

Letter

Effect of triphenylphosphine concentration on the kinetics of homogeneous Heck reaction in different solvents

Fengyu Zhao, Bhalchandra M. Bhanage, Masayuki Shirai, Masahiko Arai *

Institute for Chemical Reaction Science, Tohoku University, Katahira, Aoba-ku, Sendai 980-8577, Japan

Received 11 June 1998; accepted 24 September 1998

Abstract

The vinylation of methyl acrylate and iodobenzene was studied using the homogeneous Pd(OAc)₂ catalyst in octane, toluene, *N*-methylpyrrolidone, acetonitrile, ethanol and *N,N'*-dimethylacetamide solvents with various triphenylphosphine (PPh₃) concentrations. In polar solvents the rate of reaction is very high as compared with nonpolar solvents. In polar solvents the rate of reaction shows significant drop with increase in PPh₃ concentration whereas in nonpolar solvents it passes through a maximum at a PPh₃/Pd ratio of 2. There is no effect of different bases such as Et₃N and KOAc on the dependence of the rate of reaction on the PPh₃/Pd ratio. These results are explained based on Heck reaction mechanism previously proposed. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Heck reaction; Phosphine ligands; Palladium; Solvent effects; Aryl halides

1. Introduction

Heck reaction has received considerable attention in recent years as it offers versatile method for generating new C–C bond [1,2]. Cinnamic esters, derived from aryl halide and alkyl acrylates, are used as UV absorbers, antioxidants in plastic, and intermediates in pharmaceuticals [3]. Intramolecular Heck reaction is a key step in synthesizing basic tricyclic skeleton of taxol molecule [4]. It is also useful in synthesis of new antitumor antibiotic CC-1065 [5]. Hoechst is about to commercialize the two phase catalysed Suzuki coupling reaction [6]. Many researchers reported important role of solvents during their studies on Heck vinylation reactions [1,2,7–9]. Most of these studies deal with optimizing best solvent. Dipolar aprotic solvents such as dimethyl formamide (DMF), *N*-methylpyrrolidone (NMP), dimethyl sulfoxide and acetonitrile are very common solvents used in the Heck

* Corresponding author. Tel.: +81-22-217-5630; Fax: +81-22-217-5631; E-mail: marai@icrs.tohoku.ac.jp

Table 1
Solvents used and their dielectric constant and dipole moment [11,12]

Solvent	Dielectric constant	Dipole moment
Octane	1.948 (20°C)	0D (20°C)
Toluene	2.379 (25°C)	0.37D (r.t.)
Ethanol	24.55 (25°C)	1.66D (20°C)
Propionitrile	27.2 (20°C)	3.57D (20°C)
NMAc	–	3.79D (30°C)
NMP	31.5 (r.t.)	4.09D (r.t.)
Acetonitrile	37.5 (25°C)	3.44D (20°C)

vinylation. Ohrai et al. [10] have reported effects of solvents and additives in asymmetric Heck reaction of alkenyl triflates. They observed different product distribution according to polarity of solvent. Herrmann et al. [9] have reported the influence of PPh_3/Pd ratio in Heck reaction in *N*-methylacetamide solvent system (PPh_3 : triphenylphosphine). They observed that the rate of reaction drops significantly with increase in this ratio. In the present paper we wish to report new results on kinetics of Heck reaction in different solvent systems with variable PPh_3 concentration. These data are useful in selection of better solvent and PPh_3/Pd ratio as well as give many indirect evidences that support proposed Heck reaction mechanism [1,2].

Table 2
Results of Heck reactions of iodobenzene and methyl acrylate with a base of Et_3N in different solvents

Solvent	Reaction temperature (°C)	$\text{PPh}_3/\text{Pd}(\text{OAc})_2$ ratio (–)	Initial rate of reaction ($\text{mol m}^{-3} \text{ s}^{-1}$)	Conversion (%)	TON ($\text{mol mol}_{\text{Pd}}^{-1}$)
Octane	95	0 ^a	0	0	0
		2	1.57	11.3	45
		4	0	0	0
Toluene	95	0 ^a	1.20	17.5	70
		2	2.40	39.7	159
		4	1.48	21.9	88
Ethanol	60	0 ^b	0.62	5.70	23
		2	4.80	24.3	97
		4	0	0	0
Propionitrile	85	0 ^a	3.70	24.5	98
		2	19.0	83.2	333
		4	0	0	0
NMAc	85	0	81.0	100	> 400
		2	75.0	95.1	380
		4	16.3	93.6	374
NMP	60	0	16.7	99.3	397
		2	4.48	73.9	296
		4	2.82	68.9	276
Acetonitrile	75	0 ^b	2.80	11.5	46
		2	11.0	65.5	262
		4	0	0	0

Conversion and TON: data obtained after 60 min.

^{a,b}Pd metal precipitated during and before reaction, respectively.

$\text{Pd}(\text{OAc})_2$: 0.05 mmol; PPh_3 : 0.10 mmol; iodobenzene: 20 mmol; methyl acrylate: 20 mmol; Et_3N : 20 mmol; solvent: 15 cm^3 .

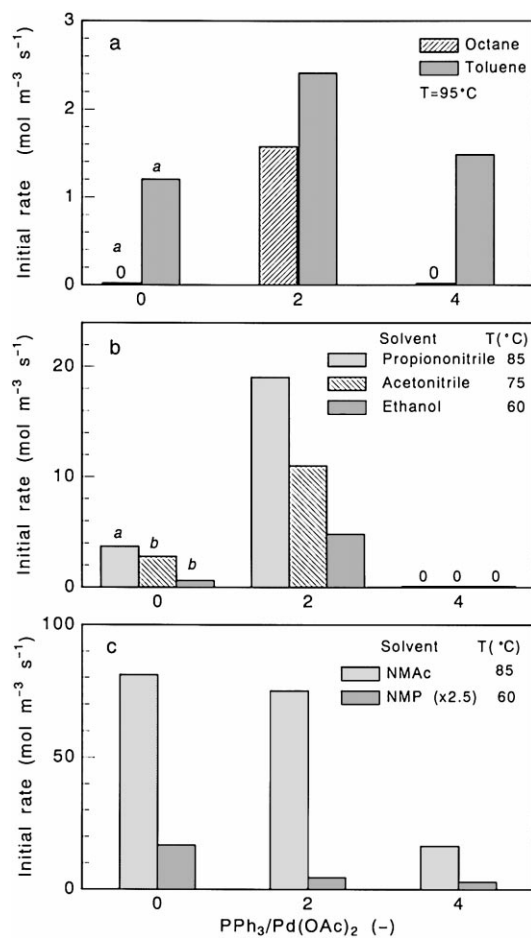


Fig. 1. Influence of PPh₃/Pd ratio on the initial rate of Heck reaction of iodobenzene and methyl acrylate with a base of Et₃N in different solvents at temperatures given. In some cases at PPh₃/Pd = 0 marked with *a* and *b*, Pd catalyst was observed to precipitate to Pd metal during and before reaction, respectively.

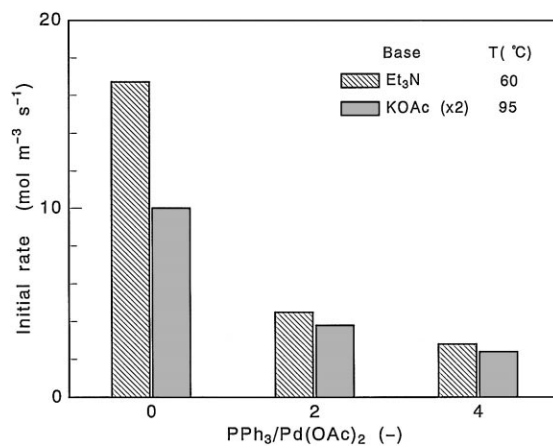


Fig. 2. Initial rates of Heck reaction of iodobenzene and methyl acrylate in NMP using Et₃N and KOAc as bases at 60°C and 95°C, respectively.

2. Experimental

All chemicals and solvents were purchased from Wako Pure Chem., Japan and used without further purification. Solvents used are shown in Table 1, which were distilled and degassed before use. In a well agitated glass reactor with sampling provision, Pd(OAc)₂ (0.05 mmol), PPh₃ (0.1 mmol), iodobenzene (20 mmol), methyl acrylate (20 mmol), triethylamine (20 mmol) and solvent 15 cm³ were added. The reaction was carried out for 60 min at 60–95°C depending on the solvent under argon atmosphere. Reaction mixture was sampled at various time intervals and analyzed using GC (Yanaco G3800, Silicone OV-1, 6 m). The initial rate of reaction was calculated for first 20% conversion by time sampling at different intervals.

3. Results and discussion

Homogeneous palladium catalyzed vinylation of iodobenzene with methyl acrylate was studied for different solvent systems in which the concentration of PPh₃ ligand was changed.

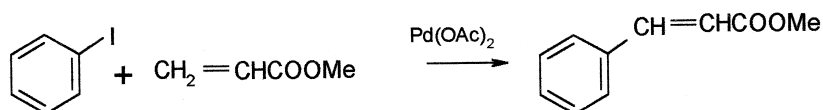
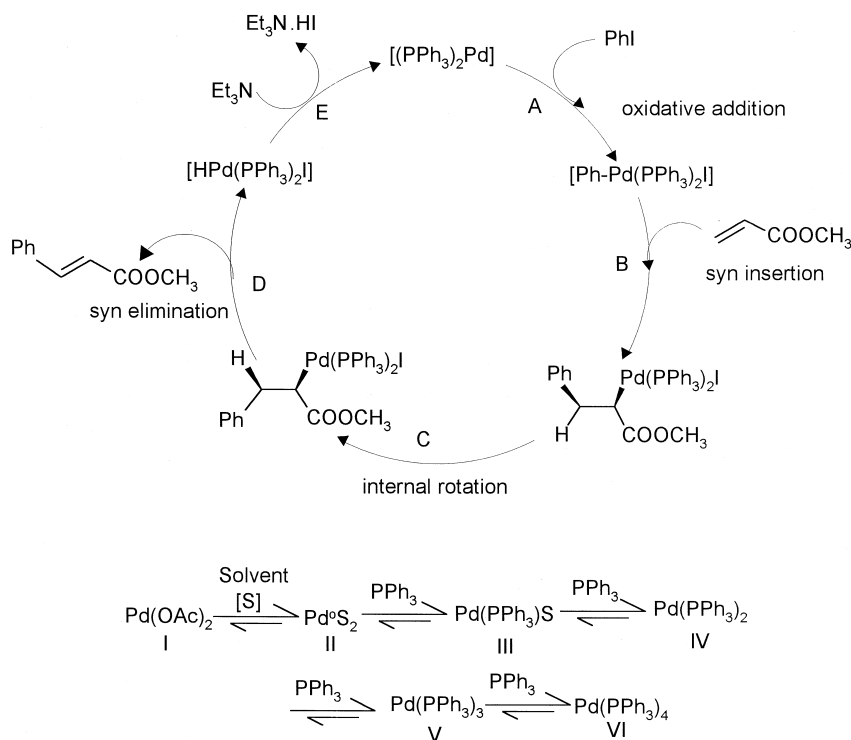


Table 2 shows data on the initial reaction rate, conversion and TON obtained in various solvents, indicating that the rates of reaction in polar solvents such as *N,N'*-dimethylacetamide (NMAc) and *N*-methylpyrrolidone (NMP) are even larger than those in nonpolar solvents. It is also indicated that the ligand concentration has strong impact on the rate of reaction in different manners depending on the solvent used. Fig. 1a shows the rate of reaction with different PPh₃/Pd ratio in nonpolar solvents such as toluene and octane. The rate of reaction passes through a maximum at a PPh₃/Pd ratio of 2. Fig. 1c indicates the results with different PPh₃/Pd ratio in polar solvents such as NMAc and NMP. In these cases the rate of reaction decreases with increase in PPh₃/Pd ratio. Fig. 1b indicates the data in polar solvents such as propionitrile, acetonitrile and ethanol. In these solvents, the reaction is not due to active homogeneous catalyst at PPh₃/Pd = 0, as the homogeneous catalyst is not stable and precipitates to Pd metal. At PPh₃/Pd = 2, 4, however, the catalyst was not shown to precipitate to Pd metal. Effect of two different bases of Et₃N (organic base) and KOAc (inorganic base) on the rate of reaction in NMP is shown in Fig. 2. Similar decreases with the PPh₃/Pd ratio were observed irrespective of the nature of base used.

These results can be explained on well-accepted mechanism of Heck reaction given in Scheme 1 [1,2]. The solvents are known to coordinate Pd and form different types of active catalytic species. Reduction of Pd(OAc)₂ to active Pd(0) species such as Pd⁰S₂ (II) proceeds fast and reducing agents known for this process include phosphine ligands [9,13], olefinic substrates [14], amines [15] and solvent [10]. The results observed can be explained based on the equilibrium sequence I to VI shown in Scheme 1. In polar solvents such as NMAc and NMP active species equilibrium shifts towards II, Pd⁰S₂, active species and without any PPh₃ ligand. These polar solvents have better Pd stabilizing tendency as compared with acetonitrile, propionitrile and ethanol. In the cases of acetonitrile and ethanol, these solvents are not able to coordinate with Pd and precipitate Pd metal before reaction. Hence at PPh₃/Pd = 0, the rate of reaction is not so high as compared with NMAc and NMP. In



nonpolar solvents equilibrium between I and II is more favored towards I as there is weak coordination of solvent with catalyst, hence rate of reaction is much lower as compared to polar solvents. With the addition of 2 equivalent of PPh_3 in the reaction mixture equilibrium moves from highly active Pd^0S_2 (II) to active $\text{Pd}(\text{PPh}_3)_2$ (IV), well characterized compound [2]. In polar solvents this reduces reaction rate since activity of Pd^0S_2 (II) is more than $\text{Pd}(\text{PPh}_3)_2$ (IV). However stability of such catalyst is very high. In nonpolar solvents, formation of $\text{Pd}(\text{PPh}_3)_2$ (IV) occurs with the addition of strong coordinating ligands like PPh_3 and hence the reaction rate increases. It is interesting to note that the rate of reaction is more or less in the same range irrespective of the nature of solvent and the PPh_3/Pd equal to 2 indicating species $\text{Pd}(\text{PPh}_3)_2$ (IV) is a major contributor to catalytic cycle. With further increase in the ligand concentration the equilibrium shifts from $\text{Pd}(\text{PPh}_3)_2$ (IV) to $\text{Pd}(\text{PPh}_3)_4$ (V) from active catalytic species to inactive catalytic species and hence the reaction rate drops significantly. We observed that the reaction rate did not change at PPh_3/Pd ratios above 4. Fig. 2 shows the effect of different types of bases such as KOAc and Et_3N on the rate of reaction with variable PPh_3/Pd ratios in NMP solvent, indicating similar changes of the reaction rate irrespective of the nature of base used. This indicates that the base takes part in reductive elimination of HX (step E, Scheme 1). In Fig. 3, we correlated the initial rate of reaction in different solvents with respect to dielectric constant and dipole moment. Although the reaction temperatures are different, one can say that the rate of reaction depends strongly on the polarity of solvent used at a PPh_3/Pd ratio of 2 but less strongly at a higher PPh_3/Pd ratio of 4. The data for $\text{PPh}_3/\text{Pd} = 0$ is not included because in many cases Pd species precipitate to Pd metal and hence the reactions are not true homogeneous catalytic reactions.

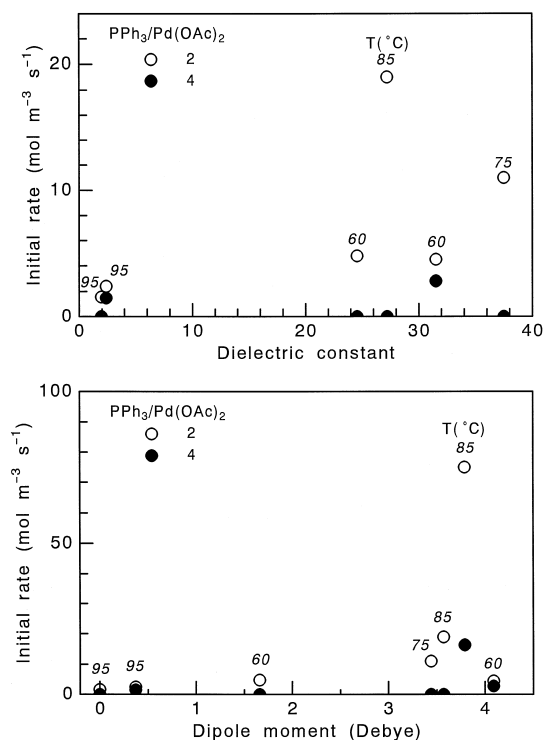


Fig. 3. Correlation of the initial rate of Heck reaction with the dielectric constant and dipole moment of the solvent used. Open and closed circles indicate the results at PPh₃/Pd ratios of 2 and 4, respectively, and italic figures given show reaction temperatures.

In conclusion, the rate of Heck reaction in polar solvents is very high and decreases with increase in PPh₃/Pd ratio and in nonpolar solvents it passes through a maximum due to the formation of active Pd(PPh₃)₂ species, which later converts to Pd(PPh₃)₄ inactive species.

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