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Application of dimeric *ortho*-palladated complex of 2-methoxyphenethylamine in the Heck coupling reaction

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ABSTRACT

The application of the $[Pd\{C_6H_3(CH_2CH_2NH_2)\text{-}4\text{-}OMe\text{-}5\text{-}\kappa^2\text{-}C,N\}(\mu\text{-}Br)]_2$ complex of 2-methoxyphenethylamine in the Heck coupling reaction was considered under both conventional and microwave irradiation conditions, and their results were compared. This complex is an efficient, stable and non-sensitive to air and moisture catalyst for the vinylation of substituted aryl halides with different electronic properties. The cross-coupled products were produced in good to excellent yields using a catalytic amount of this complex in *N*-methyl-2-pyrrolidone (NMP) at 130 °C. In comparison to conventional heating conditions, the reactions under microwave irradiation gave higher yields in shorter reaction times.

Keywords: Heck reaction, 2-Methoxyphenethylamine, Cyclopalladated complex, Catalyst, Microwave irradiation.

1. Introduction

In modern organic synthesis, palladium-catalyzed cross-coupling reactions are of the most versatile and efficient methods for carbon-carbon bond formation [1-5]. Amongst them, the Heck reaction is one of the most powerful tools in synthetic chemistry for constructing aromatic carbon-carbon bonds [6-12], especially in the synthesis of pharmaceuticals, agrochemicals, complex natural products, heterocycles, dyes and novel materials [9,11-13]. Much effort has been devoted to finding new catalytic systems and methodologies to improve Heck reaction conditions. Various approaches towards catalyst improvement have been described including the use of sterically hindered phosphanes [14], heterogeneous catalysts such as Pd/C [15], nanostructured palladium clusters [16], *N*-heterocyclic carbenes (NHC) [17] and palladacycles. Among the new methods, the palladacycle catalysts are important class of catalysts that used as very efficient catalysts with very low concentration in organic synthesis and material science [18,19]. Phospha-palladacycles were investigated as excellent catalysts in C–C coupling reactions [20-22]. Because of the sensitivity of phosphine-based ligands to air and/or moisture, in recent years, phosphine-free ligands such as *N*-heterocyclic carbenes (NHCs) or nitrogen-donor ligands have also been employed. Although carbene-type ligands are more stable than phosphines, they must be synthesized through multi-step processes [23,24]. The high productivity of the palladacycle catalysts is due to the slow generation of low ligated Pd(0) complexes from a stable palladium(II) pre-catalyst [25]. Transition-metal-catalyzed cross-coupling reactions usually require long reaction times and an inert atmosphere to reach complete conversion with traditional heating. Microwave-assisted heating under controlled conditions is an alternative to traditional heating. The real advantage of microwave irradiation is that it is quicker and cleaner than conventional heating, reducing reaction times, yielding products in high yields with less side products and increasing the selectivity. The use of homogeneous metal catalysts in conjunction with microwaves leads to an increased lifetime of the catalyst [25,26]. In continuation of our recent investigations on the synthesis of the palladacycle catalysts, and application of these complexes in microwave assisted cross coupling reactions [27-32], we now wish to report the extension of *ortho*-palladated complex, $[Pd\{C_6H_3(CH_2CH_2NH_2)\text{-}4\text{-}OMe\text{-}5\text{-}\kappa^2\text{-}C,N\}(\mu\text{-}Br)]_2$ (**A**) homogeneous complex, as a thermally stable and oxygen insensitive catalyst for the cross-coupling reaction of various aryl halides with olefins under both conventional and microwave irradiation conditions.

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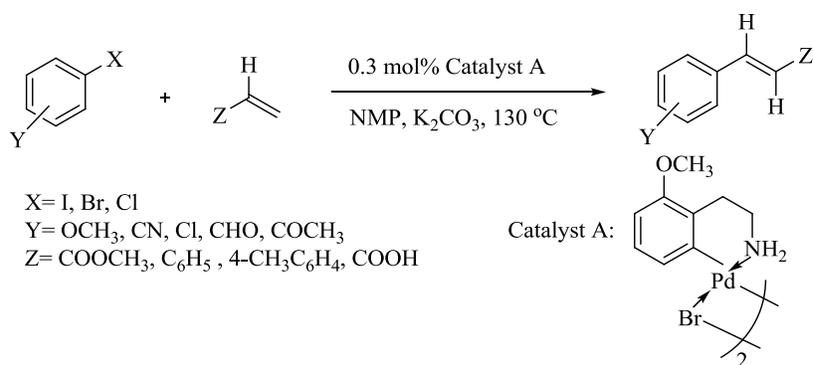
Scheme 1. The Heck cross-coupling reaction.

2. Experimental

All melting points were determined in open capillaries with a Gallenkamp instrument and were uncorrected. The FT-IR adsorption spectra were run on a spectrophotometer (Jasco-680, Japan) as KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker, 500 and 125 MHz, respectively; using CDCl$_3$ as solvent at room temperature (TMS was used as an internal standard). Also we used GC (BEIFIN 3420 Gas Chromatograph equipped a Varian CP SIL 5CB column- 30 m, 0.32 mm, 0.25 μm) for examination of reaction completion. Microwave experiments were carried out using a Microwave Labstation for Synthesis (Milestone microwave). All chemicals were purchased from Merck, Aldrich and Acros and were used as received.

2.1. General procedure for the Heck reaction of aryl halides with olefins

In a round-bottom flask equipped with a magnetic stirring bar to a mixture of aryl halide (1 mmol), olefin (2.5 mmol) and K$_2$CO$_3$ (1.1 mmol) in NMP (3 ml) was added 0.3 mol% of palladacycle complex **A** and equipped with a condenser for refluxing in Milestone microwave or an oil bath. Initially, the microwave irradiation was set at 500 W and the temperature was ramped from room temperature to the desired temperature of 130 °C. Once this was reached, the reaction mixture was held at this temperature until the reaction was completed. During this time, the power was modulated automatically to keep the reaction mixture at 130 °C. The reaction progress was followed by TLC (hexane/EtOAc, 4:1, as eluent) and GC. After completion of the reaction, the mixture was cooled to room temperature and was diluted with n-hexane and water. Then the organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated under reduced pressure using rotary evaporator to give the crude product that was purified by recrystallization from ethanol. All synthesized cross-coupled products were characterized by spectral data (IR, ^{1}H and ^{13}C NMR), their melting points and comparison them with authentic samples [33-38].

3. Results and Discussion

In our previous work, we synthesized [Pd{C$_6$H$_2$(CH$_2$CH$_2$NH$_2$)–(OMe)$_2$,3,4} (μ-Br)]$_2$ and investigated its application in different coupling reactions including Heck reaction [31,32]. In this complex, the electron donating nature of OCH$_3$ group in *ortho* position, makes the C-Pd bond stronger. So, in this complex the C-Pd bond dissociation occurs later and leads to lower reaction rates. The search for new complexes in order to overcome these deficiencies lead us to [Pd{C$_6$H$_3$(CH$_2$CH$_2$NH$_2$)-4-OMe-5-κ^2-C,N}(μ-Br)]$_2$ which catalyzed the Heck reactions very faster than the former complex. Meanwhile, in homoveratrylamine (3,4- dimethoxyphenethylamine) ligand, there are two position for forming the palladacycle, while in 2- methoxyphenethylamine, only one palladacycle can be formed. Furthermore, the latter complex has easier procedure for synthesis and purification.
[Pd{C$_6$H$_3$(CH$_2$CH$_2$NH$_2$)-4-OMe-5-κ^2-C,N}(μ-Br)]$_2$ (**A**) as a palladacycle complex was synthesized according to our previous work [27]. The application of this complex as a catalyst for the Heck reaction of various types of aryl halides with different olefins was examined (Scheme 1).

Table 1. The solvent and base effects in the Heck reaction of iodobenzene with methyl acrylate [a].

Entry	Base	solvent	Temperature (°C)	Time (min)	Conversion[b] (%)
1	K$_2$CO$_3$	NMP	130	20	96
2	K$_2$CO$_3$	DMF	130	20	87
3	K$_2$CO$_3$	CH$_3$CN	Reflux	20	40
4	K$_2$CO$_3$	Toluene	Reflux	20	20
5	NaOAc	NMP	130	20	88
6	Cs$_2$CO$_3$	NMP	130	20	100

[a]Reaction were carried out with iodobenzene (1 mmol), methyl acrylate (2.5 mmol), base (1.1 mmol) in solvent (3.0 mL).
[b]Determined by GC

Table 2. The effect of concentration of catalyst in the Heck reaction of 4-iodoanisole with methyl acrylate [a].

catalyst mol%	Time (min)	Temperature (ºC)	Conversion[b] (%)
None	30	130	0
0.05	30	130	48
0.1	30	130	68
0.2	30	130	83
0.3	30	130	97
0.4	30	130	100

[a]Reactions were carried out with 4-iodoanisol (1.0 mmol), methyl acrylate (2.5 mmol), K_2CO_3 (1.1 mmol) and various concentration of palladacycle **A** in NMP (3.0 mL).
[b]Determined by GC

In order to improve the efficiency of the reaction, the solvent and base effects were both optimized. Initially, the Heck reaction conditions were optimized for the reaction of iodobenzene and methyl acrylate in the presence of various solvents and bases using 0.4 mol% of catalyst. Several organic solvents such as toluene, acetonitrile, *N,N*-dimethylformamide (DMF) and *N*-methyl-2-pyrrolidone (NMP) were examined. The results showed that NMP was the best solvent for the Heck reaction. An investigation of

the effect of base indicated that although K_2CO_3 and Cs_2CO_3 have approximately the same efficiency in their reactions, K_2CO_3 was chosen as the best base for Heck reaction since Cs_2CO_3 is more expensive (Table 1).

The concentration of catalyst was also optimized by employing various amounts of catalyst (**A**) for the reaction of 4-iodoanisole and methyl acrylate. In this reaction, 0.3 mol% of catalyst (**A**) gave the best result (Table 2). Since this catalyst is not sensitive to oxygen, the reactions were carried out under an air atmosphere.

These reaction conditions were applied in the Heck reaction of different types of aryl halides under both conventional and microwave irradiation conditions (Table 3).

Various attempts have been made to find better catalysts for coupling aryl chlorides which are cheaper, more easily available and more industrially important than bromides and iodides in the Heck reaction. Aryl chlorides react very slowly with palladium catalysts due to the strength of the C–Cl bond which delays the oxidation addition to Pd(II) complexes. We investigated the reactivity of the palladacycle complex **A** in the Heck coupling of aryl chlorides (chorobenzene and 4-chloroacetophenone) with methyl acrylate and styrene under thermal heating and microwave irradiation conditions (Table 3, entries 3, 8 and 15). The reaction of methyl acrylate with activated 4-chloroacetophenone slower than that chlorobenzene because

Table 3. Heck reaction of various aryl halides with different olefins using catalyst **A**[a].

Entry	X	Y	Z	Time (min) (Yield(%)[b])		m.p. (°C)
				Oil bath	MW	
1	I	H	CO_2Me	30(93)	1(95)	34-37
2	Br	H	CO_2Me	45(90)	2(92)	34-37
3	Cl	H	CO_2Me	90(85)	4(89)	34-37
4	Br	4-CN	CO_2Me	25(87)	3(92)	118-120
5	Br	4-CHO	CO_2Me	75(89)	5(94)	84-85
6	Br	$3-CH_3CO$	CO_2Me	80(83)	12(87)	oil
7	Br	$4-CH_3CO$	CO_2Me	60(89)	4(91)	30-33
8	Cl	$4-CH_3CO$	CO_2Me	180(58)	15(67)	30-33
9	Br	3-Cl	CO_2Me	25(89)	3(92)	oil
10	Br	4-Cl	CO_2Me	40(90)	5(91)	74-76
11	I	$4-CH_3O$	Ph	120(75)	8(81)	132-134
12	Br	4-CN	Ph	90(81)	10(91)	116-118
13	Br	4-CHO	Ph	110(88)	12(90)	111-112
14	Br	$4-CH_3CO$	Ph	80(83)	10(87)	138-141
15	Cl	$4-CH_3CO$	Ph	200(51)	30(59)	138-141
16	I	$4-CH_3O$	$4-CH_3C_6H_4$	150(80)	15(83)	132-134
17	I	H	$4-CH_3C_6H_4$	80(85)	7(91)	120-122
18	I	H	COOH	30(79)	8(82)	130-133

[a]Reaction conditions: aryl halide (1 mmol), olefin (2.5 mmol), K_2CO_3 (1.1 mmol), 0.3 mol% palladacycle **A**, NMP (3 mL), 130ºC.
[b]Isolated yields.

Table 4. Comparsion of various catalysts in *trans*-4-acetylstilbene formation

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)	Ref.
1		DMAc	130	72	86	20
2		DMAc	130	16	52	20
3		DMF	125	24	82	39
4		NMP	130	10	80	31
5	Palladacycle catalyst **A**	NMP	130	1:20	80	This work
6	PdCl$_2$/IL[a]	—	120	10	72	40
7	Pd(OAc)$_2$/LHX[b]	H$_2$O	100	3	93	41

a)
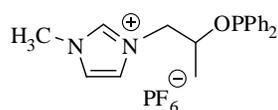
b)
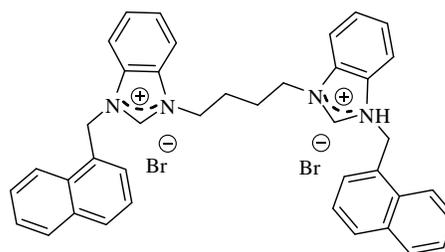
in the rate determinig step of the reaction i.e. oxidative addition reaction, different groups should be bind to Pd in the mechanism of the reaction. So, in the case of the acetophenone derivative, the presence of more steric hiderance on the substrate can slow down the reaction rate; however there is not such hinderance in the chlorobenzene; so this reaction was completed faster than 4-chloroacetophenone. Under this condition, moderate yields of the desired products were obtained. The chemo-selectivity of the procedure was examined using chloro-bromobenzene derivatives. In the case of 1-bromo-3-

chlorobenzene and 1-bromo-4-chlorobenzene, only the Br was substituted in each case using stoichiometric amount of olefins, though this procedure could in principle activate the C-C1 bond (Table 3, entries 9 and 10).

The results summarized in Table 3 show that the use of homogenous metal catalysts in conjunction with microwave irradiation, in comparison to conventional heating conditions, led to reduced reaction times. The dramatic rate enhancement is due to the rapid and uniform heating of the reaction mixture and increased catalyst lifetime by the elimination of wall effects in a microwave versus oil-bath

heating. Microwave irradiation raises the temperature of the whole volume simultaneously (bulk heating) whereas in the oil-heated tube, the reaction mixture in contact with the vessel wall is heated first [26].

A constant temperature program was set for all reactions. Temperature control of the reaction mixture was carried out with the IR sensors using a software enabling us to directly monitor the temperature and pressure of the reaction mixture. This is gained by regulation of microwave power out-put. The monitoring system for reaction times, temperature and power in microwave reactor led to an excellent control of reaction parameters which generally leads to rapid optimization and more reproducible reaction conditions.

To indicate the efficiency of this palladacycle catalyst, the *trans*-4-acetylstilbene formation was considered and this system is compared with other palladium based catalytic systems. As can be seen in Table 4, this palladacycle complex gave better yield in shorter time [39-41].

Based on the results, production of exclusively the *trans* isomers and complete conversions (exception of 4-chloroacetophenone) by this method are great advantages of the presented catalyst.

4. Conclusion

In summary, the application of dimeric *ortho*-palladated complex of 2-methoxyphenethylamine in the Heck reaction of various aryl halides with olefins was investigated. The results showed that this complex is an efficient catalyst for the Heck reaction and its coupling products were obtained in good to excellent yields. The advantages of using this catalyst are its easy preparation, handling, stability, moisture insensitivity and production of exclusively the *trans* isomers. The combination of dimeric complex as homogenous catalyst and microwave irradiation caused to increase the lifetime of the catalyst, improve the yields of the reactions and decrease the reaction times.

Acknowledgements

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