 100%, 100%, 67%, 45%, < 5% (Table 3), the selectivity being constant. The apparent loss of activity could have several reasons, including mechanical mass loss during the recycling protocol (centrifugation, decantation) or real catalytic site deactivation (including poisoning by sodium salts). Nevertheless, the activity of the recycled catalysts remains good over the 2nd and 3rd run before dramatically decreasing. Interestingly, the ICP-AES analyses carried out on the liquid phase after cooling at the end of each run showed < 0.5 ppm palladium. TEM analysis of the recycled catalyst showed highly dispersed Pd nanoparticules (*ca.* 2–3 nm) inside the zeolite cavities, preventing thus Pd aggregation, and therefore the dehalogenation reaction (Figure 2a). More rigorous attempts to detect catalytically active palladium in solution were performed in an independent series of experiments (*vide infra*).

Leaching was examined for the coupling reaction of 2-bromonaphthalene **1a** and acrolein diethyl acetal under optimised reaction conditions using the hot filtration method: a catalytic run was started as for a standard reaction, and after 10 min of reaction corresponding to *ca.* 28% conversion, the reaction mixture was filtered through a warmed celite pad to afford a clear filtrate (Figure 3). The clear filtrate was then treated as the usual catalytic test, and its composition was followed by GC and compared to that of a standard catalytic run.

Figure 3 showed clearly that the catalytic activity observed using the $[Pd(NH_3)_4]/NaY$ catalyst is mainly due to dissolved active Pd species since after removal of the heterogeneous catalyst by hot filtration the conversion of 2-bromonaphthalene **1a** rose from 28% to 51% over two hours. However, one should note that the overall activity observed for the clear filtrate is not as high as that observed in the presence of the heterogeneous catalyst that can be seen as a reservoir

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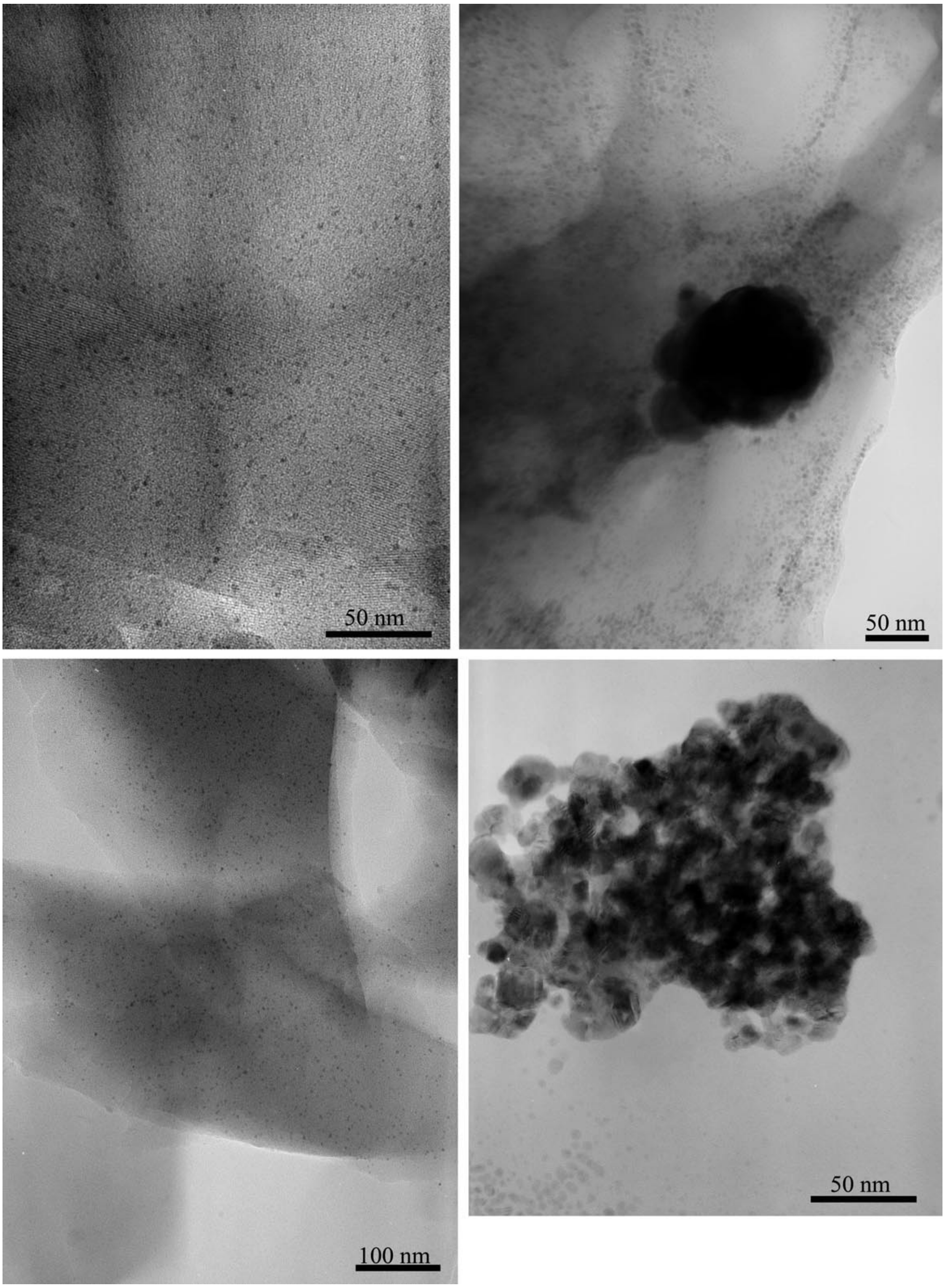


Figure 2. TEM (*left*) of the used [Pd(NH_3)$_4$]/NaY under Heck conditions; (*right*) under Cacchi conditions (potasium is observed in these used catalysts issued probably from decomposition of KCl or KOH under the electron beam).

source of active Pd species. ICP-AES analyses of the clear filtrate obtained by hot filtration are in good agreement with these results: a Pd content of 12 ppm was determined for the catalytically active filtrate recovered from the [Pd(NH_3)$_4$]/NaY-catalysed reaction. One could note that such a level of leaching corresponds to 0.04 mol% Pd/substrate made available during the coupling reaction corresponding to a TON

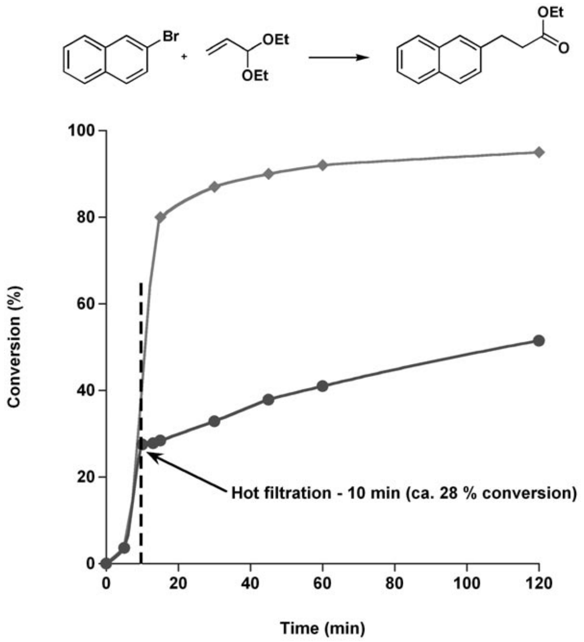


Figure 3. Leaching of active Pd-species in solution using the [Pd(NH_3)$_4$]/NaY catalyst. Residual catalytic activity after hot filtration (●) after 10 min reaction *versus* standard catalytic run (◆). *Reaction conditions:* 2.4 mmol 2-bromonaphthalene, 7,2 mmol acrolein diethyl acetal, 2 mol% [Pd(NH_3)$_4$]/NaY, 8 mL NMP, 140 °C.

of *ca.* 6000, somewhat higher than the results reported by Santelli and co-workers using the {Tedicyp ligand/[Pd(η^3-C_3H_5)Cl]$_2$} catalytic system (TON of *ca.* 1000) for comparable reactions (1-bromonaphthalene with acrolein ethylene acetal).[42] This result contrasts with that obtained from ICP-AES analyses of the clear supernatant solutions while evaluating the recycling, attesting clearly that dissolution-redeposition equilibrium occurs during such coupling reactions, as has often been suggested in the literature.[73,83–85] This equilibrium is therefore clearly dependent on the reaction temperature, and is strongly displaced toward the redeposition at low (ambient) temperatures.

After demonstrating the applicability of the heterogeneous [Pd(NH_3)$_4$]/NaY catalyst for the selective synthesis of 3-arylpropionic esters, we extended the study to the selective synthesis of cinnamaldehydes **3**. In previous studies, we reported the direct preparation of cinnamaldehydes from acrolein and various aryl halides using a homogeneous palladacycle.[27] However, we also found that, while possible, the use of heterogeneous catalysts like [Pd(NH_3)$_4$]/NaY remained limited due to low conversions (typically 12–30% for bromobenzene with various α,β-unsaturated aldehydes).

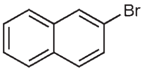
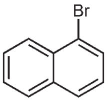
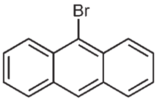
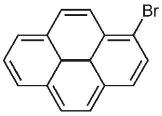
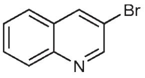
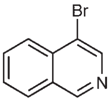
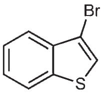
As an interesting alternative, we decided to evaluate the procedure reported by Cacchi and co-workers[31] from acrolein diethyl acetal in the case of the heterogeneous [Pd(NH_3)$_4$]/NaY catalyst. Various aryl and heteroaryl halides were engaged in reaction in the presence of tetrabutylammonium acetate and potassium chloride (2.4 mmol aryl bromide, 7.2 mmol acrolein diethyl acetal, 2 mol% Pd catalyst, 4.8 mmol *n*-Bu_4NOAc, 2.4 mmol KCl, 3.6 mmol K_2CO_3, 8 mL DMF, 110 °C). The results are reported in Table 4 and compared to those obtained from homogeneous procedure (Table 4).

Under such reaction conditions, the catalytic activity was lower than those reported in the first part of this study. After 24 h, the conversion of bromopyrene **1d** reached only 53% (Table 4, entry 4). Similar conversions were achieved with both homogeneous and heterogeneous catalytic systems. As expected, the aldehyde **3** was obtained as the main product together with the ester **2**. However a third product was also observed under these reaction conditions corresponding to the dehalogenation reaction. For polyaromatics **1a–d**, both the homogeneous and heterogeneous catalytic systems led to close ester/aldehyde selectivities in favour to the aldehyde **3**, except for the 9-bromoanthracene **1c** that yielded mainly the ester whatever the catalytic system used. Interestingly, when reacting the heteroaromatics **1e–g**, higher selectivities in **3** were observed using the heterogeneous [Pd(NH_3)$_4$]/NaY catalyst. The most attractive outcome concerned the rates of dehalogenation side reactions: using the [Pd(NH_3)$_4$]/NaY as a [Pd] source reduces considerably the dehalogenation rates, particularly for the bromoisoquinoline **1f** (0% *versus* 85%) and the bromothiophene **1g** (0% *versus* 90%). In previous studies, we demonstrated that the dehalogenation was mainly due to the formation of palladium particles or agglomerates in the reaction media, while the Heck arylation resulted from soluble molecular Pd species.[83] The results presented here suggest that, depending on the substrate, rapid Pd agglomeration could occur while using homogeneous ligand-free Pd(OAc)$_2$, whereas the use of the [Pd(NH_3)$_4$]/NaY retards such agglomeration.

As previously mentioned, differences between both reaction conditions (Heck: [Pd] catalyst, NaOAc, NMP, 140 °C *versus* Cacchi: [Pd] catalysts, *n*-Bu_4NOAc, KCl, K_2CO_3, DMF, 110 °C) were found in terms of reaction times. While under standard Heck conditions it was found that the heterogeneous catalyst was more active than the homogeneous palladacycle, under Cacchi conditions, except for specific substrates like **1f** and **1g**, both the homogeneous and heterogeneous catalysts afforded similar conversions at the same time.

When using the heteroaromatics **1f** and **1g**, the reaction time required to get the complete conversion using the Pd(OAc)$_2$ is much shorter (6 h) than that required for the heterogeneous catalyst (24 h). However, this catalytic system is here unusable as under homogeneously Pd-catalysed conditions a high dehalo-

Table 4. Heck arylation of acrolein diethyl acetal with various aryl and heteroaryl halides using the Cacchi conditions.[a]

Entry	Substrate	[Pd] source	Time [h]	Conversion [%][b,c]	Selectivity (**2**/**3**) [%][d]	Yield **3** [%][e]
1	**1a** 	$[Pd(NH_3)_4]/NaY$	24	100	9/91	75
2		$Pd(OAc)_2$	24	100 (17)	0/100	-
3	**1b** 	$[Pd(NH_3)_4]/NaY$	24	73	5/95	53
4		$Pd(OAc)_2$	6	73 (14)	0/100	-
5	**1c** 	$[Pd(NH_3)_4]/NaY$	24	100	68/32	21
6		$Pd(OAc)_2$	24	100 (2)	67/33	-
7	**1d** 	$[Pd(NH_3)_4]/NaY$	24	53 (3)	27/73	35
8		$Pd(OAc)_2$	24	100 (2)	33/67	42
9	**1e** 	$[Pd(NH_3)_4]/NaY$	6	100	0/100	63
10		$Pd(OAc)_2$	6	100	21/79	-
11	**1f** 	$[Pd(NH_3)_4]/NaY$	24	67	16/84	51
12		$Pd(OAc)_2$	6	100 (85)	34/66	-
13	**1g** 	$[Pd(NH_3)_4]/NaY$	24	21	0/100	19
14		$Pd(OAc)_2$	6	100 (90)	30/70	-

[a] *Reaction conditions*: 2.4 mmol aryl bromide, 7.2 mmol acrolein diethyl acetal, 2 mol% Pd catalyst, 4.8 mmol n-Bu_4NOAc, 2.4 mmol KCl, 3.6 mmol K_2CO_3, 8 mL DMF, 110 °C.

[b] Conversions based on unreacted aryl bromide were determined by GC.

[c] Dehalogenation GC-yields are reported in brackets.

[d] Selectivities were determined by GC on the basis of area percentage. The selectivity did not account for dehalogenation rate.

[e] Isolated yields are reported, when available.

genation rate was observed (respectively, 85% and 90%). This side reaction is well known to be faster than the expected Heck reaction, bringing here a clear account for these observations.

These observations support the formation of metallic Pd(0) particles as the active species (or as their precursors) independently of the Pd source used under the Cacchi conditions in presence of KCl and n-Bu_4NOAc. This is further supported by recycling experiment of $[Pd(NH_3)_4]/NaY$ catalyst for the coupling reaction of 3-bromoquinoline with acrolein diethyl acetal: since in the second run strong deactivation is observed leading to only 38% conversion (Table 3), mainly due to the formation of quinoline (27% yield, i.e., 70% selectivity) through dehalogenation. TEM analysis of the reused catalysts under Cacchi's conditions showed that large palladium aggregates (>50 nm) were formed during the first runs of the catalyst outside of the zeolite's framework (Figure 2b). Comparison of this result with that obtain for the $[Pd(NH_3)_4]/NaY$ catalyst used under standard Heck conditions (Figure 2a) suggests that the use of n-Bu_4NOAc hindered the return of leached palladium inside the zeolite cavity favouring thus the palladium aggregation and therefore the dehalogenation side reaction.

Better insights concerning the reactivity of homogeneous and heterogeneous catalytic systems were obtained from kinetic experiments for the coupling reaction of 3-bromoquinoline with acrolein diethyl acetal. Figure 4 clearly demonstrates similar reactivity for the homogeneous and heterogeneous catalytic systems. Both catalytic systems showed an initiation period before being active: *ca.* 3 min for the homogeneous catalyst and 5 min for the heterogeneous catalyst. The "apparent" initial activities: $Ai_{homo} = 31\ mmol/g_{Pd}/min$ *versus* $Ai_{hetero} = 29\ mmol/g_{Pd}/min$ are of the same order, accounting for the observed results.

All these results indicate that the active palladium species produced under different reaction conditions are specific and involve therefore different reaction mechanisms. When performing the reaction under the well established Heck conditions (polar solvent; i.e., NMP, base, 140 °C) molecular species, whatever introduced as a soluble precatalyst or generated through palladium dissolution, can be regarded as the active

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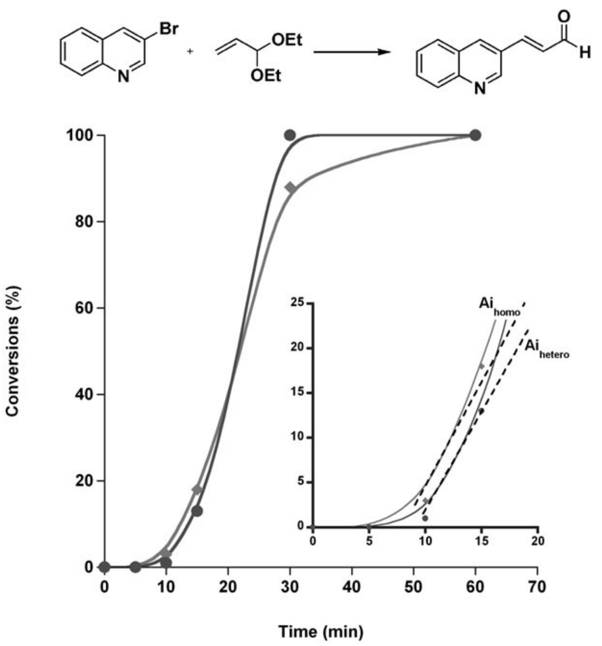


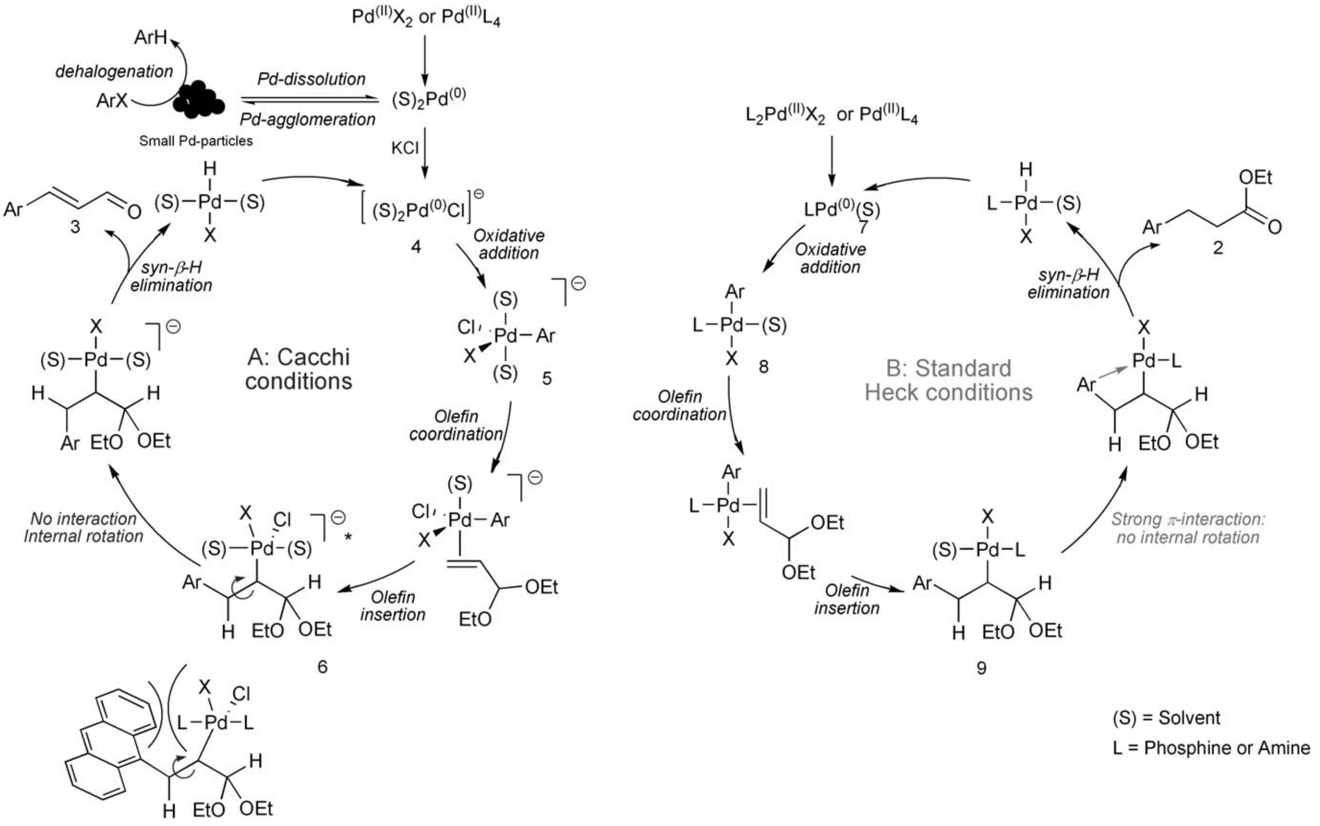
Figure 4. Conversions *versus* the time for the coupling reaction of 3-bromoquinoline with the acrolein diethyl acetal under the Cacchi conditions using the $Pd(OAc)_2$ (◆) or the $[Pd(NH_3)_4]$/NaY (●), respectively. Increasing dehalogenation was observed in the case of $Pd(OAc)_2$ from *ca.* 3% to 7% after 15 min.

species. Several reports issuing from homogeneous or heterogeneous catalysis research appeared recently and supported such an interpretation.[84,85] On the contrary, when the reaction was carried out under the solid-liquid phase-transfer conditions developed by Cacchi et al. (DMF, KCl, phase-transfer agent, base, 110 °C), based on the earlier work done by Jeffery, it should be suggested that Pd nanoparticles are generated at the beginning of the reaction that either give back dissolved molecular species (i.e., Heck coupling) or agglomerate to form larger Pd particles leading to high dehalogenation rates. This interpretation is rather supported by several works done by Reetz and co-workers who established unambiguously that palladium salts precipitated to Pd(0) particules under Jeffery's reactions conditions.[86–88] For the latter, the selectivity of the reaction towards the Heck coupling or the dehalogenation will be affected by the Pd concentration in the reaction media. In that case it was found that the use of $[Pd(NH_3)_4]$/NaY as the Pd source represents an advantage over the use of $Pd(OAc)_2$ since less palladium is made available during the reaction (generally < 15 ppm *versus* > 600 ppm for classical homogeneous reactions).

As previously described, the selectivity of the reaction toward the ester **2** or the aldehyde **3**, depending on the reaction conditions, could be easily explained through the formation of different active Pd species. Under the phosphine-free Cacchi conditions (Table 4), "naked" palladium acting as active species will be generated. The use of a stoichiometric amount of KCl would favour the formation of anionic palladium species $\{[L_2Pd(0)Cl]^-, K^+\}$ **4** as the active species in the catalytic cycle (Figure 5, route A).[89–91,92] Under the standard Heck conditions, whatever the palladium source used as catalyst precursor, neutral palladium complexes coordinated by two ligands L (phosphine or solvent; the complex being depicted as [LPd(0)(S)] **7** in Figure 5, route B) would be involved as the catalytically active species in the initial phase of the catalytic cycle, as reported recently by Jutand et al.[93] In that case, additional strong interactions between the Pd(II) centre and the aromatic ring of the bromo substrates in the carbopalladated adduct **9** (Figure 5, route B) would prevent the internal rotation along the Ar**CH−CH(Pd)**CHR bond that is usually reported in the Heck mechanism. As a consequence, the *syn* β-hydrogen elimination would mainly occur *via* the H *gem* to the diacetal yielding thus the ester. Such interactions would be restricted where anionic palladium(II) complexes were involved due to the initial formation of the pentacoordinated Pd(II) complex **5** by the oxidative addition of the aryl halide: as a consequence the formation of the aldehyde would be predominant (Figure 5, route A). In some cases (**1c–1g**), the rotation could be limited due to steric hindrance giving a mixture of ester **2** and aldehyde **3**.

These explanations based on the use of soluble palladium complexes [$Pd(OAc)_2$ or Herrmann's palladacycle] could be unambiguously extended to the use of the heterogeneous $[Pd(NH_3)_4]$/NaY catalyst. This catalyst furnished soluble palladium species in bulk solution through leaching, probably as a $[Pd(NH_3)_4]^{2+}$ complex. This complex is known to decompose relatively quickly under the reaction conditions in two steps, leading to the formation of $[Pd(NH_3)_2]^{2+}$ that further decompose to lead to Pd(0) species stabilised through the solvent.[94] These species can enter both catalytic cycles giving either $[(S)_2Pd(0)Cl]^-$ (type **4**) or $[Pd(0)(S)_2]$ (type **7**) depending on the reaction conditions.

The selectivity ester **2**/aldehyde **3** is not significantly affected by the nature of the aryl halide, the use of standard Heck conditions (NMP, base, 140 °C) leading mainly to formation of the ester **2**, while the use of the Cacchi conditions (DMF, KCl, phase-transfer agent, base, 110 °C) gives almost exclusively the aldehyde **3**. For the latter catalytic system, given that the pentacoordinated anionic Pd(II) complex **5** centre is in equilibrium with the original "naked" neutral species (type **4**), the ratio of aldehyde **3** to ester **2** probably also depends on the hindrance of the aromatic moiety, as lower selectivity was achieved with 9-bromoanthracene **1c** and 1-bromopyrene **1d** (Table 4, entries 3 and 4). Additional interactions with heteroatom of heteroaryl halides **1e–g** can also be suggested,



* Limitations for large aryl derivatives (here antracyl is depicted)

Figure 5. Proposed routes for the Heck arylation of acrolein diethyl acetal depending on the reaction conditions used.

yielding similarly lower selectivity in aldehyde **3** (Table 4, entries 5–7).

Conclusions

In this contribution we demonstrated that the heterogeneous [Pd(NH$_3$)$_4$]/NaY catalyst offered a viable alternative to the use of soluble palladium complexes for the Heck arylation of acrolein diethyl acetal. Depending on the reaction conditions, selective syntheses toward cinnamaldehydes (NMP, base, 140 °C) or aryl propionic ester (DMF, KCl, *n*-Bu$_4$NOAc, base, 110 °C) were achieved. These relatively common reaction conditions were applied successfully to various aryl and heteroaryl bromides with success, giving generally good to high conversions and selectivities.

Among the latter, it was found that, for difficult substrates like heteroaryl halides, the heterogeneous catalyst showed higher efficacy since no or a low dehalogenation rate was observed. This was mainly attributed to the "homeopathic" palladium concentration generally observed for such reactions.[82]

The stability of the heterogeneous catalyst upon several cycles was evaluated. Under classical Heck conditions, it was found that the activity remains constant over 3 cycles. All results indicates that the [Pd(NH$_3$)$_4$]/NaY catalyst used under Heck conditions acts really as a palladium reservoir delivering into solution small palladium concentrations (*ca.* 12 ppm) preventing thus agglomeration and bringing good recyclability. This situation is quite different from what observed when using the catalyst under the so-called "Cacchi conditions". In that case, it was found that the heterogeneous catalysts could not be reused, leading to low conversion (<40%) and to strong dehalogenation rates (>70%). This was attributed to the formation of large Pd aggregates outside the zeolite framework, as observed by TEM analysis.

The hot filtration experiment clearly indicates that the activity of the heterogeneous catalysts is due to leached species during the reaction that confirmed previous results described in the literature. However, as expected form the well documented dissolution-redeposition process, generally a low palladium concentration remains in solution after cooling the reaction media at room temperature, helping towards palladium removal. This is particularly important for fine chemical applications where no palladium must be present in the final product.

Experimental Section

General Remarks

All manipulations were conducted under a strictly inert atmosphere or vacuum conditions using Schlenk techniques, including the transfer of the catalysts to the reaction vessel. All glassware was base- and acid-washed and oven-dried. The solvents used for the synthesis of the molecular palladium precursors and catalysts were dried using standard methods and stored over activated 4 Å molecular sieves. All other chemicals (organic reagents and solvents) were deaerated by an argon flow before they were used.

The catalytic reactions were carried out in a three-necked flask, or alternatively in pressure sealed tubes, under argon. The qualitative and quantitative analysis of the reactants and the products was made by gas chromatography. Conversions and yields were determined by GC based on the relative area of GC signals referred to an internal standard (diethylene glycol di-*n*-butyl ether) calibrated to the corresponding pure compound.

The palladium content determinations of the heterogeneous catalyst $\{[Pd(NH_3)_4]^{2+}/NaY\}$ were performed by ICP-AES spectroscopy from a solution obtained by treatment of the catalysts with a mixture of HBF_4, HNO_3 and HCl in a Teflon reactor at 180 °C.

Liquid NMR spectra were recorded on a Bruker AC-250 spectrometer. All chemical shifts were measured relative to residual ^{1}H or ^{13}C NMR resonances in the deuterated solvents: $CDCl_3$, δ 7.25 ppm for ^{1}H, 77 ppm for ^{13}C. IR spectra were recorded on a Bruker Vector 22 spectrometer. High resolution mass spectra (HR-MS) were recorded on a Thermo Finnigan MAT 95 XL spectrometer, with isobutane as reactant gas for CI. Transmission electron microscopy (TEM) was carried out on a JEOL 2010 microscope with an instrumental magnification of 50,000× to 100,000× and an acceleration voltage of 200 kV. Flash chromatography was performed at a pressure slightly greater than atmospheric pressure using silica (Merck Silica Gel 60, 230–400 mesh). Thin layer chromatography was performed on Fluka Silica Gel 60 F_{254}.

GC analyses were performed on a HP 4890 chromatograph equipped with a FID detector, a HP 6890 autosampler and a HP-5 column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm i. d. × 0.25 μm film thickness). Nitrogen is used as carrier gas. The mass spectra were obtained on a HP 6890 gas chromatograph equipped with a HP 5973 mass detector and a HP-5 MS column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm i. d. × 0.25 μm film thickness). Helium is used as carrier gas. The experimental error was estimated to be $\Delta_{rel} = \pm 5\%$.

Catalysts Preparation

The homogeneous "palladacycle" $\{Pd[P(o\text{-}C_6H_4CH_3)_2(C_6H_4CH_2)][OCOCH_3]\}_2$ catalyst was prepared from $Pd(OAc)_2$ and tri(*o*-tolyl)phosphine following the procedure reported by Herrmann et al.[80,81]

The heterogeneous $[Pd(NH_3)_4]/NaY$ catalyst was prepared as follows:[62] A 0.1 M ammonia solution of $[Pd(NH_3)_4]Cl_2$ – prepared from $PdCl_2$ and a commercial ammonia solution – was added dropwise (1 mL g $^{-1}$zeolite, corresponding to *ca.* 1 $\%_{wt}$ Pd in the final catalyst) to a suspension of the zeolite NaY in bidistilled water (100 mL g $^{-1}$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 ($AgNO_3$ test). Then the zeolite was allowed to dry at room temperature to give the entrapped $[Pd(NH_3)_4]/NaY$ catalyst as slightly yellow material. ICP-AES analysis: 1.0 $\%_{wt}$ Pd.

General Procedure for the Catalytic Tests under Heck Conditions (Ester 2 Synthesis)

2.4 mmol of aryl halide, 7.2 mmol of acrolein diethyl acetal, 3.6 mmol of NaOAc and 2 mol% of Pd catalyst were introduced in a pressure tube under argon. 8 mL of solvent NMP 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 6–23 h under vigorous stirring and then cooled to room temperature before the reaction mixture was analysed by GC. At completion of the reaction, the mixture was diluted with 150 mL of HCl 1 N and the resulting mixture was extracted with 4× 20 mL CH_2Cl_2 or EtOAc. The combined organic layers were washed three times with 15 mL of H_2O, then 15 mL of brine, dried over $MgSO_4$ and evaporated. The residue was then purified by flash chromatography on silica gel.

General Procedure for the Catalytic Tests under Cacchi Conditions (Aldehyde 3 Synthesis)

2.4 mmol of aryl halide, 7.2 mmol of acrolein diethyl acetal, 3.6 mmol of K_2CO_3, 2.4 mmol of KCl, 4.8 mmol of *n*-Bu_4OAc and 2 mol% of Pd catalyst were introduced in a pressure tube under argon. 8 mL of solvent DMF previously deaerated were added and the mixture was deaerated by an argon flow for 5 min. The reactor was then placed in a preheated oil bath at 110 °C for 6–24 h under vigorous stirring and then cooled to room temperature before the reaction mixture was analysed by GC. The same procedure as described before was used for extraction and purification.

General Procedure for the Recycling of the Heterogeneous Catalysts

For recycling experiments the catalyst used in a first run was separated by centrifugation, washed with the same solvent as for the reaction and reused after drying at room temperature as described for the fresh catalyst.

Procedure for the Determination of Leaching (Hot Filtration)

2.4 mmol of aryl halide, 7.2 mmol of acrolein diethyl acetal, 3.6 mmol of base and 2 mol% of $[Pd(NH_3)_4]/NaY$ were introduced in a three-necked flask under argon. Then 4–8 mL of solvent previously deaerated was added and the mixture was further deaerated by an argon flow for 5 min. The reactor was placed in a preheated oil bath at 90 °C or 140 °C. The reaction was conducted under vigorous stirring for 10–15 min of reaction. To remove all fine particles the supernatant solution was filtered through a celite pad that was continuously heated in order to avoid precipitation of dissolved palladium species. The celite pad was then washed with 3 mL of warmed solvent and the resulted clear mixture was treated for further 6 h under the standard reaction conditions.

The reaction was monitored over the total period by GC and the results compared to a standard catalytic reaction.

Characterizations of Organic Compounds

Esters **2** and aldehydes **3** were fully characterised through ^{1}H and ^{13}C NMR, IR, elemental analysis, GC-MS and HR-MS. Aldehydes **3a**, **3b** and **3c** gave analytical data in accordance with the literature.[31,32] Data are available in the Supporting Information.

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