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# Influence of the catalytic conditions on the selectivity of the Pd-catalyzed Heck arylation of acrolein derivatives

Sébastien Noël, Laurent Djakovitch* and Catherine Pinel

*Institut de Recherches sur la Catalyse, UPR-CNRS 5401, 2 Avenue Albert Einstein, 69626 Villeurbanne, France*

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**Abstract**—The Heck arylation of acrolein with a variety of condensed aryl and heteroaryl halides is described. Depending on the substrate, up to 87% isolated yield to the expected aldehydes was achieved. When the reaction was run on diethylacetal acrolein, the choice of catalytic system dramatically affected the selectivity of the reaction: the catalyst system based on Herrmann's palladacycle complex gave mainly saturated esters **2**, whereas Cacchi's conditions led to the formation of α,β-unsaturated aldehydes **1**.

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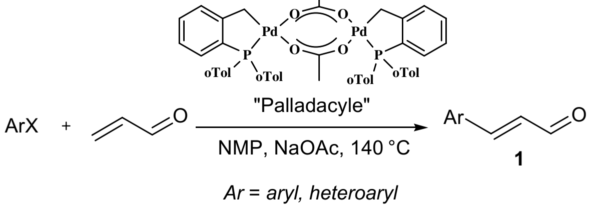
Cinnamaldehyde and its derivatives are important intermediates in the cosmetic, pharmaceutical, and agrochemical industries.[1–3] For example, cinnamaldehyde is commonly used as cinnamon flavoring compound in the food industry, and the *trans*-cinnamaldehyde derivatives possess antifungal or antibacterial properties.

Several methods based on the Perkin and Claisen condensations of aromatic aldehydes have been reported for the synthesis of cinnamaldehyde derivatives at the industrial scale.[4] However, the applicability of these methods remains limited due to the difficult and costly synthesis of the starting materials.[5] Recently several palladium catalyzed syntheses, based on the Heck reaction, have been reported from the acrolein.[6–8] However, this arylation was found in some cases to lead to a mixture of aldehyde and saturated ester under different reaction conditions. Thus, the selective synthesis of aldehydes via the direct palladium-catalyzed Heck arylation of acrolein, under standard reaction conditions (polar solvent, base, commercially available palladium catalyst), would undoubtedly represent a route of choice.

We previously reported results on the Heck arylation of α,β-unsaturated aldehydes, including acrolein, in which we demonstrated that both mono- or di-arylation were possible.[9] The scope of this initial study was limited to the uses of simple aryl bromides. In the present contribution, we report the Heck arylation of acrolein using a large variety of condensed aryl halides and heteroaryl halides, and compare the result to those issued from the Heck arylation of diethyl acetal acrolein under strictly the same reaction conditions.

Initially, the Heck arylation of acrolein using various aromatic and heteroaromatic bromides was studied using the reaction conditions optimized for bromobenzene (1 equiv aryl bromide, 3 equiv acrolein, 1.5 equiv NaOAc, 2 mol % [Pd] cat., 8 mL NMP, 140 °C) (Scheme 1).[9,10] The results are reported in Table 1.

After 6 h, the conversions of the bromoaryl derivatives and the selectivities toward the expected aldehydes are high, with the exception of 1-bromonaphthalene and 9-bromoanthracene: the former led to a low (32%) but



Scheme 1. Heck arylation of acrolein. Reaction conditions: 2.4 mmol aryl halide, 7.2 mmol acrolein, 3.6 mmol NaOAc, 2 mol % Pd-catalyst, 8 mL NMP, 140 °C.

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*Keywords*: Heck arylation; Acrolein; Acrolein diethyl acetal; Cinnamon derivatives; Aromatic compounds; Heteroaromatic compounds.

* Corresponding author. Tel.: +33 4 72 44 53 81; fax: +33 4 72 44 53 99; e-mail: laurent.djakovitch@catalyse.cnrs.fr

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
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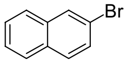
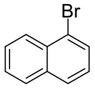
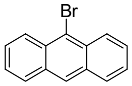
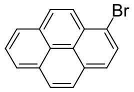
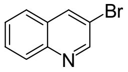
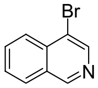
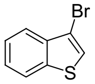
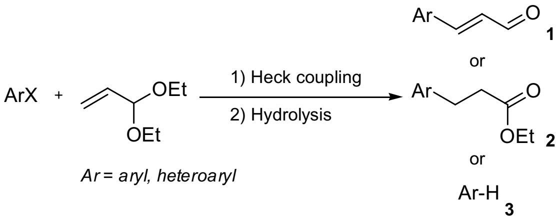
**Table 1.** Heck arylation of acrolein[10] (Scheme 1)

| ArX | Conversion[a] (%) | Product/selectivity[a] (%) | Isolated yield (%) |
|---|---|---|---|
|  | 96 | **1a**/100 | 87 |
|  | 32 | **1b**/100 | 21 |
|  | 35 | Mixture[b] | — |
|  | 90 | **1d**/90 | 67 |
|  | 98 | **1e**/100 | 82 |
|  | 63 | **1f**/100 | 83 |
|  | 73 | **1h**/70 | 40 |

[a] Conversion and selectivity were determined by GC ($\Delta_{rel} = \pm 5\%$).

[b] This reaction gave a mixture of three products (**3c**: 48% and coupling compounds: 52%) that could not be separated from each other.

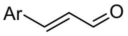
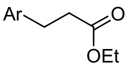
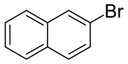
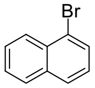
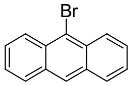
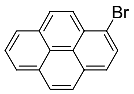
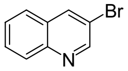
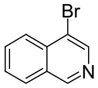
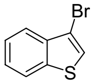


**Scheme 2.** Heck arylation of acrolein diethyl acetal. Reaction conditions: (1) 2.4 mmol aryl halide, 7.2 mmol acrolein, 3.6 mmol base, 2–5 mol % Pd-catalyst (i.e., palladacycle or $Pd(OAc)_2$, KCl, $n$-$Bu_4NOAc$), 8 mL solvent, 90–140 °C. (2) HCl (1 N), $H_2O$.

selective conversion to the expected aldehyde, while the latter led to the formation of a mixture of products with low conversion. Analysis of the product mixture in the latter case showed that anthracene, formed by dehalogenation, was the major product (48%, identified by GC–MS analysis), with the remainder apparently composed of two cross-coupling isomers (further purification and analysis was not undertaken).

No reports concerned the Heck reaction between heteroaryl halides and acrolein, while such coupling products would be highly valuable for the synthesis of important ketolide antibiotics like Cethromycin.[11] As reported in Table 1, all heteroaryl halides, including the benzothiophene, gave reasonable to high isolated yield (40–83%) to the expected aldehydes, thanks to the high conversions (>80%) and selectivities (>70%).

**Table 2.** Heck arylation of acrolein diethyl acetal (Scheme 2)

| ArX | Conditions[a] | Conv.[b] (%) |  1 | Selectivity[c] (%)  2 | Ar-H 3 |
|---|---|---|---|---|---|
|  | Cacchi's A<br>Herrmann's B | 70<br>82 | 83 (32) | <br>85 (75) | 17<br>15 |
|  | Cacchi's A<br>Herrmann's B | 73<br>90 | 86<br>5 | <br>95 | 14 |
|  | Cacchi's A<br>Herrmann's B | 85<br>100 | 40 | 60<br>100 (84) | |
|  | Cacchi's A<br>Herrmann's B | 90<br>95 | 67 (42) | 33<br>100 (95) | |
|  | Cacchi's A<br>Herrmann's B | 100<br>100 | 79<br>15 | 21<br>85 | |
|  | Cacchi's A<br>Herrmann's B | 100<br>85 | 33 | 17<br>100 | 50 |
|  | Cacchi's A<br>Herrmann's B | 100<br>35 | 7<br>5 | 3<br>90 | 90<br>5 |

[a] Reaction conditions: (A) $Pd(OAc)_2$ 5 mol %, $K_2CO_3$, $n$-$Bu_4NOAc$, KCl, DMF, 90 °C, 6 h. (B) 'palladacycle' 2 mol %, NaOAc, NMP, 140 °C, 6 h.

[b] Conversion based on unreacted aryl halide were determined by GC ($\Delta_{rel} = \pm 5\%$).

[c] Selectivity determined by GC. When available, isolated yields (%) are given in brackets.

Given these initial results, we were interested in comparing the direct arylation of acrolein to that of its diethylacetal derivative, both methods affording the same compounds (Scheme 2). Particularly, we compared the methodology used previously ('palladacycle',[12] NaOAc, NMP) to that reported by Cacchi and co-workers,[6] which was based on Jeffery's[13] phase transfer reaction conditions ($Pd(OAc)_2$, $n$-$Bu_4NOAc$, $K_2CO_3$, KCl, DMF), which had been found to be very efficient for the preparation of cinnamaldehydes.

As reported in Table 2, the catalytic system (**A**) described by Cacchi and co-workers[6,7] led to good conversions, and the selectivity was favorable to the formation of the aldehydes, except for the case of 9-bromoanthracene, that afforded a mixture of aldehyde **1** and ester **2** in a 40:60 ratio. High reactivity of heteroarylbromides was also observed with this catalytic system, but in those cases dehalogenation was observed, especially with benzothiophenic bromide.

The nature of the catalytic system dramatically influenced the selectivity of this coupling reaction: in the presence of the Herrmann's palladacycle (system **B**), ester **2** was formed as the main product whatever the substrate.

The formation of saturated ester **2**, rather than aldehyde **1**, for these aryl halides was expectable from previous works described in the literature. Heck and Zebovitz,[14] and later Cacchi and co-workers,[7] correlated the formation of the ester to the hydridic character of the benzylic hydrogen in the carbopalladated adduct type **9** (Fig. 1, route B). However, as can be observed in Table 2, the aldehyde/ester selectivity was affected by the reaction conditions. Cacchi's conditions involved phosphine free catalytic system, for which it is generally admitted that 'naked' palladium acted as active species. The use of a stoichiometric amount of KCl as an additive would favor the formation of the so-called 'anionic' palladium species $\{[L_2Pd^{(0)}Cl]^-, K^+\}$ **4** as the active species in the catalytic cycle, as has been proposed by Jutand (Fig. 1a).[15–19]

In the presence of a phosphine ligand, neutral palladium complexes (type **7**) would be involved as the catalytically active species. However, using the Hermann's palladacycle as catalyst precursor would result in the initial formation of palladium active species coordinated by only one phosphine ligand; these species being stabilized by solvent coordination, as reported recently by Jutand.[20] In that case, we suggest the existence of additional strong interactions between the Pd(II) center and the aromatic ring of the bromo substrates in the carbopalladated adduct **9** (Fig. 1, route B). These interactions 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, thus yielding the ester.

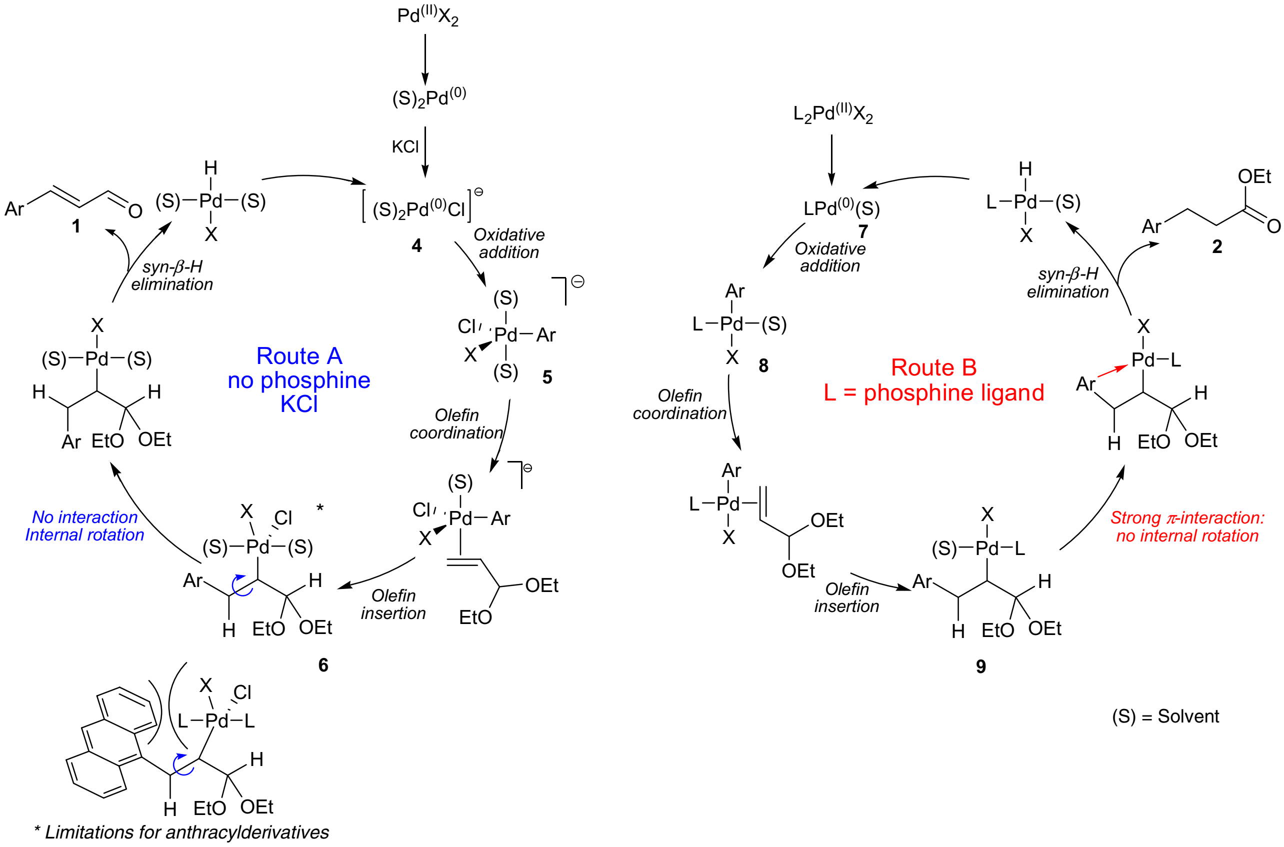


**Figure 1.** Proposed routes for the Heck arylation of acrolein diethyl acetal depending on the catalyst used.

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 (Fig. 1, route A). However, the rotation was also limited with the anthracene derivative due to steric hindrance induced by the condensed aromatic group. The selectivity of the ester/aldehyde is not affected by the nature of the aryl halide, the use of the palladacycle as catalyst leading almost exclusively to the formation of ester **2**, while the use of the Cacchi's catalytic system gives mainly aldehyde **1**. For the latter catalytic system, given that the pentacoordinated anionic Pd(II)-complex **5** center is in equilibrium with the original 'naked' neutral species (type **8**), the ratio of aldehyde **1** to ester **2** probably also depends on the hindrance of the aromatic moiety.

In conclusion, we have shown that the direct arylation of acrolein in the context of the synthesis of cinnamaldehyde derivatives is an efficient procedure. Using the Herrmann's palladacycle as catalyst, aldehydes **1** were prepared with up to 87% isolated yield from condensed aryl halides, and that was extended successfully to heteroaryl halides, like bromoquinolines and bromobenzothiophene (40–83% yield). Using diethyl acetal acrolein as substrate, the selective formation of saturated ester **2** was attained under the same reaction conditions, leading to a very efficient synthesis of the industrially important arylpropionate esters.

## Acknowledgment

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10. Typical procedure for the reaction with acrolein: 2.4 mmol of aryl halide, 7.2 mmol of acrolein, 3.6 mmol of NaOAc and 2 mol % [Pd] as of 'palladacycle' were introduced in a pressure tube under argon. Eight milliliter 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 h under vigorous stirring and then cooled to room temperature before the reaction mixture was analyzed by GC. At completion of the reaction, the mixture was diluted with 150 mL of water and the resulting mixture was extracted with $4 \times 20$ mL $CH_2Cl_2$ or EtOAc. The combined organic layers were washed three times with 15 mL $H_2O$, then 15 mL brine, dried over $MgSO_4$ and evaporated. The residue was then purified by flash chromatography on silica gel. Similar procedure was used for acrolein diethylacetal, except that at completion of the reaction, the mixture was diluted with 150 mL HCl 1 N.
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