

## The effect of ultrasound on the yields of Heck reaction using Pd-catalyst in DMF/water

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**Abstract:** The heck reaction of aryl bromide with styrene in *N,N*-dimethyl formamide/water as solvent has been studied using different catalysts under ultrasonic irradiation at room temperature. The effect of the solvent, the base, and the catalyst of the transfer phase were studied. The results show that ultrasonic irradiation increases the heck reaction yield and becomes faster with the amount of aliquat-336.

**Keywords:** Arylation; palladium catalysts; ultrasonic activation; phase transfer catalysis.

### Introduction

Heck reaction is one of the most widely used carbon-carbon bond formation methods in organic synthesis<sup>1-7</sup>. The reaction is normally carried out with a palladium catalyst, a phosphine ligand, and a base in a homogeneous solution<sup>8</sup>. Various organic (Et<sub>3</sub>N, NaOAc) and inorganic (K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, and Na<sub>3</sub>PO<sub>4</sub>...) bases<sup>9-12</sup> as well ligands, such as triphenylphosphine, N-heterocyclic carbenes, imine, amine palladacycles, oxime palladacycles, diazabutadine derivatives, 1,4-bis(2-hydroxy-3,5-di-tert-butylbenzyl)piperazine, 1-(2,3-dihydroxypropyl)-3-methylimidazolium hexafluorophosphate, bidentate chelating ligands (O-O, N-O, P-P, N-N)<sup>13-19</sup>, have been employed in the heck reaction.

Ultrasound has recently been utilized to accelerate a number of synthetically useful reactions<sup>8,20-26</sup>. The use of ultrasound in chemistry is commonly known as sonochemistry and their effects observed on organic reactions are due to cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid. Cavitation induces very high local temperatures and pressures inside the bubbles, leading to a turbulent flow in the liquid and enhanced mass transfer<sup>8,25,26</sup>. The sonochemical arylation of active methylene compounds with haloarenes has been extensively investigated<sup>27</sup>. In fact, sonication has been reported to increase the reaction rate and to help avoid the use of high reaction temperatures<sup>8</sup>. Srinivasan et al. have, for instance, reported on the use of ultrasound for heck reactions using Pd(OAc)<sub>2</sub> and an ionic liquid under an argon atmosphere<sup>28</sup>.

The present study was undertaken with the aim of investigating the individual and synergistic effects of catalysis and ultrasound irradiation on arylation reactions of ethylenic compounds.

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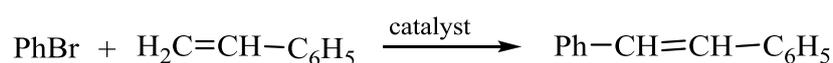
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The more appropriate procedure will be employed for the synthesis of various stilbenes by heck reactions.

## Results and discussion

Different catalysts were studied for heck reaction under ultrasonic irradiation (5min at room temperature) or under thermal condition (2h at 95°C) (table 1). The reactions were performed in DMF/water as solvent in the presence or absence of aliquat-336. Compared to conventional heating, the sonochemical reaction was noted to have a significant effect on the reaction yield. Results are in agreement with those described previously<sup>26</sup>. Moreover, when the amount of Pd(OAc)<sub>2</sub> was doubled, the yield was increased from 78 to 80 % and from 85 to 90% under conventional heating and ultrasound, respectively (table 1, entries 1 and 4). This confirms that the increase in the quantity of the catalyst does not seem to affect greatly reaction yield. Low yields were obtained when PdCl<sub>2</sub> (table 1, entry 2) and PdCl<sub>2</sub>(C<sub>6</sub>H<sub>5</sub>CN)<sub>2</sub> (table 1, entry 3) were used as catalysts. In fact, similar results were reported on in a previous study<sup>29</sup> where the sonochemical arylation of active methylene compounds in DMSO under K<sub>2</sub>CO<sub>3</sub> catalysis was shown to be slightly better than the one achieved with classical reactions. In the same context, Zhang et al. reported that heck reaction occurs under ultrasonic irradiation in aqueous media to afford high yields of corresponding products<sup>30</sup>.



**Table 1.** Effect of different catalysts on the heck reaction.

Entry	Catalyst	Yields <sup>c</sup> (%)	Yields <sup>d</sup> (%)
1 <sup>a</sup>	Pd(OAc) <sub>2</sub>	78	85
2 <sup>a</sup>	PdCl <sub>2</sub>	65	70
3 <sup>a</sup>	PdCl <sub>2</sub> (C <sub>6</sub> H <sub>5</sub> CN) <sub>2</sub>	60	65
4 <sup>b</sup>	Pd(OAc) <sub>2</sub>	80	90

<sup>a</sup> Bromobenzene (10 mmol), styrene (9 mmol), K<sub>2</sub>CO<sub>3</sub> (15 mmol), catalyst (1% mmol), DMF (4 mL), water (4 mL), aliquat-336 (5 mmol).

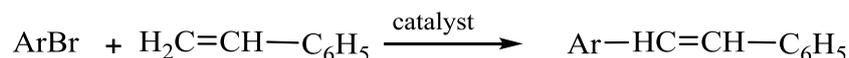
<sup>b</sup> amount of Pd(OAc)<sub>2</sub> was doubled.

<sup>c</sup> (2h, 95°C).

<sup>d</sup> Under ultrasound (5 min at room temperature).

The reactions were also studied in different conditions using different catalysts (table 2). The yields obtained under ultrasonic irradiation were better than those achieved under conventional heating. While good yields of 96 and 99 % were, for instance, observed under conventional heating and ultrasonic irradiation using CNC<sub>6</sub>H<sub>4</sub>Br with Pd(OAc)<sub>2</sub> as catalyst, respectively (table 2, entry 5), low yields (58 and 63%) were obtained using MeOC<sub>6</sub>H<sub>4</sub>Br (table 2, entry 3). As far as the PdCl<sub>2</sub> catalyst was concerned, the highest yield values obtained using CNC<sub>6</sub>H<sub>4</sub>Br were of 92 and 96% for both cases (table 2, entry 13). The yields were, however, noted to decrease up to 54 and 59 %, using conventional heating and ultrasonic irradiation, respectively (table 2, entry 11). This result shows that the CN group is highly efficient for it enhances the stability of aryl bromide. We note that aryl bromide with electron-withdrawing group is more active. This behaviour is presumably due to the stabilization of

Ar-Pd-X intermediate formed by the initial oxidative addition of Ar-X to Pd(0)<sup>3,26</sup>. The regiochemistry of the heck reaction was also be studied under different conditions and using different catalysts. In fact, only the *E*-isomer was observed under ultrasound using MeCOC<sub>6</sub>H<sub>4</sub>Br associated to Pd(OAc)<sub>2</sub> and PdCl<sub>2</sub> (table 2, entries 4 and 12). Excellent regioselectivity was obtained using the Me, MeO, and MeCO groups (table 2, entries 2-4). The yields underwent a marked decrease when Pd(OAc)<sub>2</sub> was substituted by PdCl<sub>2</sub> as a catalyst (table 2, entries 9-14). It is worth noting in this context that ultrasonic waves can generally be used as a tool to influence selectivity and yield of reactions<sup>31</sup>.



**Table 2.** Coupling of aryl bromide and styrene in different condition using different catalysts.

Entry	Ar	Catalyst	Yields <sup>a</sup> (%)	<i>E/Z</i>	Yields <sup>b</sup> (%)	<i>E/Z</i>
1	C <sub>6</sub> H <sub>5</sub>	Pd(OAc) <sub>2</sub>	78	75/25	85	95/5
2	4-MeC <sub>6</sub> H <sub>4</sub>	Pd(OAc) <sub>2</sub>	74	80/20	78	95/5
3	4-MeOC <sub>6</sub> H <sub>4</sub>	Pd(OAc) <sub>2</sub>	58	80/20	63	98/2
4	4-MeCOC <sub>6</sub> H <sub>4</sub>	Pd(OAc) <sub>2</sub>	92	80/20	96	100/0
5	4-CNC <sub>6</sub> H <sub>4</sub>	Pd(OAc) <sub>2</sub>	96	78/22	99	98/2
6	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Pd(OAc) <sub>2</sub>	95	78/22	98	98/2
7	4-HOC <sub>6</sub> H <sub>4</sub>	Pd(OAc) <sub>2</sub>	62	78/22	68	95/5
8	4-H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Pd(OAc) <sub>2</sub>	60	78/22	66	95/5
9	C <sub>6</sub> H <sub>5</sub>	PdCl <sub>2</sub>	80	72/28	85	95/5
10	4-MeC <sub>6</sub> H <sub>4</sub>	PdCl <sub>2</sub>	71	76/24	76	95/5
11	4-MeOC <sub>6</sub> H <sub>4</sub>	PdCl <sub>2</sub>	54	76/24	59	98/2
12	4-MeCOC <sub>6</sub> H <sub>4</sub>	PdCl <sub>2</sub>	88	76/24	92	100/0
13	4-CNC <sub>6</sub> H <sub>4</sub>	PdCl <sub>2</sub>	92	74/26	96	98/2
14	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	PdCl <sub>2</sub>	90	74/26	95	98/2

Reaction conditions: aryl bromide (10 mmol), styrene (9 mmol), K<sub>2</sub>CO<sub>3</sub> (15 mmol), catalyst (1% mmol), DMF (4 mL),

water (4 mL), aliquat-336 (5mmol).

a (2 h, 95°C).

b Under ultrasound (5 min at room temperature).

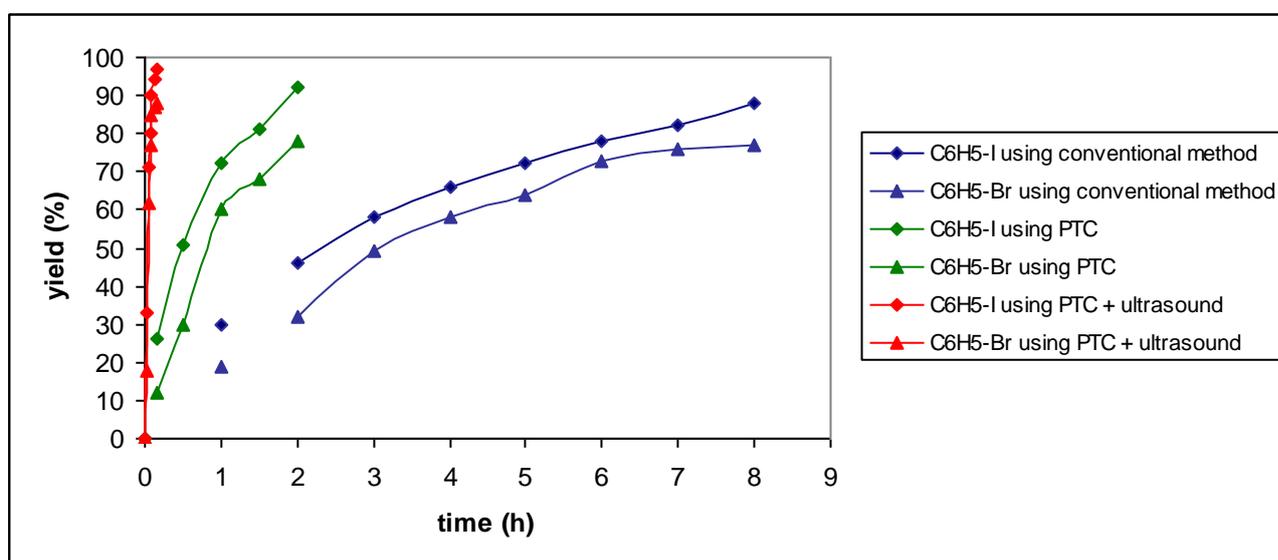
The obtained results revealed that high reaction yields and low reaction time were achieved when aliquat-336 and ultrasonic irradiation were used (figure 1). This significant yield is attributed to the ability of aliquat-336 to mediate mass transfer between the catalyst and the bulk solution responsible for the changes in the reaction time<sup>32,33</sup>. It is also attributed to ability of ultrasound to accelerate the reaction through monoelectronic transfer. In fact, good reaction yields were obtained at short time intervals using aryl iodides as compared to aryl bromides. When the reactions were performed in aqueous media using conventional methods, however, the non-water-soluble aryl iodide gave incomplete conversion rates, slow reaction speeds and low production yields. In fact, the difference between bromide and iodide is attributed to the high reactivity of iodide.

However, the type of the base has a significant effect on the reaction yield (figure 2). Compared to other inorganic bases investigated, potassium carbonate, piperidine,

triethylamine, and potassium acetate were noted to exhibit better activities (higher than 50%). Interestingly, potassium carbonate was the best base for heck reaction and was, therefore, selected and retained for the subsequent further studies. This is, in part, due to the fact that this type of base is active for the heck reaction in the biphasic medium, which is consistent with the results previously described by Hajipour et al.<sup>34</sup> who reported that potassium carbonate gave good reaction yields when palladacycle was used instead of Pd(OAc)<sub>2</sub>. In fact, when triethylamine and sodium acetate were used as a base the reaction yield is low. The findings showed that they gave low reaction yield.

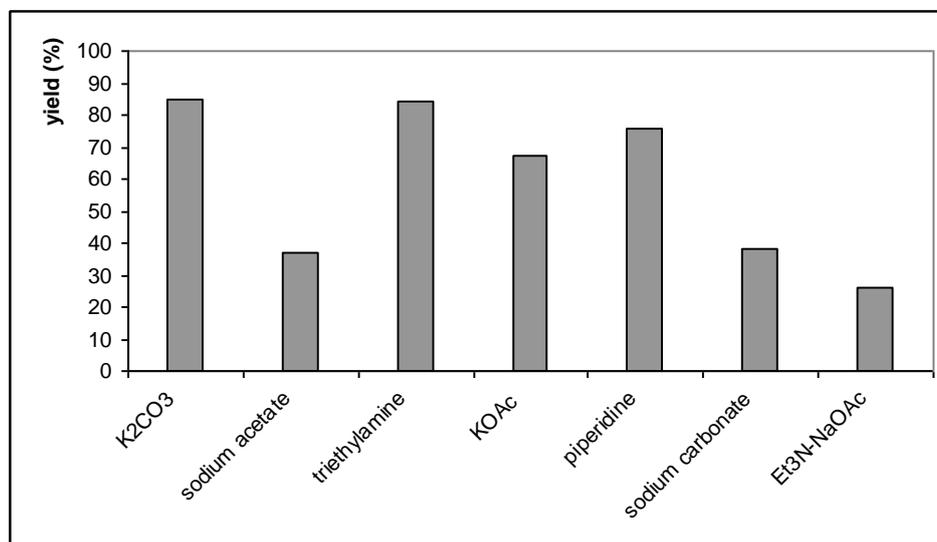
**Figure 1.** Variation in yields depending on the time of heck reaction using different methods using Pd(OAc)<sub>2</sub> catalyst.

Reaction conditions: halobenzene (10 mmol), styrene (9 mmol), K<sub>2</sub>CO<sub>3</sub> (15 mmol), catalyst (1% mmol), DMF (4mL), water (4 mL), aliquat-336 (5mmol), temperature: 95°C. (PTC: aliquat-336).



**Figure 2.** Effect of different bases on the heck reaction.

Reaction conditions: Bromobenzene (10 mmol), atyrene (9 mmol), Pd(OAc)<sub>2</sub> (1% mmol), base (15 mmol), DMF (4 mL), water (4 mL), aliquat-336 (5 mmol), room temperature, ultrasonic irradiation, 5 min.



## Conclusion

The present study aimed to investigate the individual and combined effects of catalysis and ultrasound irradiation on arylation reactions of ethylenic compounds. The findings demonstrate that ultrasound can facilitate the homogeneity of heck reaction when aryl halides are coupled with methyl styrene in DMF/water as solvents using different catalysts. Tables 1 and 2 clearly show that the reaction yields achieved through the ultrasonic irradiation method are higher than those attained via the more conventional ones. The *E*-isomer was only obtained under the ultrasound method using MeCOC<sub>6</sub>H<sub>4</sub>Br coupled with styrene for different catalysts. The reaction was also observed to become faster when ultrasound and Aliquat-336 were used. Different bases were also investigated in terms of their effects on heck reaction and the best yields were obtained with K<sub>2</sub>CO<sub>3</sub>.

## Experimental

### General procedure:

The coupling reaction of aryl halides (10 mmol) and styrene (9 mmol) were carried out in DMF/Water (4 mL/4 mL) with catalyst (1% mol), K<sub>2</sub>CO<sub>3</sub> (15 mmol), Aliquat-336 (5mmol) for 2h at 95°C. The reaction mixture was extracted with water and brine and dried over anhydrous magnesium sulphate. The solution was filtered, the solvent was evaporated, and the product was purified by flash chromatography (hexane /ethyl acetate) or recrystallization.

### Ultrasonic irradiation:

The method remains identical except that the reaction mixture was submitted to ultrasonic irradiation during 5 min at room temperature.

All compounds were characterized by IR, <sup>1</sup>H NMR spectra, and <sup>13</sup>C NMR spectra. <sup>1</sup>H NMR spectra (300 MHz) and <sup>13</sup>C NMR (75MHz) spectra were recorded on an AC 300 Brüker spectrometer in CDCl<sub>3</sub>, using tetramethylsilane (TMS) as an internal reference. IR spectra were recorded on a JASCO FT-IR-420 device in KBr pellets. The melting points were taken on a Reichert-Heizbank apparatus.

All products were confirmed by comparing their melting points, <sup>1</sup>H NMR and <sup>13</sup>C NMR data with literature data<sup>3,13,25,26</sup>.

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