

## Revisiting *p*-coumarate esters production by Heck reaction

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### Abstract

Carbon–carbon bond formation reactions between *p*-iodophenol and methyl acrylate using distinct Palladium catalysts in the presence and absence of phosphines were performed in order to optimize the application of the Heck reaction in the preparation of methyl *p*-coumarate. It has been made possible to optimize the reaction in phosphine free systems using homogeneous or heterogeneous palladium sources.

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### 1. Introduction

Carbon–carbon bond forming reactions are key steps in the syntheses of a series of organic compounds, including natural products, with many industrial applications [1,2]. Palladium-catalyzed cross-coupling reaction has emerged over the past 30 years as a one of the most versatile and selective methods for carbon–carbon bond formation in organic synthesis [3–5]. For the construction of carbon–carbon single bond, Heck reaction has become one of the standard protocols in the organic synthesis just as a benchmark to estimate the efficiency of a catalytic system [6–9]. The traditional Heck reaction usually proceeds using phosphine-based palladium catalysts in the presence of a suitable base [10,11]. The main employment of phosphine ligands is to stabilize the Pd(0) as PdL<sub>4</sub>/PdL<sub>3</sub> species, which can enter the catalytic cycle and consequently prevent the formation of inactive palladium black [12,13]. However, the use of phosphorus ligands exhibits serious limitations for industrial applications. They are usually expensive, dif-

ficult to handle (e.g. air sensitive, unstable at high temperature), toxic, and environmentally dangerous [6,14,15].

Therefore, it is not surprising the crescent interest in the development of new (phosphine-free) catalytic systems. Among the new generation of catalytic systems, use of heterogeneous supported palladium (e.g. Pd/C, Pd/Al<sub>2</sub>O<sub>3</sub>, Pd/SiO<sub>2</sub>, Pd/Zeolite [16,17], Pd/CaCO<sub>3</sub> [18,19], and Pd/BaSO<sub>4</sub> [20] as catalyst reservoirs) has been reported to be effective for formation carbon–carbon bond. Other ligand-free Heck catalytic systems have also recently emerged as more advantageous operationally, economically and environmentally [21–27].

There are several examples in which aryl halides bearing electron-donating groups are reported to disfavor the Heck reaction [28–30]. For example, Ziegler and Heck obtained only 5% yield of (*E*)-methyl-*p*-coumarate from the reaction of *p*-bromophenol with methyl acrylate catalyzed by 1 mol% of (AcO)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>Pd [11]. Recently, Tullberg et al. have not observed the coupling product between *p*-iodophenol and aminoacrylates [31].

Considering the fact that *p*-coumarate esters are very important models for the synthesis of natural compounds and the fact that cross-coupling reactions with compounds having electron donor groups are still a challenge, in the

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present study the use of different palladium catalysts was investigated on the Heck reaction between *p*-iodophenol and methyl acrylate with the main objective of finding out suitable phosphine-free systems.

## 2. Results and discussion

Although it is known the existence of several reports claiming that Heck reaction is disfavored in the presence of aryl halides containing strongly electron-donating substituents, we decided to study the Heck reaction among *p*-iodophenol and methyl acrylate using distinct palladium catalysts in presence and in absence of triphenylphosphine (PPh<sub>3</sub>). The reactions were carried out in the *N,N*-dimethylformamide (DMF) solvent using carbonate potassium (K<sub>2</sub>CO<sub>3</sub>) as base at 100 °C during 24 h (Scheme 1).

We have initially investigated the Heck reaction the *p*-iodophenol and methyl acrylate employing homogeneous catalytic systems under conditions described above. It has been shown that all homogeneous palladium catalysts summarized in Table 1 exhibited high catalytic activity, resulting in high conversions. Although best selectivities were obtained using Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub> and Pd(PPh<sub>3</sub>)<sub>4</sub> in presence of PPh<sub>3</sub> (Entries 1, 3, 5, 6 and 7), phosphine-free catalyst systems for the respective Heck reactions presented excellent conversions and good selectivities for the (*E*)-isomer (Entries 2, 4 and 8) so justifying the use of phosphine-free systems [32–35].

In the conditions in which PPh<sub>3</sub> was added (Entries 1, 3, 5 and 7), the pre-catalyst is claimed to be Pd(PPh<sub>3</sub>)<sub>*n*</sub> and reactive species are considered to be unsaturated Pd(PPh<sub>3</sub>)<sub>3</sub> which is able to effect the oxidative addition pathway. Thus, as previously known, PPh<sub>3</sub> stabilizes Pd(0) species [32] and consequently does not allow the formation of inactive palladium black, which in fact occurred in absence of phosphines. In entry 5 it can be seen that further addition of PPh<sub>3</sub> does not have a noticeable effect in reaction yields, that is, it do not jeopardize, kinetically, the oxidative addition step.

Although the homogeneous catalytic systems applied in this study showed to be efficient for the production of the (*E*)-methyl coumarate, we decided to evaluate heterogeneous palladium sources due the fact that our group has been showing that these insoluble sources act as catalysts reservoirs [18,19,33].

Under the reaction conditions described above, different heterogeneous palladium sources (with or without PPh<sub>3</sub> addition) were successfully tested in the coupling of *p*-iodophenol with methyl acrylate. The results are summarized in

Table 1

Influence of the homogeneous palladium catalysts on the Heck reaction between *p*-iodophenol and methyl acrylate

| Entry | [Pd]                               | Conditions <sup>a</sup> | Conversion (%) <sup>b</sup> | Selectivity (%) <sup>c</sup> |
|-------|------------------------------------|-------------------------|-----------------------------|------------------------------|
| 1     | Pd(OAc) <sub>2</sub>               | A                       | 99                          | 99                           |
| 2     | Pd(OAc) <sub>2</sub>               | B                       | 100                         | 72                           |
| 3     | PdCl <sub>2</sub>                  | A                       | 100                         | 99                           |
| 4     | PdCl <sub>2</sub>                  | B                       | 100                         | 95                           |
| 5     | Pd(PPh <sub>3</sub> ) <sub>4</sub> | A                       | 98                          | 99                           |
| 6     | Pd(PPh <sub>3</sub> ) <sub>4</sub> | B                       | 95                          | 99                           |
| 7     | Pd <sub>2</sub> (dba) <sub>3</sub> | A                       | 97                          | 99                           |
| 8     | Pd <sub>2</sub> (dba) <sub>3</sub> | B                       | 97                          | 67                           |

<sup>a</sup> Reaction conditions A: *p*-iodophenol (2.3 mmol), methyl acrylate (11.5 mmol), K<sub>2</sub>CO<sub>3</sub> (6.9 mmol), catalyst (4 mol%), PPh<sub>3</sub> (8 mol%), DMF (7 mL), 100 °C, 24 h. Reaction conditions B: *p*-iodophenol (2.3 mmol), methyl acrylate (11.5 mmol), K<sub>2</sub>CO<sub>3</sub> (6.9 mmol), catalyst (4 mol%), DMF (7 mL), 100 °C, 24 h.

<sup>b</sup> Conversion was determined by GC–MS and GC from the amount of *p*-iodophenol, which did not react.

<sup>c</sup> Selectivity of *E*-isomer was determined by GC–MS and GC.

Table 2. It can also be observed is that in the Heck reactions between *p*-iodophenol and methyl acrylate in the phosphine-free catalytic systems high conversions and good selectivities (Entries 2, 4, 6 and 8 in Table 2) were obtained, so phosphine-free catalytic systems can be considered as good choices for application of this model reaction. At this point it must be stated that in these heterogeneous systems containing Palladium sources, PPh<sub>3</sub> was added to in an attempt to stabilize Pd(0/II) species in solution generated from these sources. It has been

Table 2

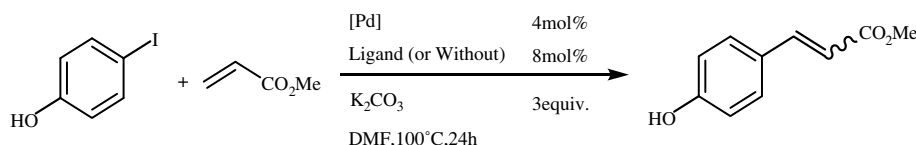
Influence of the heterogeneous palladium catalysts on the Heck reaction between *p*-iodophenol and methyl acrylate

| Entry | [Pd]                 | Conditions <sup>a</sup> | Conversion (%) <sup>b</sup> | Selectivity (%) <sup>c</sup> |
|-------|----------------------|-------------------------|-----------------------------|------------------------------|
| 1     | Pd/C                 | A                       | 96                          | 99                           |
| 2     | Pd/C                 | B                       | 98                          | 98                           |
| 3     | Pd/CaCO <sub>3</sub> | A                       | 98                          | 62                           |
| 4     | Pd/CaCO <sub>3</sub> | B                       | 100                         | 86                           |
| 5     | Pd/BaSO <sub>4</sub> | A                       | 97                          | 81                           |
| 6     | Pd/BaSO <sub>4</sub> | B                       | 100                         | 90                           |
| 7     | Pd/Alumina           | A                       | 99                          | 98                           |
| 8     | Pd/Alumina           | B                       | 100                         | 93                           |

<sup>a</sup> Reaction conditions A: *p*-iodophenol (2.3 mmol), methyl acrylate (11.5 mmol), K<sub>2</sub>CO<sub>3</sub> (6.9 mmol), catalyst (4 mol%), PPh<sub>3</sub> (8 mol%), DMF (7 mL), 100 °C, 24 h. Reaction conditions B: *p*-iodophenol (2.3 mmol), methyl acrylate (11.5 mmol), K<sub>2</sub>CO<sub>3</sub> (6.9 mmol), catalyst (4 mol%), DMF (7 mL), 100 °C, 24 h.

<sup>b</sup> Conversion was determined by GC–MS and GC from the amount of *p*-iodophenol, which did not react.

<sup>c</sup> Selectivity of *E*-isomer was determined by GC–MS and GC.



Scheme 1. Heck reaction between *p*-iodophenol and methyl acrylate.

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