Applied Catalysis A: General 469 (2014) 250–258

Contents lists available at ScienceDirect

Applied Catalysis A: General

journal homepage: www.elsevier.com/locate/apcata

Base directed palladium catalysed Heck arylation of acrolein diethyl acetal in water

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ARTICLE INFO

Article history:
Received 23 July 2013
Received in revised form
30 September 2013
Accepted 3 October 2013
Available online 12 October 2013

Keywords:
Heck arylation
Water
Cyclodextrins
Palladium catalysts
Acrolein
Cinnamaldehyde
3-Arylpropionic esters

ABSTRACT

The selective Heck arylation of acrolein diethyl acetal catalysed by $[Pd(NH_3)_4]Cl_2$ in the presence of RAME-β-CD in water as solvent is described. Depending on the base (i.e. NaOAc or HN(*i*-Pr)$_2$) good to high selectivity's towards, respectively, the cinnamaldehydes **2** or the 3-arylpropionic esters **1** were achieved. The results support that depending on the base different palladium intermediate complexes are formed. Using NaOAc, {[ArPdX$(H_2O)_2$]} complex is preferentially generated giving the cinnamaldehyde **2.** On the other hand, in the presence of HN(*i*-Pr)$_2$, a L-type ligand, [ArPdX(HN(*i*-Pr)$_2(H_2O)$] or [ArPdX(HN(*i*-Pr)$_2$(HN(*i*-Pr)$_2$)] will be generated leading to the formation of the 3-arylpropionic ester **1**. For the last, coordinated amine participates very probably to the formation of the esters through intramolecular *syn* β-H elimination.

1. Introduction

Cinnamaldehyde derivatives found applications in food, cosmetic agrochemical and pharmaceutical industries while 3-aryl propionic acids are common building blocks in organic synthesis. Therefore, several multi-step and costly organic methods have been reported for their synthesis [1,2]. These have been supplanted by palladium-catalysed Heck procedures [3], mainly devoted to cinnamaldehydes, from allylic alcohol [4–7] or acrolein [8–10]. In the last, some degradation was observed [11] that can be avoided by using acrolein dialkyl acetal [8]. However, the reaction was not selective and mixtures of aldehyde and ester were obtained those selectivity could be directed by the nature of the catalytic system. For example, the group of Cacchi reported a procedure in DMF at 90 °C to prepare selectively cinnamaldehydes ($Pd(OAc)_2$, Bu_4NOAc, K_2CO_3, KCl)[12] or 3-arylpropionic ester ($Pd(OAc)_2$, *n*-Bu_4NCl, *n*-Bu_3N) [13]. Similarly, Santelli and Doucet reported the synthesis of cinnamaldehydes or 3-arylpropionic from 3,3-diacetoxypropene [14] or acrolein ethylene acetal [15]. In previous works, we extended this approach to a large variety of condensed aryl and heteroaryl substrates using either homogeneous [10,16] or heterogeneous [17] palladium catalysts. Under similar conditions to ours, Najera and Botella reported the preparation of cinnamaldehyde derivatives using a dimeric 4-hydroxyacetophenone oxime-derived palladacycle as catalyst [18,19]. While successful, these palladium catalysed methodologies remain linked to the use of polar organic solvents like DMF or DMAc that have been recently prohibited in most of the chemical industries.

In this context, the use of alternative non-toxic solvents appears to be very attractive. Water emerges as a good candidate in regards to previous industrial development [20] and successful transposition of Heck arylation of olefins in this media [21,22]. Initially, Beletskaya and co-workers reported the arylation of acrylic acid by diaryliodonium salts in presence of $Pd(OAc)_2$ and Na_2CO_3 in water at 100 °C leading to significant yields (50–94%) of cinnamic acids [23]. The methodology was then adapted to styrene arylation [24,25] and was regarded as a green approach for the preparation of cinnamic derivatives [26]. Extension of these pioneering work concerned mainly development of water soluble systems based on hydrophilic phosphine [27] or reaction under microwave irradiations using hypervalent iodonium salts [28].

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http://dx.doi.org/10.1016/j.apcata.2013.10.004

These examples, while interesting, remain quite limited due to the exclusive use of water soluble substrates to achieve good yields. Some authors used additives in order to circumvent such limitation in which the use of phase transfer agent like tetraalkyl ammonium salts [29,30] appeared particularly successful. Originally, Jeffery reported the coupling of iodobenzene with acrylates in the presence of tetrabutyl ammonium salts [29], followed by Tsai and co-workers who used palladium cationic complexes in the presence of TBAB [30]. Recently, Iranpoor and al. reported the use of phosphazane ligands for base-free Pd(II) catalysed Heck coupling reaction of aryl iodides, bromides and chlorides in water with styrene, *n*-butylacrylate, 1-octene and cyclohexene. The palladium complex is easily separated by filtration and reused for several runs [31].

Pursuing our efforts to develop sustainable processes for fine chemical syntheses we investigated in detail the Heck arylation of acrolein diethyl acetal to cinnamaldehydes or 3-arylpropionic acids in water (Scheme 1) [32–35]. The effect of various cyclodextrins on reaction rate and selectivity was also evaluated. Indeed it is known that cyclodextrins can play a positive role in large range of water phase reaction [32–35], to the best of our knowledge no study was reported on the Heck arylation in the presence of homogeneous catalysts despite the few existing examples concerning the use of heterogeneous catalyst [36–39].

2. Experimental

They include the general information, the preparation of the catalysts, the syntheses and the analytical data (^{1}H NMR, ^{13}C NMR, Mass Spectra) relative to the cyclodextrins and the procedures for the catalytic tests. Mars microwave of CEM Corporation was used for the syntheses of cyclodextrin. It delivers an energy output of 800 w at a frequency of 2450 MHz. Teflon microwave-transparent XP-1500 vessels with inboard RTP-300 Plus temperature sensor control were used. With this configuration, the system regulates the microwave power out-put to maintain the desired reaction temperature.

2.1. Procedure for the synthesis of β-CD-NEt$_2$

β-CD-OTs (2.0 g, 1.56 mmol) in diethylamine (60 mL) was stirred and irradiated at 90 °C in closed reactor for 2 h under microwaves. After total evaporation of the amine, the crude product was dissolved in minimum distilled water and heated at 60 °C Cooling the solution to 20 °C resulted in precipitation of white crystalline needles. Filtration on a glass filter and subsequent drying under vacuum gave β-CD-NEt$_2$ with 76% yield.

2.2. Procedure for the synthesis of RAME-β-CD-OTs

NaOH solution (18 g, 450 mmol, in 50 mL of water) was added dropwise to a suspension of β-CD-OTs (19 g, 15 mmol) in water (50 mL) at 0 °C over a period of 10 min. A solution of dimethylsulfate (90 mL, 950 mmol) in THF (15 mL) at 0 °C was then added dropwise to the resulting clear solution. Ethanol (10 mL) was added to the solution which was brought to room temperature and stirred for 5 h. After, THF was evaporated and the product was extracted from the aqueous phase with chloroform (3 × 500 mL). The organic phase was dried with anhydrous $MgSO_4$. Chloroform was removed under reduced pressure to give RAME-β-CD-OTs with 57% yield.

2.3. Procedure for the synthesis of RAME-β-CD-NEt$_2$

RAME-β-CD-OTs (2.5 g, 1.56 mmol) in diethylamine (60 mL) was stirred and irradiated at 90 °C on closed reactor for 2 h under microwaves. After total evaporation of the amine, the crude product was dissolved in 50 mL of distilled water and the product was extracted from the aqueous phase with chloroform (3 × 250 mL). The organic phase was dried with anhydrous $MgSO_4$. Chloroform was removed under reduced pressure to give RAME-β-CD-NEt$_2$ with 52% yield.

2.4. Procedure for the catalytic tests

1 mmol of aryl halide, 3 mmol of acrolein diethyl acetal, 1.5 mmol base and 2 mol% of Pd-catalyst, and when applied *x*mol% CDs were introduced in a pressure tube. 2 mL water was added and the reactor was then placed in a pre-heated oil bath at 100 °C for 24 h under vigorous stirring. After cooling to room temperature few drops HCl 1 N were added to the reaction mixture that was extracted with 10 mL of a standard solution as EtOAc/dodecane (0.001 M). The organic layers were dried over $MgSO_4$ (an aliquot is removed to perform GC analyses) and evaporated under reduced pressure and the residue was then purified by flash chromatography on silica gel.

2.5. Procedure for the catalysts recycling tests

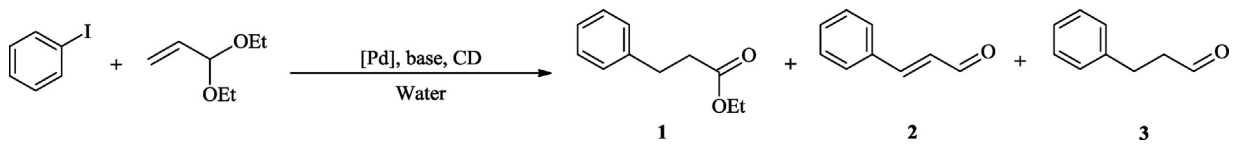
In a typical experiment fresh catalyst was used as for a standard catalytic run (2 mmol aryl halide, 6 mmol acrolein diethyl acetal, 3.5 mmol base, 2 mol% Pd-catalyst, 4 ml water, 90 °C, 24 h). After 24 hours reaction an aliquot was removed from the reaction mixture in order to perform GC-analyses and new amounts of reagents (2 mmol of aryl halide, 6 mmol of acrolein diethyl acetal, 3.5 mmol base) were added. The volume of solvent was adjusted to initial volume in order to restore the concentrations of reagents to that of the initial run. Immediately after addition, based on GC analyses, the concentration of the aryl halide was set to 100% and the concentration in products to 0%. The reaction was followed by GC for another 24 h and the procedure was repeated four times.

3. Results and discussion

3.1. Initial studies

Several commercially available palladium salts (i.e. $Pd(OAc)_2$, $PdCl_2$, Na_2PdCl_4, $Pd(NH_3)_4Cl_2$) and home-made palladium catalyst {Pd[P(*o*-Tol)$_3$(OAc)]}$_2$ (i.e. Herrmann–Beller palladacycle; prepared following reported procedure [40]) were evaluated and compared one with each other's in the Heck arylation of acrolein diethyl acetal in pure water.

In some reactions, cyclodextrins were used as additive in order to increase the catalyst activity. For this purpose, several structurally different cyclodextrins (Fig. 1) were evaluated. Except the



Scheme 1.

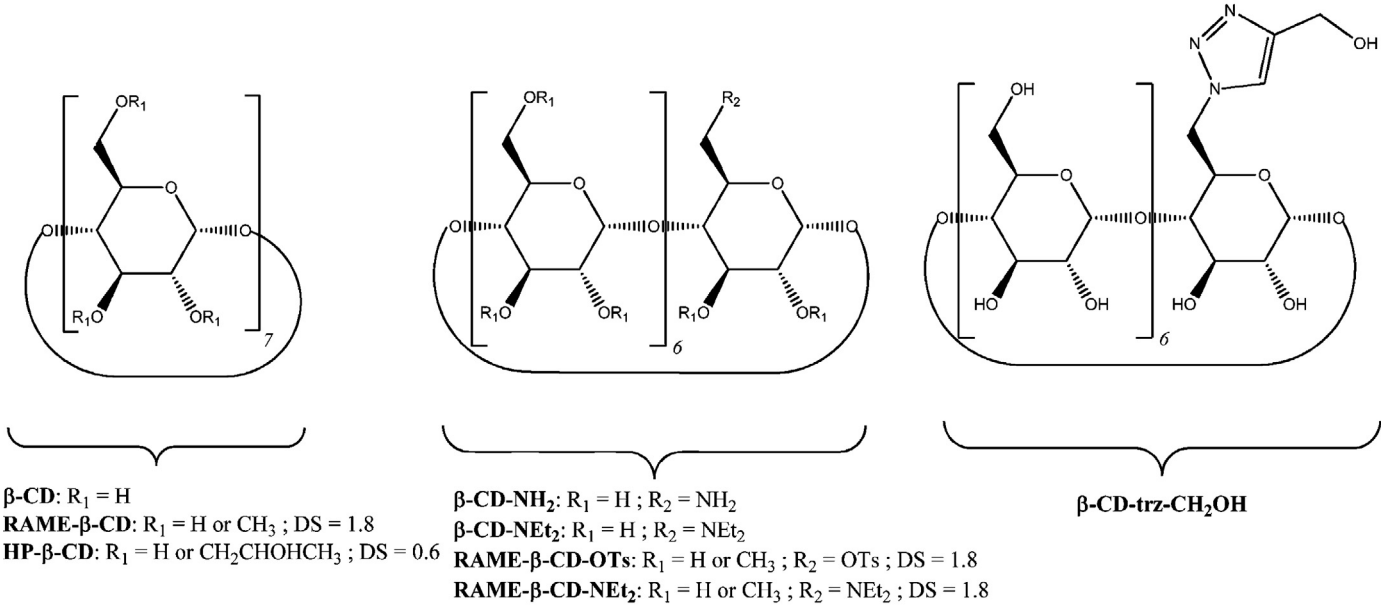


Fig. 1. Cyclodextrins used in the study. DS: degrees of substitution representing the average number of substituants (CH_3 or $CH_2CHOHCH_3$ groups) per glucopyranose unit on the C-2, C-3 and C-6 positions.

commercially available β-cyclodextrin (i.e. β-CD), RAME-β-CD and 2-hydroxypropyl-β-cyclodextrin (i.e. HP-β-CD), β-CD-NH_2 [41], β-CD-trz-CH_2OH [42], RAME-α-CD [43] and **RAME-γ-CD** [43] were synthesised and characterised according procedures previously described.

The synthesis of β-CD-NEt_2 has been carried out in one step from the β-CD-OTs derivative under microwaves (MW) irradiation and easily isolated after recrystallization from hot water in 76% yield.

The RAME-β-CD-NEt_2 has been obtained in two steps from the β-CD-OTs. In the first step, the RAME-β-CD-OTs was synthesised by reaction of β-CD-OTs in alkaline conditions at 0 °C with a dimethyl sulfate solution. After work-up, RAME-β-CD-OTs was isolated as a pale yellowish-white powder in 57% yield. For the second step, RAME-β-CD-OTs was dissolved in diethylamine and the solution was heated up to 90 °C in a closed reactor using microwave irradiation for 2 h. The randomly RAME-β-CD-NEt_2 was obtained in 52% yield as a mixture of partially methylated β-CDs with an average degree of substitution of 1.8 methyl groups per glucopyranose unit.

In order to discern which reaction conditions allowed to perform the Heck arylation of acrolein diethyl acetal in water, we realised a preliminary study comparing the performances of various sources of palladium in two solvents, namely NMP previously described [17] and water. Iodobenzene was chosen for this set of reaction (Table 1). Based on our previous results [17], the reaction was carried out for 24 h using sodium acetate as base.

As expected, all reaction carried out in NMP led to high conversions and good to high selectivities (i.e. >65%) towards the 3-arylpropionic ester **1** (Table 1, entries 1, 3) independently on the source of the palladium catalyst. In water, the results are quite different. Generally moderate conversion was achieved using the Herrmann-Beller palladacycle (i.e. 40%); Table 1, entries 2) whereas low conversion (i.e. <15%; Table 1, entries 4) was observed when engaging the $Pd(OAc)_2$ as catalyst. Noticeably, in water reverse selectivity towards aldehyde **2** is observed (i.e. selectivity >80%). Whatever the Pd-catalyst used, the conversion remained low (i.e. <40%). In a few cases (Table 1, entries 5, 6 and 7) saturated aldehyde **3** was also observed in low amount, mainly when palladium chloride derivatives were engaged. Presumably this compound is formed according to mechanism depicted in Fig. 2 [44]. After formation of the C—C bond, the palladium complex **A** isomerises to the enolate intermediate **B** that yields the observed saturated aldehyde **3** after hydrolysis.

Even if modest conversions were observed, these preliminary results have shown that Heck coupling of acrolein diethyl acetal in water is feasible.

3.2. Adding cyclodextrins

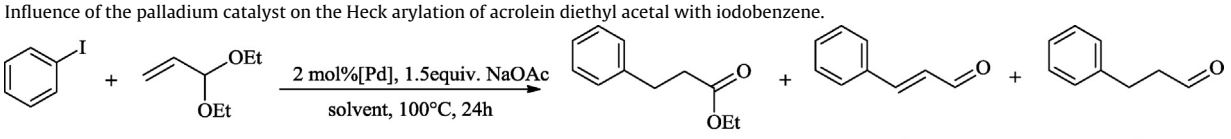
Among all evaluated catalysts, the $[Pd(NH_3)_4]Cl_2$ catalyst was chosen to evaluate further various reactions parameters for converting acrolein diethyl acetal and iodobenzene to cinnamaldehydes **2** in water in the presence of NaOAc. Here, we were interested in improving the efficiency of the catalytic system to propose a procedure competitive to those using organic solvent.

With this aim, we evaluated the influence of various cyclodextrins (Fig. 1) on both the conversion and the selectivity of this transformation (Table 2).

The nature of cyclodextrins has a dramatic influence on the evolution of the reaction. While addition of RAME-α-CD and RAME-γ-CD induced lower conversion (22% and 24%, respectively; Table 2, entries 9–10); addition of RAME-β-CD allowed increasing noticeably the conversion of iodobenzene (86% vs 33%; Table 2, entries 3 and 1, respectively). Regardless of the cyclodextrin, the selectivity of the reaction remained unchanged (75–78% in favour of aldehyde **2**). Considering the positive effect of β-cyclodextrin family, we evaluated a range of substituted β-CDs on the conversion and the selectivity of the reaction. β-CD-NH_2 and β-CD-trz-CH_2OH increased slightly the conversion up to 39% (Table 4, entry 7) and 52% (Table 2, entry 4), respectively, while native **β-CD** allowed increasing the conversion by a factor 2 (Table 2, entry 2). In a similar fashion, HP-β-CD, β-CD-NEt_2 and RAME-β-CD-NEt_2 promoted efficiently the reaction achieving high conversions (96–100%), with, however, a strongly decreased selectivity when using RAME-β-CD-NEt_2. To summarise, the best result was obtained with the randomly easily available methylated RAME-β-CD that gave 86% conversion without affecting the selectivity (78% in **2**) (Table 2, entry 2).

Next we evaluated the influence of the RAME-β-CD loading (i.e. the CD/iodobenzene ratio) on the conversion and the selectivity under previously optimised reaction conditions (Fig. 3).

Table 1
Influence of the palladium catalyst on the Heck arylation of acrolein diethyl acetal with iodobenzene.



Entries	Pd-catalyst	Solvent	Conversion (%)[a]	Selectivity (%)[a,b] **1**/**2**/**3**
1	$Pd[P(o\text{-}Tol)_3(OAc)]\}_2$	NMP	100	**80**/**20**/**0**
2		H_2O	40	0/**84**/0
3	$Pd(OAc)_2$	NMP	90	**82**/18/0
4		H_2O	15	0/**95**/0
5	$PdCl_2$	H_2O	36	0/**90**/10
6	Na_2PdCl_4	H_2O	26	0/**86**/11
7	$[Pd(NH_3)_4]Cl_2$	H_2O	33	0/**78**/22

Reaction conditions: 1 mmol PhI, 3 mmol acrolein diethyl acetal, 1.5 mmol NaOAc, 2mol% [Pd], 2 ml solvent, reflux, 24 h.
[a] Conversion and selectivity determined by GC. Dodecane was used as external standard for GC-quantitative determination.
[b] Ar–Ar < 10%.

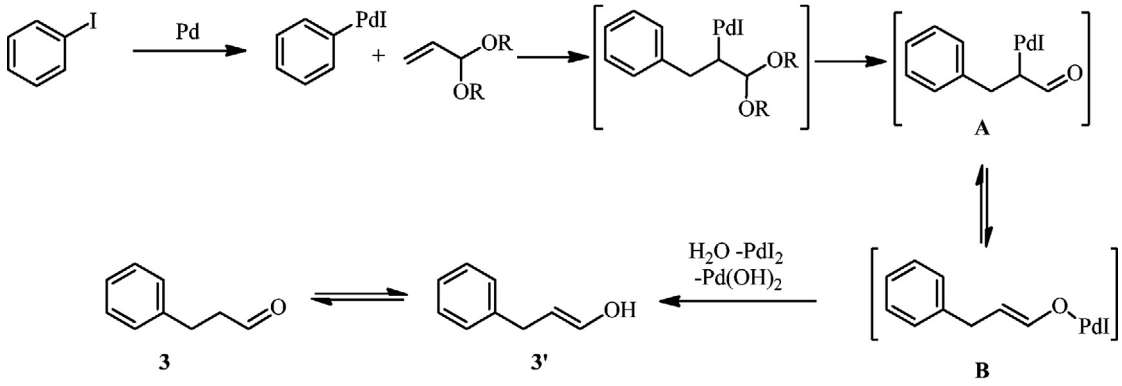


Fig. 2. Proposed pathways to account for the formation of **3** (based on reference [44]).

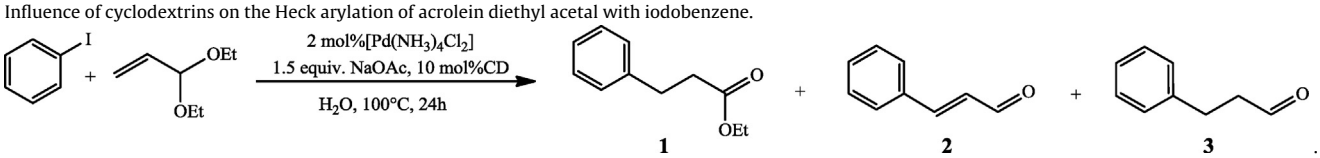
Fig. 3 clearly indicates the positive influence of adding RAME-β-CD. Since addition of 1 mol% CD, the initial activity of the reaction increases by a factor 2 to rise to 0.14 mol/$mol_{[Pd]}$/min. Increasing the CD/iodobenzene ratio resulted in enhanced activity and with 20 mol% RAME-β-CD a gap in activity that arises 0.28 mol/$mol_{[Pd]}$/min was observed.

The selectivity of the reaction is constant during the course of the reaction and is not affected by adding cyclodextrin as it remains relatively close in all reaction sets in favour of the cinnamaldehyde **2**. The small differences observed are in the error range of the analytical method (72–78%).

3.3. Influence of the nature of the base

We decided to investigate deeply the influence of the nature of the base (i.e. organic and inorganic bases) on the Heck arylation of acrolein diethyl acetal with iodobenzene, firstly without additive.

Table 2
Influence of cyclodextrins on the Heck arylation of acrolein diethyl acetal with iodobenzene.



Entries	CD	Conversion (%)[a]	Selectivity (%)[a,b] **1**/**2**/**3**
1	–	33	0/**78**/22
2	β-CD	68	7/**65**/23
3	RAME-β-CD	86	6/**78**/9
4	β-CD-trz-CH_2OH	52	14/**60**/26
5	RAME-β-CD-NEt_2	96	25/**52**/11
6	β-CD-NEt_2	97	18/**82**/0
7	β-CD-NH_2	39	16/**54**/30
8	HP-β-CD	100	12/**75**/13
9	RAME-α-CD	22	9/**76**/13
10	RAME-γ-CD	24	12/**75**/13

[a] Conversion and selectivity determined by GC. Dodecane was used as external standard for GC-quantitative determination.
[b] Ar–Ar < 10%.

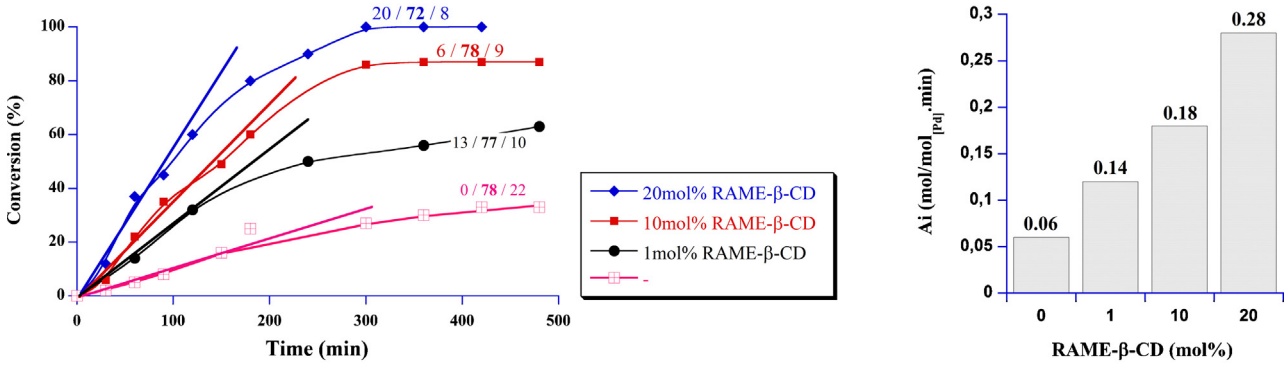


Fig. 3. Influence of RAME-β-CD loading on the conversion of iodobenzene versus the time. Selectivities (product: **1/2/3**; see scheme in Table 1) are indicated on the curves; Initial activities depending on RAME-β-CD loading are given on histograms. Reaction conditions: 2 mmol PhI, 6 mmol acrolein diethyl acetal, 3 mmol NaOAc, 2 mol% $[Pd(NH_3)_4Cl_2]$, 0–20 mol% CD, 4 ml water, $T = 100\,^{\circ}C$.

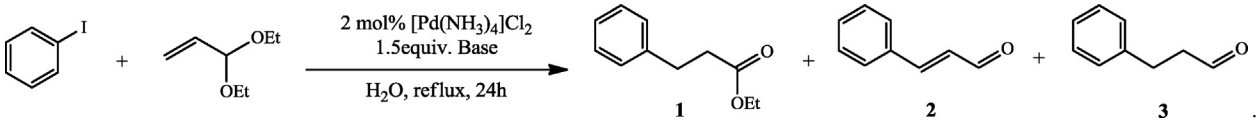
The use of mineral bases like hydroxide, carbonate and phosphate salts did not allow enhancing the conversion compared to NaOAc, except for NaOH that gave 61% of conversion (Table 3, entries 6–9). In all cases, aldehyde **2** is mainly formed (>90%, entries 5–8). Tertiary amines like Et_3N or $EtN(i\text{-}Pr)_2$ led generally to moderate to good conversions (i.e. 80%); however with a mixture of aldehyde **2** and ester **1** (Table 3, entries 2 and 5).

Unexpectedly, the use of diisopropylamine resulted in high activity together with a complete reverse selectivity in favour of the 3-arylpropionic ester **1**. Another issue concerned the conversion of iodobenzene that increased considerably reaching quantitative conversion after 5 h (Table 3, entry 3). In that case it was demonstrated that reducing the Pd-catalyst loading down to 0.5 mol% $[Pd(NH_3)_4]Cl_2$ (in regards to iodobenzene) did not strongly affect the efficiency of the system since 83% of conversion was achieved within 24 h (Table 3, entry 4). Very few reports concern the use of such secondary amines in Heck reaction. Dawood and al. reported the use of $NH(i\text{-}Pr)_2$ in Heck coupling of 4-bromoacetophenone with *t*Butyl acrylate in DMF and water. In water, they observed a full conversion using $NH(i\text{-}Pr)_2$ whereas only 5% was obtained with NaOAc [45]. Similar trends were observed in our hands.

To sum up, in water using NaOAc as the base gave mainly aldehyde **2** in moderate conversion while diisopropylamine led to the formation of ester **1** in high yields. Thus, the nature of the base influenced not only the activity of the reaction but also its selectivity. Base on literature reports and according to the experimental observations, it is rather reasonable to propose that the reverse selectivity results from the respective electronic nature of intermediate palladium complexes generated under the reaction conditions. In organic solvent, the formation of ester takes place via the *syn*-β-hydride elimination of hydrogen borne by the acetal while that of aldehydes results from *syn*-β-hydride elimination of benzylic hydrogen [17,46]. In water, the situation is quite different. Whatever the initial "naked" Pd-species generated at the first stage of the reaction, after oxidative addition solvent participate to the stabilisation of the $ArPd^{(II)}X$ complex through coordination. In the absence of other L-type ligand, $\{[ArPdX(H_2O)_2]\}$ complex will be preferentially generated (Fig. 4, route (a)). This complex will led, after olefin coordination and insertion, to the formation of aldehyde **2** since internal Pd-coordination by the ethoxy group in intermediate **C** would prevent the internal rotation along $PdCH\text{-}CH(OEt)_2$ axis.

On the other hand, in the presence of diisopropylamine as base, according to Jutand's reports [47], $[ArPdX(HN(i\text{-}Pr)_2(H_2O)]$ (Fig. 4, route (b)) or $[ArPdX(HN(i\text{-}Pr)_2(HN(i\text{-}Pr)_2)]$ (Fig. 4, route (c)) will be generated as $NH(i\text{-}Pr)_2$ is a stronger coordinating ligand than water, and given the $Pd/NH(i\text{-}Pr)_2$ ratio (1/175). In both cases, amine coordination to Pd will prevent further internal coordination by ethoxy groups due to steric hindrance and would thus favour the internal rotation along the $PdCH\text{-}CH(OEt)_2$ axis. This last step could be accelerated by intramolecular hydrogen bond (NH···OEt) between the diisopropylamine ligand and the ethoxy

Table 3
Influence of base on the Heck arylation of acrolein diethyl acetal with iodobenzene in pure water catalysed by the $[Pd(NH_3)_4]Cl_2$.



Entries	Base	Conversion (%)[a]	Selectivity (%)[a] **1/2/3**
1	NaOAc	33	0/**78**/22
2	Et_3N	80	31/**65**/0
3	$NH(i\text{-}Pr)_2$	100(5 h)	**70**/27/0
4	$NH(i\text{-}Pr)_2$[b]	83	**62**/33/0
5	$EtN(i\text{-}Pr)_2$	80	30/**70**/0
6	NaOH	61	6/**90**/0
7	KOH	35	0/**100**/0
8	K_2CO_3	32	8/**90**/0
9	K_3PO_4	30	4/**94**/0

Reaction conditions: 1 mmol PhI, 3 mmol acrolein diethyl acetal, 1.5 mmol Base, 2 mol% [Pd], 2 ml water, reflux, 24 h.
[a] Conversion and selectivity determined by GC. Dodecane was used as external standard for GC-quantitative determination.
[b] 0.5 mol% [Pd].

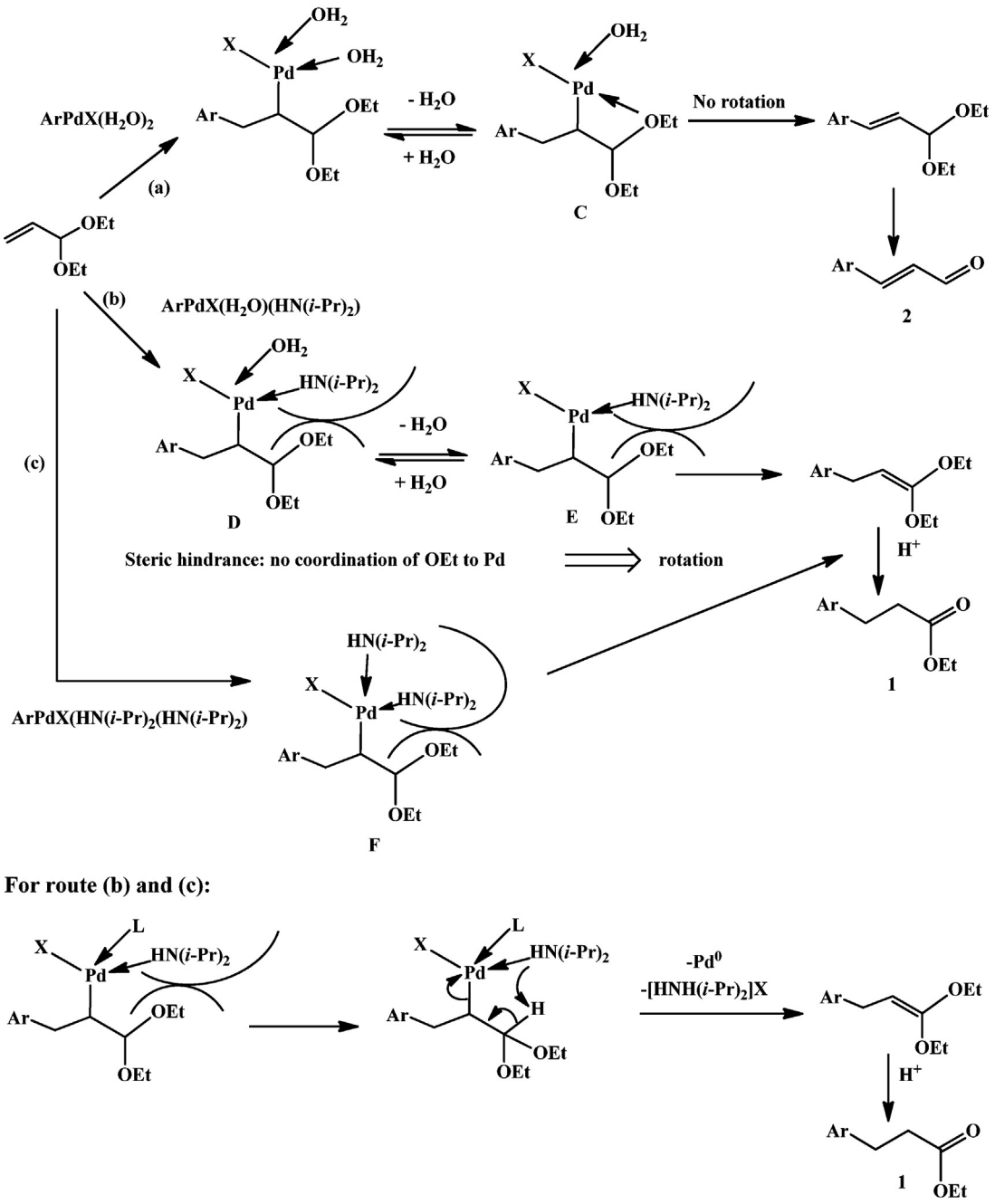


Fig. 4. Proposed mechanisms to account for the formation of either the aldehydes **2** or the 3-arylpropionic ester **1** in the Heck arylation of acrolein diethyl acetal in water depending on the nature of the base.

group. Additionally, it is strongly suggested that coordinated amine participates intramoleculary to the *syn* β-hydrogen elimination via the H *gem* to the diacetal yielding thus the ester.

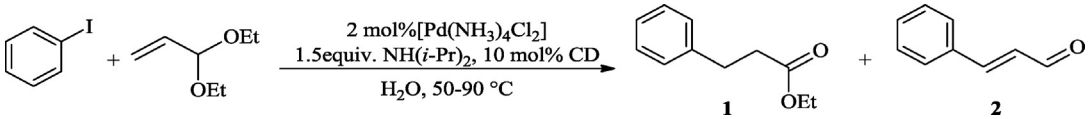
With these results in hand, likely to NaOAc, we evaluated the influence of adding cyclodextrin when using NH(*i*-Pr)$_2$ as the base (Table 4).

In the presence of NH(*i*-Pr)$_2$ the nature of CD impacted the performances of the catalytic system: native **β-CD** led to decrease activity while RAME-β-CD resulted in slightly increased efficiency (Table 4, entries 1–3). These observations were confirmed by kinetic investigations performed at 90 °C: while the highest activity of the reaction performed in absence of CDs arises 0.45 mol/mol$_{[Pd]}$/min that in the presence of native β-CD drops to 0.25 mol/mol$_{[Pd]}$/min. On the contrary, the use of RAME-β-CD did not affect the efficiency of the catalytic system (A_{max} = 0.45 mol/mol$_{[Pd]}$/min). Interestingly, addition of RAME-β-CD allowed stabilising the catalytic system as quantitative conversion of iodobenzene was observed after 3 h versus 5 h in its absence (see Fig. S1 in supporting information). Decreasing the reaction temperature allowed to observe further the positive influence of adding RAME-β-CD as clearly higher conversion was achieved versus the time in presence of RAME-β-CD (Table 4, entries 7 versus 7).

The selectivity of the reaction in favour of the ethyl 3-phenylpropionate **1** was not affected by adding cyclodextrins to the reaction medium.

Encouraged by this stabilising effect, we evaluated the recycling of the reaction medium using the following procedure: after a first

Table 4
Influence of cyclodextrins on the Heck arylation of acrolein diethyl acetal with iodobenzene.



Entries	CD	Time (h)	Temperature (°C)	Conversion (%)[a]	Selectivity **1**/**2** (%)[a]	A_{max} (mol/mol$_{[Pd]}$/min)
1	–	5	90	100	**70**/27	0.45
2	β-CD	24	90	100	**65**/35	0.25
3	RAME-β-CD	3	90	100	**78**/22	0.45
4	–	6/24	70	50/90	**60**/35	–
5	RAME-β-CD	6/24	70	85/100	**63**/31	–
6	–	24	50	34	**76**/22	–
7	RAME-β-CD	24	50	60	**73**/25	–

[a] Conversion and selectivity determined by GC. Dodecane was used as external standard for GC-quantitative determination.

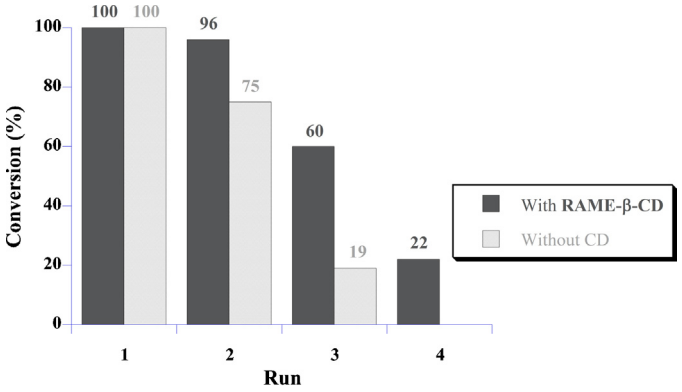


Fig. 5. Influence of RAME-β-CD on recycling. Reaction conditions: run 1: 2 mmol PhI, 6 mmol acrolein diethyl acetal, 3.5 mmol NH(*i*-Pr)$_2$, 2 mol% [Pd(NH$_3$)$_4$Cl$_2$], 4 ml water, 90 °C; run 2–4: adding 2 mmol PhI, 6 mmol acrolein diethyl acetal, 3.5 mmol NH(*i*-Pr)$_2$ and adjusting the solvent volume to the initial value.

run with the fresh catalytic system (24 h), new amounts of reagents (i.e. 2 mmol PhI, 6 mmol acrolein diethyl acetal and 3.5 mmol NH(*i*-Pr)$_2$) were added to the reaction mixture. At the same time, the solvent volume was restored to initial volume in order to recover the same reagent and palladium concentrations as in the initial run (see Experimental for detailed procedure). Fig. 5 clearly indicated that addition of RAME-β-CD allowed higher recycling potential, demonstrating the stabilising effect. Unfortunately, even in the presence of cyclodextrin, some deactivation, that could not be fully related to mass loss due to sampling, was observed but to a lesser extent. It could be attributed either to effective catalyst deactivation due to the formation of low active palladium aggregates or to the higher viscosity of the solution that prevent efficient mass transfer between the aqueous and organic phase.

To end, with NH(*i*-Pr)$_2$ as the base, we examined the influence of the RAME-β-CD/iodobenzene ratio when decreasing the Pd-catalyst loading to 0.5 mol% (Table 5). A stark effect was observed as generally 6–7 h versus 24 h were enough to achieve quantitative conversion of iodobenzene. Thus, the stabilising effect provided by using RAME-β-CD allowed reducing the palladium concentration without affecting neither the conversion nor the selectivity.

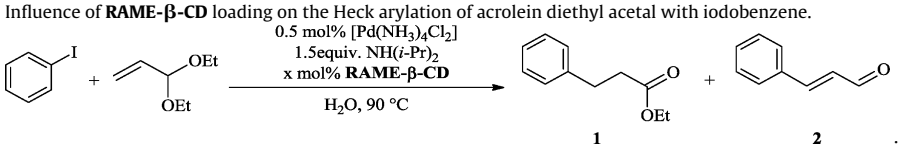
3.4. Influence of the nature of the aryl halide

Finally we evaluated the influence of electron-donating or withdrawing substituents on the aromatic ring (Table 6).

To summarise the results with iodobenzene, using NH(*i*-Pr)$_2$ as the base high conversions and high yields in ester **1** were obtained (Table 6, entries 3–4) whereas in presence of NaOAc as the base the selectivity turn to the aldehyde **2**; however in low conversion except when RAME-β-CD was used as additive (Table 6, entries 1–2). To extend further applications of this procedure, p*ara*-iodoanisole was engaged as a representative of the electron donating derivatives. In the presence NH(*i*-Pr)$_2$ as the base, high conversion towards the expected corresponding ester **1** was achieved; adding RAME-β-CD in the reaction mixture allowed to reduce the reaction time from 24 h to 8 h (Table 6, entries 7–8). With this substrate, we performed a set of reaction using NaOAc as the base. As could be expected, lower conversions were achieved despite the use of RAME-β-CD; but high selectivity towards the aldehyde **2** was observed (Table 6, entries 5–6).

With arylbromides the results are strongly linked to the nature of the substituents, according to Tsai and co-workers who used TBAB as additive for the Heck arylation of *n*-butyl acrylate in water [30]. Bromobenzene was found unreactive under all applied reaction conditions leading to traces of products (Table 6, entries 9–12).

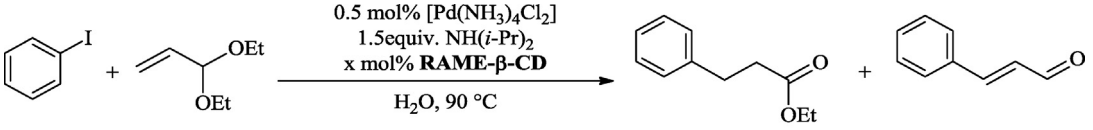
Table 5
Influence of **RAME-β-CD** loading on the Heck arylation of acrolein diethyl acetal with iodobenzene.



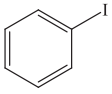
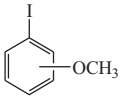
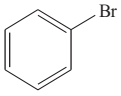
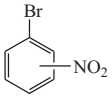
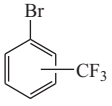
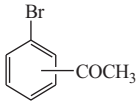
Entries	RAME-β-CD loading (mol%)	Time	Conversion (%)[a]	Selectivity (%)[a] **1**/**2**
1	–	24	83	**61**/33
2	1	7	78	**65**/33
3	10	7	91	**65**/30
4	20	6	100	**65**/33

[a] Conversion and selectivity determined by GC. Dodecane was used as external standard for GC-quantitative determination.

Table 6
Heck arylation of acrolein diethyl acetal with substituted aryl halides in water.



1 **2** .

	ArX	Base	CD	Conversion (%)[a]	Selectivity (%)[a] 1/2
1		NaOAc	–	33	0/**78**
2			RAME-β-CD	86	6/**78**
3			–	100	**70**/27
4		$NH(i\text{-}Pr)_2$	RAME-β-CD	100[d]	**78**/22
5		NaOAc	–	13	0/**100**
6			RAME-β-CD	34	10/**90**
7		$NH(i\text{-}Pr)_2$	–	100	**74**/26
8			RAME-β-CD	100[b]	**75**/25
9		NaOAc	–	2	–
10			RAME-β-CD	0	–
11		$NH(i\text{-}Pr)_2$	–	6.5	–
12			RAME-β-CD	8	–
13		$NH(i\text{-}Pr)_2$	–	100[c]	**90**/10
14			RAME-β-CD	100[c]	**92**/8
15		$NH(i\text{-}Pr)_2$	–	100	**78**/22
16			RAME-β-CD	95[d]	**70**/30
17		$NH(i\text{-}Pr)_2$	–	40	**60**/40
18			RAME-β-CD	70	**74**/26
19		$NH(i\text{-}Pr)_2$	–	53	**65**/35
20			RAME-β-CD	66	**63**/37
21		$NH(i\text{-}Pr)_2$	–	90	**58**/42
22			RAME-β-CD	100[d]	**60**/40

Reaction conditions: 2 mmol ArX, 6 mmol acrolein diethyl acetal, 3.5 mmol base, 2 mol% $[Pd](NH_3)_4Cl_2$, 0 mol% or 10 mol% **RAME-β-CD** as specified, 4 ml water, reflux, 24 h.
[a] Conversion and selectivity determined by GC. Dodecane was used as external standard for GC-quantitative determination.
[b] 8 h.
[c] 120 °C
[d] 6 h.

Particularly, using NaOAc as the base very low conversions were observed, a result that was found to be quite general with substituted aryl bromides, encouraging us to evaluate further only the reaction sets with $NH(i\text{-}Pr)_2$ as the base.

Thus, whatever the nature of the aryl halide, high conversions and good (i.e. 60%) to high (i.e. 92%) selectivities towards the ester **1** were achieved when $NH(i\text{-}Pr)_2$ was used as the base. As expected, electron withdrawing substituents such as NO_2 (Table 6, entries 13–16) or $COCH_3$ (Table 6, entries 21–22) gave the highest conversion under described reaction conditions. Only for *ortho* substituents, higher reaction temperature (i.e. 120 °C) allowed us to achieve full conversion in 24 h (Table 6, entries 13–14). Generally, for these derivatives, the use of RAME-β-CD allowed to reduce the reaction time from 24 h to 6 h for complete conversion. Only the case of CF_3 substituted derivatives gave unexpected low conversions (40% for the *meta*-derivative and 50% for the *para*-derivative – Table 6 entries 17 and 19) despite the high electron withdrawing property of this substituent. This can be noticeably improved by adding RAME-β-CD in the reaction mixture (i.e. 70% and 66%, respectively Table 6 entries 18 and 20).

4. Conclusion

At this stage of our studies, it is interesting to compare the *in* and *ex-aqua* methodologies for the Heck arylation of acrolein diethyl acetal. Both media allowed controlling the selectivity of the reaction towards either the cinnamaldehydes or 3-arylpropanoates either by adapting the catalytic system in organic solvent or by changing the nature of the base when working in water.

To conclude, a procedure for the arylation of acrolein diethyl acetal by the Heck reaction catalysed by the ligandless commercially available $[Pd(NH_3)_4Cl_2]$ in pure water have been developed. Remarkably, by just changing the base we were able to achieve, after optimisation, either the synthesis of cinnamaldehydes **2** {[Pd], NaOAc, RAME-β-CD} or that of ethyl 3-arylpropionate **1** {[Pd], $NH(i\text{-}Pr)_2$}.

The study revealed that the use of CD was critical in the synthesis of cinnamaldehydes to achieve high conversions of aryl halides with high selectivity towards the expected compound. Unfortunately, this study pointed also out that it was limited to aryl iodides since aryl bromides were found to exhibit lower reactivity.

Acknowledgement

The authors gratefully acknowledge the National Agency of Research (CATAQ N° ANR-07-CP2D-0167-01/02) for funding.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.apcata.2013.10.004.

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